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PREFACE

The Preface to the Integrated Science Assessment for Particulate Matter (PM ISA) outlines the legislative requirements of a National Ambient Air Quality Standard (NAAQS) review and the history of the PM NAAQS. This information provides an understanding of the function of the ISA, and in terms of providing a starting point for this PM ISA, presents the basis for the decisions that supported the previous PM NAAQS review. In addition, the Preface details the purpose of the ISA as well as specific issues pertinent to the evaluation of the scientific evidence that takes place within this ISA, including the scope of the ISA and discipline specific decisions that governed parts of the review.

P.1 Legislative Requirements for the Review of the National Ambient Air Quality Standards

Two sections of the Clean Air Act (CAA) govern the establishment, review, and revision of the National Ambient Air Quality Standards (NAAQS). Section 108 [42 U.S. Code (U.S.C.) 7408] directs the Administrator to identify and list certain air pollutants and then to issue air quality criteria for those pollutants. The Administrator is to list those air pollutants that in their "judgment, cause or contribute to air pollution which may reasonably be anticipated to endanger public health or welfare," "the presence of which in the ambient air results from numerous or diverse mobile or stationary sources," and "for which … [the Administrator] plans to issue air quality criteria …" [42 U.S.C. 7408(a)(1); (CAA, 1990a)]. Air quality criteria are intended to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare, which may be expected from the presence of [a] pollutant in the ambient air …" [42 U.S.C. 7408(b)]. Section 109 [42 U.S.C. 7409; (CAA, 1990b)] directs the Administrator to propose and promulgate "primary" and "secondary" NAAQS for pollutants for which air quality criteria are issued. Section 109(b)(1) defines a primary standard as one "the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health."[4] A secondary standard, as defined in Section 109(b)(2), must "specify a level of air quality the attainment and maintenance of which, in the judgment of the Administrator, based on such criteria, is requisite to protect

[4] The legislative history of Section 109 indicates that a primary standard is to be set at "… the maximum permissible ambient air level…which will protect the health of any [sensitive] group of the population," and that for this purpose "reference should be made to a representative sample of persons comprising the sensitive group rather than to a single person in such a group" S. Rep. No. 91:1196, 91st Cong., 2d Sess. 10 (1970).

the public welfare from any known or anticipated adverse effects associated with the presence of [the] air pollutant in the ambient air."[5]

The requirement that primary standards provide an adequate margin of safety was intended to address uncertainties associated with inconclusive scientific and technical information available at the time of standard setting. It was also intended to provide a reasonable degree of protection against hazards that research has not yet identified.[6] Both kinds of uncertainty are components of the risk associated with pollution at levels below those at which human health effects can be said to occur with reasonable scientific certainty. Thus, in selecting primary standards that provide an adequate margin of safety, the Administrator is seeking not only to prevent pollution levels that have been demonstrated to be harmful but also to prevent lower pollutant levels that may pose an unacceptable risk of harm, even if the risk is not precisely identified as to nature or degree. The CAA does not require the Administrator to establish a primary NAAQS at a zero-risk level or at background concentration levels, but rather at a level that reduces risk sufficiently so as to protect public health with an adequate margin of safety.[7] In so doing, protection is provided for both the population as a whole and those groups and lifestages potentially at increased risk for health effects from exposure to the air pollutant for which each NAAQS is set.

In addressing the requirement for an adequate margin of safety, the U.S. Environmental Protection Agency (U.S. EPA) considers such factors as the nature and severity of the health effects involved, the size of the sensitive group(s), and the kind and degree of the uncertainties. The selection of any particular approach to providing an adequate margin of safety is a policy choice left specifically to the Administrator's judgment.[8]

In setting standards that are "requisite" to protect public health and welfare as provided in Section 109(b), the U.S. EPA's task is to establish standards that are neither more nor less stringent than necessary for these purposes. In so doing, the U.S. EPA may not consider the costs of implementing the standards.[9] Likewise, "[a]ttainability and technological feasibility are not relevant considerations in the promulgation of national ambient air quality standards."[10]

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[5] Section 302(h) of the Act [42 U.S.C. 7602(h)] provides that all language referring to effects on welfare includes, but is not limited to, "effects on soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility and climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and on personal comfort and well-being…" (CAA, 2005).

[6] See *Lead Industries Association v. EPA*, 647 F.2d 1130, 1154 [District of Columbia Circuit (D.C. Cir.) 1980]; *American Petroleum Institute v. Costle*, 665 F.2d 1176, 1186 (D.C. Cir. 1981); *American Farm Bureau Federation v. EPA*, 559 F. 3d 512, 533 (D.C. Cir. 2009); *Association of Battery Recyclers v. EPA*, 604 F. 3d 613, 617−18 (D.C. Cir. 2010).

[7] See *Lead Industries v. EPA*, 647 F.2d at 1156 n.51; *Mississippi v. EPA*, 744 F. 3d 1334, 1339, 1351, 1353 (D.C. Cir. 2013).

[8] See *Lead Industries Association v. EPA,* 647 F.2d at 1161−62; *Mississippi v. EPA,* 744 F. 3d at 1353.

[9] See generally, *Whitman v. American Trucking Associations*, 531 U.S. 457, 465−472, 475−476 (2001).

[10] See *American Petroleum Institute v. Costle,* 665 F. 2d at 1185.

Section 109(d)(1) requires that "not later than December 31, 1980, and at 5-year intervals thereafter, the Administrator shall complete a thorough review of the criteria published under Section 108 and the national ambient air quality standards…and shall make such revisions in such criteria and standards and promulgate such new standards as may be appropriate…." Section 109(d)(2) requires that an independent scientific review committee "shall complete a review of the criteria…and the national primary and secondary ambient air quality standards…and shall recommend to the Administrator any new…standards and revisions of existing criteria and standards as may be appropriate…." Since the early 1980s, this independent review function has been performed by the Clean Air Scientific Advisory Committee (CASAC).[11]

P.1.1. Overview and History of the Reviews of the Primary and Secondary National Ambient Air Quality Standard for Particulate Matter

NAAQS are defined by four basic elements: indicator, averaging time, level, and form. The indicator defines the pollutant to be measured in the ambient air for the purpose of determining compliance with the standard. The averaging time defines the time period over which air quality measurements are to be obtained and averaged or cumulated, considering evidence of effects associated with various time periods of exposure. The level of a standard defines the air quality concentration used (i.e., an ambient concentration of the indicator pollutant) in determining whether the standard is achieved. The form of the standard defines the air quality statistic that is compared to the level of the standard in determining whether an area attains the standard. For example, the form of the current primary annual fine particulate matter ($PM_{2.5}$) standard is the annual mean averaged over 3 years. The Administrator considers these four elements collectively in evaluating the protection to public health provided by the primary NAAQS.

Particulate matter (PM) is the generic term for a broad class of chemically and physically diverse substances that exist as discrete particles (liquid droplets or solids) over a wide range of sizes. Particles originate from a variety of anthropogenic stationary and mobile sources, as well as from natural sources. Particles may be emitted directly or formed in the atmosphere by transformations of gaseous emissions such as sulfur oxides (SO_X), oxides of nitrogen (NO_X), ammonia (NH_3) and volatile organic compounds (VOC). Examples of secondary particle formation include: (1) the conversion of SO_2 to sulfuric acid (H_2SO_4) vapor that nucleates new particles or condenses on existing particles and further reacts with NH_3 to form various inorganic salts (e.g., ammonium sulfate, $[NH_4]_2SO_4$, or ammonium bisulfate, NH_4HSO_4); (2) the conversion of nitrogen dioxide (NO_2) to nitric acid (HNO_3) vapor that condenses onto existing particles and reacts further with ammonia to form ammonium nitrate (NH_4NO_3); and (3) reactions

[11] The List of CASAC members is available at: https://yosemite.epa.gov/sab/sabpeople.nsf/WebExternalCommitteeRosters?OpenView&committee=CASAC&secondname=Clean%20Air%20Scientific%20Advisory%20Committee%20.

involving gaseous VOC yielding organic compounds with low vapor pressures that nucleate or condense on existing particles to form secondary organic particulate matter (SOPM) (U.S. EPA, 2004). The chemical and physical properties of PM vary greatly with time, region, meteorology, and source category, thus complicating the assessment of health and welfare effects. These reviews are briefly described below, and further details are provided in the Integrated Review Plan (U.S. EPA, 2016).

The U.S. EPA first established NAAQS for PM in 1971 (36 FR 8186, April 30, 1971), based on the original criteria document (NAPCA, 1969).[12] The federal reference method (FRM) specified for determining attainment of the original standards was the high-volume sampler, which collects PM up to a nominal size of 25 to 45 micrometers (μm) (referred to as total suspended particulates or TSP). The primary standards were at 260 μg/m^3, 24-hour average, not to be exceeded more than once per year, and 75 μg/m^3, annual geometric mean. The secondary standards were 150 μg/m^3, 24-hour average, not to be exceeded more than once per year, and 60 μg/m^3, annual geometric mean. Since then, the Agency has completed multiple reviews of the air quality criteria and standards, as summarized in Table P-1.

Table P-1 History of the National Ambient Air Quality Standards for particulate matter, 1971−2012.

Final Rule/Decision	Indicator	Averaging Time	Level	Form
1971 36 FR 8186 Apr 30, 1971	TSP	24 h	260 μg/m^3 (primary) 150 μg/m^3 (secondary)	Not to be exceeded more than once per year
		Annual	75 μg/m^3 (primary) 60 μg/m^3 (secondary)	Annual geometric mean
1987 52 FR 24634 Jul 1, 1987	PM_{10}	24 h	150 μg/m^3	Not to be exceeded more than once per year on average over a 3-yr period
		Annual	50 μg/m^3	Annual arithmetic mean, averaged over 3 yr

[12] Prior to the review initiated in 2007 (see below), the AQCD provided the scientific basis for the NAAQS.

Table P-1 (Continued): History of the National Ambient Air Quality Standards for particulate matter, 1971−2012.

Final Rule/Decision	Indicator	Averaging Time	Level	Form
1997 62 FR 38652 Jul 18, 1997	$PM_{2.5}$	24 h	65 μg/m^3	98th percentile, averaged over 3 yr
		Annual	15 μg/m^3	Annual arithmetic mean, averaged over 3 yr[a]
	PM_{10}	24 h	150 μg/m^3	Initially promulgated 99th percentile, averaged over 3 yr; when 1997 standards were vacated in 1999, the form of 1987 standards remained in place (not to be exceeded more than once per yr on average over a 3-yr period)
		Annual	50 μg/m^3	Annual arithmetic mean, averaged over 3 yr
2006 71 FR 61144 Oct 17, 2006	$PM_{2.5}$	24 h	35 μg/m^3	98th percentile, averaged over 3 yr
		Annual	15 μg/m^3	Annual arithmetic mean, averaged over 3 yr[a]
	PM_{10}	24 h	150 μg/m^3	Not to be exceeded more than once per yr on average over a 3-yr period
2012 78 FR 3085 Jan 15, 2013	$PM_{2.5}$	24 h	35 μg/m^3	98th percentile, averaged over 3-yr[c]
		Annual	12 μg/m^3 (primary) 15 μg/m^3 (secondary)	Annual arithmetic mean, averaged over 3-yr[b]
	PM_{10}[d]	24 h	150 μg/m^3	Not to be exceeded more than once per year on average over 3-yr

TSP = total suspended particulates.

[a]The level of the 1997 annual $PM_{2.5}$ standard was to be compared to measurements made at the community-oriented monitoring site recording the highest level, or, if specific constraints were met, measurements from multiple community-oriented monitoring sites could be averaged ("spatial averaging"). This approach was judged to be consistent with the short-term exposure epidemiologic studies on which the annual $PM_{2.5}$ standard was primarily based, in which air quality data were generally averaged across multiple monitors in an area or were taken from a single monitor that was selected to represent community-wide exposures, not localized "hot spots" (62 FR 38672). These criteria and constraints were intended to ensure that spatial averaging would not result in inequities in the level of protection afforded by the $PM_{2.5}$ standards. Community-oriented monitoring sites were specified to be consistent with the intent that a spatially averaged annual standard provide protection for persons living in smaller communities, as well as those in larger population centers.

[b]In the revisions to the PM NAAQS finalized in 2006, U.S. EPA tightened the constraints on the spatial averaging criteria by further limiting the conditions under which some areas may average measurements from multiple community-oriented monitors to determine compliance (71 FR 61165-61167, October 17, 2006).

[c]The level of the 24-h standard is defined as an integer (zero decimal places) as determined by rounding. For example, a 3-yr average 98th percentile concentration of 35.49 μg/m^3 would round to 35 μg/m^3 and thus meet the 24-h standard and a 3-yr average of 35.50μg/m^3 would round to 36 and, hence, violate the 24-h standard (40 CFR Part 50 Appendix N).

[d]The U.S. EPA revoked the annual PM_{10} NAAQS in 2006.

Note: When not specified, primary and secondary standards are identical.

In October 1979 (44 FR 56730, October 2, 1979), the U.S. EPA announced the first periodic review of the air quality criteria and NAAQS for PM. Revised primary and secondary standards were promulgated in 1987 (52 FR 24634, July 1, 1987). In the 1987 decision, the U.S. EPA changed the

indicator for particles from TSP to PM_{10}, in order to focus on the subset of inhalable particles small enough to penetrate to the thoracic region of the respiratory tract (including the tracheobronchial and alveolar regions), referred to as thoracic particles.[13] The level of the 24-hour standards (primary and secondary) was set at 150 μg/m^3, and the form was one expected exceedance per year, on average over 3 years. The level of the annual standards (primary and secondary) was set at 50 μg/m^3, and the form was annual arithmetic mean, averaged over 3 years.

In April 1994, the U.S. EPA announced its plans for the second periodic review of the air quality criteria and NAAQS for PM, and in 1997 the U.S. EPA promulgated revisions to the NAAQS (62 FR 38652, July 18, 1997). In the 1997 decision, the U.S. EPA determined that the fine and coarse fractions of PM_{10} should be considered separately. This determination was based on evidence that serious health effects were associated with short- and long-term exposures to fine particles in areas that met the existing PM_{10} standards. The U.S. EPA added new standards, using $PM_{2.5}$ as the indicator for fine particles (with $PM_{2.5}$ referring to particles with a nominal mean aerodynamic diameter less than or equal to 2.5 μm). These new standards were as follows: (1) an annual standard with a level of 15.0 μg/m^3, based on the 3-year average of annual arithmetic mean $PM_{2.5}$ concentrations from single or multiple community-oriented monitors;[14] and (2) a 24-hour standard with a level of 65 μg/m^3, based on the 3-year average of the 98th percentile of 24-hour $PM_{2.5}$ concentrations at each monitor within an area. Also, the U.S. EPA established a new reference method for the measurement of $PM_{2.5}$ in the ambient air and adopted rules for determining attainment of the new standards. To continue to address the coarse fraction of PM_{10} (referred to as thoracic coarse particles or $PM_{10–2.5}$; generally including particles with a nominal mean aerodynamic diameter greater than 2.5 μm and less than or equal to 10 μm), the U.S. EPA retained the annual PM_{10} standard and revised the form of the 24-hour PM_{10} standard to be based on the 99th percentile of 24-hour PM_{10} concentrations at each monitor in an area. The U.S. EPA revised the secondary standards by setting them equal in all respects to the primary standards.

Following promulgation of the 1997 PM NAAQS, petitions for review were filed by a large number of parties, addressing a broad range of issues. In May 1999, the U.S. Court of Appeals for the District of Columbia Circuit (D.C. Circuit) upheld the U.S. EPA's decision to establish fine particle standards, holding that "the growing empirical evidence demonstrating a relationship between fine particle pollution and adverse health effects amply justifies establishment of new fine particle standards."

[13] PM_{10} refers to particles with a nominal mean aerodynamic diameter less than or equal to 10 μm. More specifically, 10 μm is the aerodynamic diameter for which the efficiency of particle collection is 50%. Larger particles are not excluded altogether, but are collected with substantially decreasing efficiency while smaller particles are collected with increasing efficiency.

[14] The level of the 1997 annual $PM_{2.5}$ standard was to be compared to measurements made at the community-oriented monitoring site recording the highest concentration or, if specific constraints were met, measurements from multiple community-oriented monitoring sites could be averaged (i.e., "spatial averaging"). In the last review (completed in 2012) the U.S. EPA replaced the term "community-oriented" monitor with the term "area-wide" monitor. Area-wide monitors are those sited at the neighborhood scale or larger, as well as those monitors sited at micro-or middle scales that are representative of many such locations in the same CBSA (78 FR 3236, January 15, 2013).

American Trucking Associations v. U.S. EPA, 175 F. 3d 1027, 1055−56 (D.C. Cir. 1999). The D.C. Circuit also found "ample support" for the U.S. EPA's decision to regulate coarse particle pollution, but vacated the 1997 PM_{10} standards, concluding that the U.S. EPA had not provided a reasonable explanation justifying use of PM_{10} as an indicator for coarse particles. 175 F. 3d at 1054−55. Pursuant to the D.C. Circuit's decision, the U.S. EPA removed the vacated 1997 PM_{10} standards, and the pre-existing 1987 PM_{10} standards remained in place (65 FR 80776, December 22, 2000). The D.C. Circuit also upheld the U.S. EPA's determination not to establish more stringent secondary standards for fine particles to address effects on visibility. 175 F. 3d at 1027.

The D.C. Circuit also addressed more general issues related to the NAAQS, including issues related to the consideration of costs in setting NAAQS and the U.S. EPA's approach to establishing the levels of NAAQS. Regarding the cost issue, the court reaffirmed prior rulings holding that in setting NAAQS the U.S. EPA is "not permitted to consider the cost of implementing those standards." Id. at 1040-41. Regarding the levels of NAAQS, the court held that the U.S. EPA's approach to establishing the level of the standards in 1997 (i.e., both for PM and for the ozone NAAQS promulgated on the same day) effected "an unconstitutional delegation of legislative authority." Id. at 1034-40. Although the court stated that "the factors U.S. EPA uses in determining the degree of public health concern associated with different levels of ozone and PM are reasonable," it remanded the rule to the U.S. EPA, stating that when the U.S. EPA considers these factors for potential non-threshold pollutants "what U.S. EPA lacks is any determinate criterion for drawing lines" to determine where the standards should be set.

The D.C. Circuit's holding on the cost and constitutional issues were appealed to the U.S. Supreme Court. In February 2001, the Supreme Court issued a unanimous decision upholding the U.S. EPA's position on both the cost and constitutional issues. Whitman v. American Trucking Associations, 531 U.S. 457, 464, 475−76. On the constitutional issue, the Court held that the statutory requirement that NAAQS be "requisite" to protect public health with an adequate margin of safety sufficiently guided the U.S. EPA's discretion, affirming the U.S. EPA's approach of setting standards that are neither more nor less stringent than necessary.[15]

In October 1997, the U.S. EPA published its plans for the third periodic review of the air quality criteria and NAAQS for PM (62 FR 55201, October 23, 1997). After the CASAC and public review of several drafts, the U.S. EPA's NCEA finalized the Air Quality Criteria Document (AQCD) in October 2004 (U.S. EPA, 2004). The U.S. EPA's OAQPS finalized a Risk Assessment and Staff Paper in

[15] The Supreme Court remanded the case to the Court of Appeals for resolution of any remaining issues that had not been addressed in that court's earlier rulings. Id. at 475−76. In a March 2002 decision, the Court of Appeals rejected all remaining challenges to the standards, holding that the EPA's $PM_{2.5}$ standards were reasonably supported by the administrative record and were not "arbitrary and capricious" American Trucking Associations v. EPA, 283 F. 3d 355, 369-72 (D.C. Cir. 2002).

December of 2005 (Abt, 2005; U.S. EPA, 2005).[16] On December 20, 2005, the U.S. EPA announced its proposed decision to revise the NAAQS for PM, and solicited comment on a broad range of options (71 FR 2620, January 17, 2006). On September 21, 2006, the U.S. EPA announced its final decisions to revise the primary and secondary NAAQS for PM to provide increased protection of public health and welfare, respectively (71 FR 61144, October 17, 2006). With regard to the primary and secondary standards for fine particles, the U.S. EPA revised the level of the 24-hour $PM_{2.5}$ standards to 35 $\mu g/m^3$, retained the level of the annual $PM_{2.5}$ standards at 15.0 $\mu g/m^3$, and revised the form of the annual $PM_{2.5}$ standards by narrowing the constraints on the optional use of spatial averaging. For the primary and secondary standards for PM_{10}, the U.S. EPA retained the 24-hour standards, with levels at 150 $\mu g/m^3$, and revoked the annual standards.[17] The Administrator judged that the available evidence generally did not suggest a link between long-term exposure to existing ambient levels of coarse particles and health or welfare effects. In addition, a new reference method was added for the measurement of $PM_{10-2.5}$ in the ambient air, in order to provide a basis for approving federal equivalent methods (FEMs) and to promote the gathering of scientific data to support future reviews of the PM NAAQS.

Several parties filed petitions for review following promulgation of the revised PM NAAQS in 2006. These petitions addressed the following issues: (1) selecting the level of the primary annual $PM_{2.5}$ standard; (2) retaining PM_{10} as the indicator of a standard for thoracic coarse particles, retaining the level and form of the 24-hour PM_{10} standard, and revoking the PM_{10} annual standard; and (3) setting the secondary $PM_{2.5}$ standards identical to the primary standards. On February 24, 2009, the U.S. Court of Appeals for the District of Columbia Circuit issued its opinion in the case American Farm Bureau Federation v. U.S. EPA, 559 F. 3d 512 (D.C. Cir. 2009). The court remanded the primary annual $PM_{2.5}$ NAAQS to U.S. EPA because U.S. EPA failed to adequately explain why the standards provided the requisite protection from both short- and long-term exposures to fine particles, including protection for at-risk populations. American Farm Bureau Federation v. U.S. EPA, 559 F. 3d 512, 520−27 (D.C. Cir. 2009). With regard to the standards for PM_{10}, the court upheld U.S. EPA's decisions to retain the 24-hour PM_{10} standard to provide protection from thoracic coarse particle exposures and to revoke the annual PM_{10} standard. American Farm Bureau Federation, 559 F. 2d at 533−38. For the secondary $PM_{2.5}$ standards, the court remanded the standards to U.S. EPA because the Agency failed to adequately explain why setting the secondary PM standards identical to the primary standards provided the required

[16] Prior to the review initiated in 2007, the Staff Paper, rather than the PA, presented the EPA staff's considerations and conclusions regarding the adequacy of existing NAAQS and, when appropriate, the potential alternative standards that could be supported by the evidence and information.

[17] In the 2006 proposal, the EPA proposed to revise the 24-hour PM_{10} standard in part by establishing a new $PM_{10-2.5}$ indicator for thoracic coarse particles (i.e., particles generally between 2.5 and 10 µm in diameter). The EPA proposed to include any ambient mix of $PM_{10-2.5}$ that was dominated by resuspended dust from high density traffic on paved roads and by PM from industrial sources and construction sources. The EPA proposed to exclude any ambient mix of $PM_{10-2.5}$ that was dominated by rural windblown dust and soils and by PM generated from agricultural and mining sources. In the final decision, the existing PM_{10} standard was retained, in part due to an "inability…to effectively and precisely identify which ambient mixes are included in the [$PM_{10-2.5}$] indicator and which are not" (71 FR 61197, October 17, 2006).

protection for public welfare, including protection from visibility impairment. American Farm Bureau Federation, 559 F. 2d at 528−32. The U.S. EPA responded to the court's remands as part of the next review of the PM NAAQS, which was initiated in 2007 (discussed below).

In June 2007, the U.S. EPA initiated the fourth periodic review of the air quality criteria and the PM NAAQS by issuing a call for information in the Federal Register (72 FR 35462, June 28, 2007). Based on the NAAQS review process, as revised in 2008 and again in 2009,[18] the U.S. EPA held science/policy issue workshops on the primary and secondary PM NAAQS (72 FR 34003, June 20, 2007; 72 FR 34005, June 20, 2007), and prepared and released the planning and assessment documents that comprise the review process [i.e., IRP (U.S. EPA, 2008), ISA (U.S. EPA, 2009a)], REA planning documents for health and welfare (Office of Air and Radiation, 2009; U.S. EPA, 2009b), a quantitative health risk assessment (U.S. EPA, 2010b)[19] and an urban-focused visibility assessment (U.S. EPA, 2010a),[20] and PA (U.S. EPA, 2011)]. In June 2012, the U.S. EPA announced its proposed decision to revise the NAAQS for PM (77 FR 38890, June 29, 2012).

In December 2012, the U.S. EPA announced its final decisions to revise the primary NAAQS for PM to provide increased protection of public health (78 FR 3086, January 15, 2013). With regard to primary standards for $PM_{2.5}$, the U.S. EPA revised the level of the annual $PM_{2.5}$ standard[21] to 12.0 $\mu g/m^3$ and retained the 24-hour $PM_{2.5}$ standard, with its level of 35 $\mu g/m^3$. For the primary PM_{10} standard, the U.S. EPA retained the 24-hour standard, with its level of 150 $\mu g/m^3$, to continue to provide protection against effects associated with short-term exposure to thoracic coarse particles (i.e., $PM_{10-2.5}$). With regard to the secondary PM standards, the U.S. EPA generally retained the 24-hour and annual $PM_{2.5}$ standards[22] and the 24-hour PM_{10} standard to address visibility and non-visibility welfare effects. On judicial review, the revised standards were upheld in all respects. NAM v U.S. EPA, 750 F.3d 921 (D.C. Cir. 2014).

[18] The history of the NAAQS review process, including revisions to the process, is discussed at http://www3.epa.gov/ttn/naaqs/review2.html.

[19] The quantitative assessment of health risks conducted in the last review was presented in the Quantitative Health Risk Assessment for Particulate Matter (U.S. EPA, 2010b). In the current review, quantitative assessments for health-related exposures and risks, if warranted, would be presented in the Health Risk and Exposure Assessment (HREA). For consistency with the documents developed under the current NAAQS process, the Quantitative Health Risk Assessment for Particulate Matter (U.S. EPA, 2010b) from the last review will be referenced in this document as the 2010 HREA.

[20] The quantitative assessment of welfare effects conducted in the last review was presented, in part, in the Urban-Focused Visibility Assessment (U.S. EPA, 2010a). In the current review, quantitative assessments for welfare effects, if warranted, would be presented in the Welfare Risk and Exposure Assessment (WREA). The Urban-Focused Visibility Assessment (U.S. EPA, 2010a) from the last review will be referenced in this document as the 2010 UFVA.

[21] The U.S. EPA also eliminated the option for spatial averaging.

[22] Consistent with the primary standard, the U.S. EPA eliminated the option for spatial averaging with the annual standard.

P.2 Purpose and Overview of the Integrated Science Assessment

The Integrated Science Assessment (ISA) is a comprehensive evaluation and synthesis of the policy-relevant science "useful in indicating the kind and extent of identifiable effects on public health or welfare which may be expected from the presence of [a] pollutant in ambient air," as described in Section 108 of the Clean Air Act (CAA, 1990a). This ISA communicates critical science judgments of the health and welfare criteria for particulate matter (PM). As such, this ISA serves as the scientific foundation for the review of the current primary (health-based) and secondary (welfare-based) National Ambient Air Quality Standards (NAAQS) for PM. In terms of the evaluation of the welfare-based evidence, the PM ISA focuses specifically on the nonecological effects of PM (i.e., visibility, materials effects, and climate) because the ecological effects are assessed in the ISA for Oxides of Nitrogen, Oxides of Sulfur, and Particulate Matter—Ecological Criteria as a result of these criteria pollutants being interrelated through complex chemical and physical atmospheric processes and all contributing to nitrogen (N) and sulfur (S) deposition (U.S. EPA, 2016). While the focus of the evaluation of the visibility and climate evidence is on PM, for materials effects, as detailed in the Integrated Review Plan (IRP), the PM ISA summarizes soiling and deterioration of materials attributable to PM and related N and S components because of the difficulty associated with isolating the effects of gaseous and particulate N and S wet deposition and because the ISA for Oxides of Nitrogen, Oxides of Sulfur, and Particulate Matter—Ecological Criteria focuses only on ecological effects (U.S. EPA, 2016).

This ISA evaluates relevant scientific literature published since the 2009 PM ISA [(U.S. EPA, 2009a) or 2009 PM ISA], integrating key information and judgments contained in the 2009 PM ISA and previous assessments of PM, i.e., 2004 AQCD for PM (U.S. EPA, 2004), 1996 AQCD for PM (U.S. EPA, 1996), 1982 AQCD for PM and Sulfur Oxides (U.S. EPA, 1982) and its Addendum (U.S. EPA, 1986), and the 1969 AQCD for PM (NAPCA, 1969). Thus, this ISA updates the state of the science that was available for the 2009 PM ISA, which informed decisions on the primary and secondary PM NAAQS in the review completed in 2012. In 2012, the U.S. EPA lowered the annual $PM_{2.5}$ standard to a mean of 12 $\mu g/m^3$, which is based on the annual mean averaged over 3 years, while retaining the 24-hour $PM_{2.5}$ standard of 35 $\mu g/m^3$, which is based on the 98th percentile averaged over 3 years (78 FR 3086). As part of the primary annual $PM_{2.5}$ standard, the U.S. EPA eliminated the spatial averaging provision to avoid disproportionate impacts on susceptible populations (i.e., populations potentially at increased risk of a PM-related health effect). The $PM_{2.5}$ standards are meant to provide increased protection for children, older adults, and people with pre-existing heart and lung disease as well as other potential susceptible populations against an array of $PM_{2.5}$-related health effects including premature mortality, increased hospital admissions and emergency department (ED) visits, and the development of chronic respiratory disease. Additionally, the U.S. EPA retained the current primary 24-hour PM_{10} standard at a level of 150 $\mu g/m^3$, which is not to be exceeded more than once per year over 3 years, to protect against health effects due to short-term exposure to thoracic coarse particles ($PM_{10–2.5}$) including premature mortality and increased hospital admissions and ED visits (78 FR 3086).

In terms of the secondary PM standards, the U.S. EPA retained the annual $PM_{2.5}$ standard at 15 $\mu g/m^3$ as well as the 24-hour $PM_{2.5}$ standard of 35 $\mu g/m^3$ and the 24-hour PM_{10} standard of 150 $\mu g/m^3$ (78 FR 3086). However, the form of the annual secondary $PM_{2.5}$ standard was changed to remove the option of spatial averaging. These secondary standards protect against non-visibility welfare effects including ecological effects, effects on materials, and climate impacts. To protect against PM-related visibility impairment, the U.S. EPA identified a target degree of protection defined as a $PM_{2.5}$ visibility index of 30 deciviews (dv), which is based on the 90th percentile of 24-hour average $PM_{2.5}$ concentrations over 3 years (78 FR 3086). However, an U.S. EPA analysis determined that the current secondary 24-hour $PM_{2.5}$ standard would provide sufficient protection, and in some cases greater protection, therefore a distinct secondary standard was not needed to provide requisite protection for both visibility and non-visibility related welfare effects.

This new review of the primary and secondary PM NAAQS is guided by several policy-relevant questions that are identified in The Integrated Review Plan for the National Ambient Air Quality Standards for Particulate Matter (U.S. EPA, 2016). To address these questions and update the scientific judgments in the 2009 PM ISA (U.S. EPA, 2009a), this ISA aims to:

- Assess whether new information (since the last PM NAAQS review) further informs the relationship between exposure to PM and specific health and nonecological welfare effects?
- Inform whether the current indicators (i.e., $PM_{2.5}$ for fine particles and PM_{10} for thoracic coarse particles), averaging times (e.g., 24-hour average, annual average), and levels of the PM NAAQS are appropriate?

In addressing policy-relevant questions, this ISA aims to characterize the independent health and welfare effects of PM, specifically $PM_{2.5}$ (fine PM; particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 m) and $PM_{10–2.5}$ (thoracic coarse or coarse PM; particulate matter with a nominal mean aerodynamic diameter greater than 2.5 μm and less than or equal to 10 μm) and whether there is evidence of an independent health effect for other size fractions [e.g., ultrafine particles (UFP), generally considered as particulates with a diameter less than or equal to 0.1 μm (typically based on physical size, thermal diffusivity or electrical mobility) (U.S. EPA, 2009a)] or specific PM components (e.g., metals). In the characterization of whether there is evidence of an independent health and welfare effect due to PM, the ISA considers possible influences of other atmospheric pollutants, including both gaseous (i.e., O_3, NO_2, SO_2, and CO) and other PM size fractions. The information summarized in this ISA will serve as the scientific foundation for the review of the current primary and secondary PM NAAQS.

P.3 Process for Developing Integrated Science Assessments

The U.S. EPA uses a structured and transparent process for evaluating scientific information and determining the causal nature of relationships between air pollution exposures and health effects [details provided in the Preamble to the Integrated Science Assessments (U.S. EPA, 2015)]. The ISA

development process describes approaches for literature searches, criteria for selecting and evaluating relevant studies, and a framework for evaluating the weight of evidence and forming causality determinations. Table P-2 provides a description of each of the five causality determinations and the types of scientific evidence that is considered for each category for both health and welfare effects.

Table P-2. Weight of evidence for causality determinations.

	Health Effects	Ecological and Other Welfare Effects
Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures (e.g., doses or exposures generally within one to two orders of magnitude of recent concentrations). That is, the pollutant has been shown to result in health effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. For example: (1) controlled human exposure studies that demonstrate consistent effects, or (2) observational studies that cannot be explained by plausible alternatives or that are supported by other lines of evidence (e.g., animal studies or mode of action information). Generally, the determination is based on multiple high-quality studies conducted by multiple research groups.	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures. That is, the pollutant has been shown to result in effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. Controlled exposure studies (laboratory or small- to medium-scale field studies) provide the strongest evidence for causality, but the scope of inference may be limited. Generally, the determination is based on multiple studies conducted by multiple research groups, and evidence that is considered sufficient to infer a causal relationship is usually obtained from the joint consideration of many lines of evidence that reinforce each other.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures. That is, the pollutant has been shown to result in health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. For example: (1) observational studies show an association, but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent, or (2) animal toxicological evidence from multiple studies from different laboratories demonstrate effects, but limited or no human data are available. Generally, the determination is based on multiple high-quality studies.	Evidence is sufficient to conclude that there is a likely causal association with relevant pollutant exposures. That is, an association has been observed between the pollutant and the outcome in studies in which chance, confounding, and other biases are minimized but uncertainties remain. For example, field studies show a relationship, but suspected interacting factors cannot be controlled, and other lines of evidence are limited or inconsistent. Generally, the determination is based on multiple studies by multiple research groups.

Table P-2. (Continued): Weight of evidence for causality determinations.

	Health Effects	Ecological and Other Welfare Effects
Suggestive of, but not sufficient to infer, a causal relationship	Evidence is suggestive of a causal relationship with relevant pollutant exposures but is limited, and chance, confounding, and other biases cannot be ruled out. For example: (1) when the body of evidence is relatively small, at least one high-quality epidemiologic study shows an association with a given health outcome and/or at least one high-quality toxicological study shows effects relevant to humans in animal species, or (2) when the body of evidence is relatively large, evidence from studies of varying quality is generally supportive but not entirely consistent, and there may be coherence across lines of evidence (e.g., animal studies or mode of action information) to support the determination.	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but chance, confounding, and other biases cannot be ruled out. For example, at least one high-quality study shows an effect, but the results of other studies are inconsistent.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect.	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect.
Not likely to be a causal relationship	Evidence indicates there is no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering at-risk populations and lifestages, are mutually consistent in not showing an effect at any level of exposure.	Evidence indicates there is no causal relationship with relevant pollutant exposures. Several adequate studies examining relationships with relevant exposures are consistent in failing to show an effect at any level of exposure.

Source: U.S. EPA (2015).

As part of this process, the ISA is reviewed by the Clean Air Scientific Advisory Committee (CASAC), which is a formal independent panel of scientific experts, and by the public. As this ISA informs the review of the primary and secondary PM NAAQS, it integrates and synthesizes information characterizing exposure to PM and potential relationships with health and welfare effects. Relevant studies include those examining atmospheric chemistry, spatial and temporal trends, and exposure assessment, as well as U.S. EPA analyses of air quality and emissions data. Relevant health research includes epidemiologic, controlled human exposure, and toxicological studies on health effects, as well as studies on dosimetry and biological plausibility. Additionally, relevant welfare research includes studies examining visibility impairment, effects on materials, and climate impacts.

The U.S. EPA initiated the current review of the primary and secondary PM NAAQS in December 2014 with a call for information from the public (U.S. EPA, 2013). Subject-area experts and the public were also able to recommend studies and reports to consider for the ISA during a science/policy issue "kick-off" workshop held at the U.S. EPA in February 2015. Thereafter, the U.S. EPA routinely conducted literature searches to identify relevant peer-reviewed studies published since the previous ISA (i.e., since May 2009). Multiple search methods were used [Preamble to the ISAs (U.S. EPA, 2015), Section 2], including searches in the PubMed and Web of Science databases. These

searches were meant to broadly capture all potentially relevant PM literature. To ensure the most policy-relevant evaluation of the current state of the science the scope of this PM ISA reflects not only the evolving PM literature base, but also the ability of the studies evaluated to directly inform the policy-relevant questions that form the basis of this review. Using both the scope of this ISA, detailed below, as well as the policy-relevant questions outlined in the PM IRP, studies that were uninformative based on title screening were excluded. Studies that were judged to be potentially relevant based on review of the abstract or full text and "considered" for inclusion in the ISA are documented in the Health and Environmental Research Online (HERO) website. The HERO project page for this ISA (https://hero.epa.gov/hero/particulate-matter) contains the references that are cited in the ISA, the references that were considered for inclusion but not cited, and electronic links to bibliographic information and abstracts.

P.3.1. Scope of the ISA

As initially detailed in the PM IRP (U.S. EPA, 2016) and further expanded upon here, when evaluating the broad body of literature across scientific disciplines, the U.S. EPA considers whether the studies fall within the scope of the PM ISA (i.e., provide information which can address key policy-relevant questions). As a result, the focus of the PM ISA with respect to the health effects evidence is on studies of short-term (i.e., hours up to 1 month) and long-term (i.e., 1 month to years) exposures conducted at concentrations of PM that are relevant to the range of human exposures across ambient microenvironments (up to 2 mg/m^3, which is one to two orders of magnitude above ambient concentrations), and (1) include a composite measure of PM[23] or (2) characterize PM and apply some approach to assess the direct effect of PM when the exposure of interest is a source-based mixture (e.g., diesel exhaust, gasoline exhaust, wood smoke). For epidemiologic studies, the scope is further refined when evaluating the evidence for those health outcomes where the 2009 PM ISA concluded that a "causal relationship exists" (i.e., short- and long-term $PM_{2.5}$ exposure and mortality and cardiovascular effects) to ensure the evaluation of the evidence focuses on the studies that are the most policy-relevant. As such, the focus is on those studies conducted in areas where mean $PM_{2.5}$ concentrations are <20 $\mu g/m^3$ or in the case of a multicity study where more than half of the cities have concentrations <20 $\mu g/m^3$. However, studies where mean $PM_{2.5}$ concentrations exceed 20 $\mu g/m^3$ are included if the studies address specific areas where the evidence was limited, as identified in the 2009 PM ISA, such as copollutant confounding. The scope is broader for experimental studies when examining biological plausibility for PM health effects, and in some cases, includes in vitro studies, studies that use intratracheal (IT) installation, studies examining relative toxicity, and studies conducted at concentrations >2 mg/m^3.

In the first case, studies that focus on a single component, group of components, or source, must also examine a composite measure of PM (e.g., mass of $PM_{2.5}$ and/or $PM_{10–2.5}$, or in the case of ultrafine particles [UFP] mass, particle number, etc.). This requirement facilitates a comparison of effects or

[23] Composite measures of PM may include mass, volume, surface area, or number concentration.

associations observed for individual components or alternative metrics to the current mass-based PM indicators. For experimental studies, to assess the relationship between $PM_{2.5}$ components and specific health effects this ISA relies on the approach initially outlined in the 2009 PM ISA and further refined in Stanek et al. (2011). This approach is consistent with the Health Effects Institute (HEI) Review Panel of the National Particle Component Toxicity (NPACT) initiative that states both source categories and component concentrations should be used directly in the health analyses with a focus on examining consistencies and differences between the two approaches (Lippmann et al., 2013). As a result, experimental studies included within this ISA fulfill the following four criteria (1) exposures examined consist of $PM_{2.5}$ from U.S. airsheds or those representative of the U.S. (e.g., Europe, Canada); (2) examined at least five PM components; (3) grouped PM components using statistical methods, for which the groups were not predefined based on common physical or chemical properties (e.g., water soluble vs. nonsoluble); and (4) applied a formal statistical analysis to investigate the relationship between groups of PM components or PM sources and health effects. The criteria applied to both experimental and epidemiologic studies in the evaluation of PM components ensures that a systematic approach is used in both identifying and evaluating those studies that examine PM components.

The second case primarily applies to experimental studies that attempt to disentangle the effect of PM on health from a complex air pollution mixture of particles, gases, and components distributed between the gas and particle phases. Studies that conduct an assessment of the PM effect from a source-based mixture (e.g., wood smoke, diesel exhaust, gasoline exhaust, etc.) are only included if they use filtration (e.g., a particle trap) or another approach to differentiate between effects due to the mixture and effects due to the particles alone.

Whereas the preceding paragraphs focused broadly on the scope of the entire PM ISA, there are additional nuances that further frame the scope of the ISA, specifically with respect to UFPs. UFPs have often been defined as particles <0.1 μm (U.S. EPA, 2009a), but depending on the scientific discipline, the methods employed and particle sizes examined to assess the UFP-health effects relationship varies. UFP exposures in animal toxicological and controlled human exposure studies typically use a particle concentrator, which can result in exposures to particles <0.30 μm (Section 2.4.3.1). While toxicological studies typically rely on examining UFP mass, epidemiologic studies examine multiple UFP metrics including particle number concentration (NC), mass concentration (MC), and surface area concentration (SC). However, depending on the monitor used and the metric, the UFP size distribution that could be included within each of these ranges can vary. Some studies that examine NC use no additional size classification, instead measuring NC over the entire size range of the particle counter. In instances where the entire size range is measured, limited available measurement data in the U.S. and Europe indicates that approximately 67 to 90% of NC represents particles <0.1 μm (Section 2.4.3.1). Studies that examine MC or SC often include a range of particle sizes up to 0.3 μm. Currently, a consensus has not been reached within the scientific community on the metric that best represents exposure to UFPs (Baldauf et al., 2016). As a result, in this ISA the focus of the evaluation of the UFP-health effects relationship is on particles <0.3 μm for MC and SC metrics included in experimental studies, and any size range that

includes particles <0.1 μm for NC. Focusing on these criteria when evaluating UFP studies will provide the most comprehensive assessment of UFPs and ensure that the metric examined represents primarily the UFP size range.

Across disciplines, studies defined as examining UFPs, but focusing on the sources, transport, and fate of fibers and unique nano-objects (namely, dots, hollow spheres, plates, rods, fibers, tubes) are not reviewed because substantial exposures to fibers and unique nano-objects generally occur in the occupational settings rather than the ambient environment. Furthermore, the in vivo disposition of unique nano-objects is not likely relevant to the behavior of ultrafine (UF) aerosols found in ambient air, which are created by combustion sources and photochemical formation of secondary organic aerosols. However, some studies focusing on engineered nano- or ultrafine particles (e.g., carbon black, titanium dioxide) are included where they contribute to an understanding of the dosimetry or biological plausibility of PM.

In addition to the specific parameters that broadly form the overall scope of the review of PM and health effects, additional criteria were applied for the evaluation of the evidence for cancer. As detailed in the PM IRP, the PM ISA focuses on whether PM can directly cause cancer through only inhalation exposures at ambient and near-ambient concentrations (i.e., up to 2 mg/m^3). When evaluating the epidemiologic evidence for cancer, consistent with the overall scope of the ISA, the focus is on those studies with composite measures of PM. Whereas the ISA tends not to focus the evaluation of the health effects evidence on in vitro studies, for the purposes of examining the mutagenicity of PM in vitro systems are discussed because they inform the biological pathways underlying cancer. While some components of PM are known carcinogens (e.g., benzene), as previously stated the focus of this ISA is on composite measures of PM (e.g., $PM_{2.5}$) and, where applicable, comparison to effects or associations observed for individual PM components to help inform the adequacy of current mass-based PM indicators. As such, the relationship between PM exposure and cancer is evaluated similarly to that of other health effects, resulting in the exclusion of studies that examine individual PM components without a composite PM measure. The evaluation of cancer includes studies that use PM filter extracts with the understanding that bioavailability of PM components in vivo is a complex issue not easily mimicked by extraction of PM collected on filters. Overall, the evaluation of cancer in the ISA will primarily focus on studies of inhaled PM since these studies are more relevant to ambient exposure conditions with the recognition of the extensive historical evaluations on the mutagenicity, genotoxicity, and carcinogenicity of whole PM exposures (i.e., not defined by size fraction).

For nonecological welfare effects (i.e., visibility, climate, and materials effects), this ISA will build on information available during the last review describing the role of PM in visibility impairment, radiative forcing resulting in global and regional climate change, and materials damage and soiling. For visibility effects, studies are included which advance our understanding of visual impairment of airborne PM, including studies of atmospheric chemistry, visibility preference, or other measures of adversity to public welfare, in urban and rural settings. For climate effects, this ISA focuses on climate as the welfare effect as listed in the Clean Air Act Amendments of 1970 with a focus on radiative forcing, surface

meteorological trends, and climate feedbacks, and not on downstream ecosystem effects, human health effects, or future air quality projections resulting from changes in climate (CAAA, 1970). The primary literature base for the evaluation of the effects of airborne and deposited PM on climate comes from recent national and international climate assessments such as the National Climate Assessment (Melillo et al., 2014) and International Panel on Climate Change (IPCC, 2014), as well as other recent and more focused reports relevant to PM climate forcing [e.g., (U.S. EPA, 2012)]. The focus is on studies that inform the independent role of PM in climate forcing as well as effects on U.S. national and regional climate. For effects on materials, studies included in the PM ISA examine the role of PM and relevant precursor gases on materials damage and soiling. Specifically, studies that examine both particulate and gaseous contributions from oxides of nitrogen and oxides of sulfur along with other PM components are included here due to the difficulty associated with isolating the effects of gaseous and particulate N and S wet deposition.

P.3.2. Evaluation of the Evidence

The Preamble to the ISAs (U.S. EPA, 2015) describes the general framework for evaluating scientific information, including criteria for assessing study quality and developing scientific conclusions. Aspects specific to evaluating studies of PM are described in the Annex to the Preface, which were applied to studies that fit the overall scope of the PM ISA. Categories of health and welfare effects were considered for evaluation in this ISA if they were examined in previous U.S. EPA assessments for PM or in multiple recent studies. Therefore, in this ISA the broad health effects categories evaluated include those considered in the 2009 PM ISA (i.e., respiratory effects, cardiovascular effects, central nervous system effects, cancer, and mortality) along with the addition of metabolic effects, while new research indicates it is more appropriate to further refine the category of reproductive and developmental effects to instead focus overall conclusions specifically on fertility and pregnancy effects, and birth outcomes separately. While the welfare effects categories evaluated include visibility impairment, effects on materials, and climate.

In forming the key science judgments for each of the health and welfare effects categories evaluated, the PM ISA draws conclusions about relationships between PM exposure and health effects by integrating information across scientific disciplines and related health outcomes and synthesizing evidence from previous and recent studies. To impart consistency in the evaluation of health effects evidence for epidemiologic studies, additional parameters to those outlined in the scope (Section P.3.1) were developed. To facilitate a comparison of results across epidemiologic studies, risk estimates were standardized to a defined increment for both short- and long-term exposure to $PM_{2.5}$ and $PM_{10–2.5}$, unless otherwise noted in the text. To determine the appropriate increment the distribution of $PM_{2.5}$ and $PM_{10–2.5}$ concentrations were examined across the three most recent years of air quality data (2012−2014) within the U.S. For both $PM_{2.5}$ and $PM_{10–2.5}$, an increment of 10 $\mu g/m^3$ was defined for short-term exposure studies which approximates the 50th−95th percentile of concentrations and accounts for the variability observed in daily $PM_{2.5}$ concentrations. An increment of 5 $\mu g/m^3$ was defined for long-term exposure

studies which approximates the 25th−75th percentile of concentrations and represents the variation observed in long-term mean concentrations. Due to the lack of an extensive monitoring network for UFPs within the U.S., results from studies examining UFP are not standardized and reflect the increment of exposure defined in each study evaluated. Additionally, in the assessment of correlations, either with other copollutants or variables, in epidemiologic studies high, moderate, or low correlations are explicitly defined as the following: low correlation, $r < 0.40$; moderate correlation, $r \geq 0.40$ and $r < 0.70$; and high correlation, $r \geq 0.70$. Consistency in the interpretation of the epidemiologic evidence through approaches such as the standardization of risk estimates and the evaluation of correlations, in combination with the integration of evidence across scientific disciplines supports a thorough evaluation of the current state of the science for PM.

In the evaluation of the evidence determinations are made about causation, not just association, and are based on judgments of aspects such as the consistency of evidence within a discipline, coherence of effects across disciplines, and biological plausibility of observed effects as well as related uncertainties. The ISA uses a formal causal framework [Table II of the Preamble to the ISAs (U.S. EPA, 2015)] to classify the weight of evidence according to the five-level hierarchy summarized below.

- Causal relationship: the pollutant has been shown to result in health and welfare effects at relevant exposures based on studies encompassing multiple lines of evidence and chance, confounding, and other biases can be ruled out with reasonable confidence.
- Likely to be a causal relationship: there are studies in which results are not explained by chance, confounding, or other biases, but uncertainties remain in the health and welfare effects evidence overall. For example, the influence of co-occurring pollutants is difficult to address, or evidence across scientific disciplines may be limited or inconsistent.
- Suggestive of, but not sufficient to infer, a causal relationship: health and welfare effects evidence is generally supportive but not entirely consistent or is limited overall. Chance, confounding, and other biases cannot be ruled out.
- Inadequate to infer the presence or absence of a causal relationship: there is insufficient quantity, quality, consistency, or statistical power of results from studies of health and welfare effects.
- Not likely to be a causal relationship: several adequate health and welfare effects studies, examining the full range of anticipated exposure concentrations and for health effects, potential at-risk populations and lifestages consistently show no effect.

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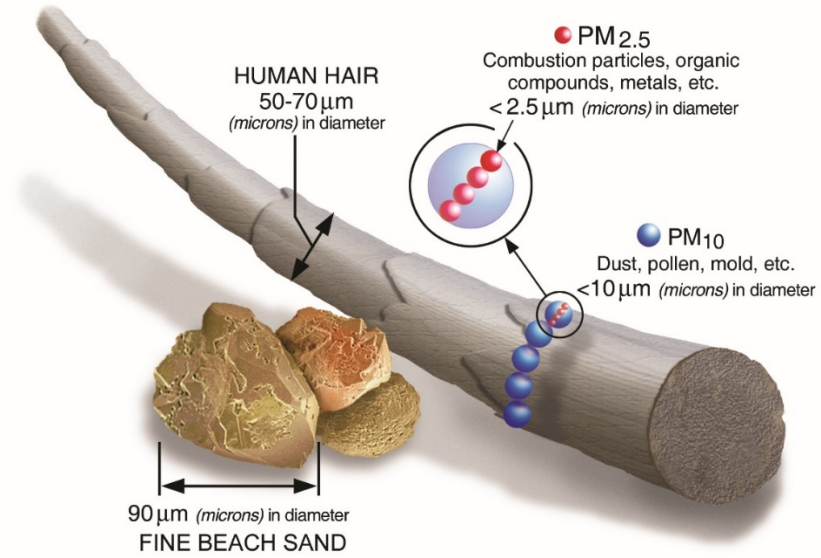
EXECUTIVE SUMMARY

Purpose and Scope of the Integrated Science Assessment

This Integrated Science Assessment (ISA) is a comprehensive evaluation and synthesis of policy-relevant science aimed at characterizing exposures to ambient particulate matter (PM), and health and welfare effects associated with these exposures.[24] PM is a mixture of solid particles and liquid droplets found in the ambient air[25], which encompasses multiple size fractions (e.g., fine PM [$PM_{2.5}$, particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm]; thoracic coarse or coarse PM [$PM_{10–2.5}$, particulate matter with a nominal mean aerodynamic diameter greater than 2.5 μm and less than or equal to 10 μm]; and ultrafine particles [UFPs, generally considered as particulates with a diameter less than or equal to 0.1 μm, typically based on physical size, thermal diffusivity or electrical mobility]) and is comprised of various components (e.g., metals, black carbon, etc.) (Figure ES-1). The evaluation of the science and the overarching conclusions of the ISA serves as the scientific foundation for the review of the primary (health-based) and secondary (welfare-based) National Ambient Air Quality Standard (NAAQS) for PM. This ISA focuses on nonecological welfare effects[26] because ecological effects resulting from deposition of PM and PM components are being considered in a separate assessment as part of the review of the secondary (welfare-based) NAAQS for oxides of nitrogen and sulfur, and PM (U.S. EPA, 2018).

[24] The general process for developing an ISA, including the framework for evaluating weight of evidence and drawing scientific conclusions and causal judgments, is described in a companion document, *Preamble to the Integrated Science Assessments* (U.S. EPA, 2015), www.epa.gov/isa.
[25] As defined by U.S. EPA, https://www.epa.gov/pm-pollution/particulate-matter-pm-basics.
[26] From this point forward referred to as welfare effects.



Source: Permission pending, U.S. EPA[27]

Figure ES-1 Comparison of PM size fractions.

In 2012, the U.S. Environmental Protection Agency (U.S. EPA) established a new annual $PM_{2.5}$ primary standard of 12 µg/m^3 (the annual mean averaged over 3 years) and retained the 24-hour $PM_{2.5}$ standard of 35 µg/m^3 (the 98th percentile averaged over 3 years) (75 FR 3086).[28] For the primary PM_{10} standard, the U.S. EPA retained the 24-hour standard of 150 µg/m^3 (not to be exceeded more than once per year on average over 3 years) to continue to provide protection against effects associated with short-term exposure to thoracic coarse particles (i.e., $PM_{10–2.5}$). Regarding the secondary PM standards, the U.S. EPA retained the 24-hour (i.e., 35 µg/m^3) and annual (i.e., 15 µg/m^3) $PM_{2.5}$ standards[29] and the 24-hour PM_{10} standard (i.e., 150 µg/m^3) to address visibility and nonvisibility welfare effects. On judicial review, the revised and retained standards were upheld in all respects. NAM v EPA, 750 F.3d 921 (D.C. Cir. 2014).

This ISA updates the 2009 ISA for Particulate Matter [(U.S. EPA, 2009) hereafter referred to as the 2009 PM ISA] with studies and reports published from January 2009 through approximately January 2018. The U.S. EPA conducted in-depth searches to identify peer-reviewed literature on relevant topics such as health and welfare effects, atmospheric chemistry, ambient concentrations, and exposure. Information was also solicited from subject-matter experts and the public during a kick-off workshop held

[27] https://www.epa.gov/pm-pollution/particulate-matter-pm-basics.
[28] The legislative requirements and history of the PM NAAQS are described in detail in the Preface to this ISA.
[29] Consistent with the primary standard, the U.S. EPA eliminated the option for spatial averaging with the annual standard.

at the U.S. EPA in February 2015. To fully describe the state of available science, the U.S. EPA also included in this ISA the most relevant studies from previous assessments.

As in the 2009 PM ISA, this ISA determines the causal nature of relationships between health effects and exposure to $PM_{2.5}$, $PM_{10–2.5}$, and UFPs (CHAPTER 5, CHAPTER 6, CHAPTER 7, CHAPTER 8, CHAPTER 9, CHAPTER 10, and CHAPTER 11). To address this task a defined scope was developed to focus on those studies that inform whether PM exposure directly causes health effects (see Preface). Health effects are considered in relation to exposures at concentrations of PM that are relevant to the range of human exposures across ambient microenvironments, specifically within one to two orders of magnitude of current conditions (i.e., up to 2 mg/m^3) (Preface, Section P.3.1). The ISA also evaluates the relationship between PM components and sources to assess whether there is evidence that a component, group of components, or source is more closely related to health effects than PM mass (see Preface). Additionally, the ISA evaluates whether specific populations or lifestages are at increased risk of PM-related health effects. The ISA also determines the causal nature of relationships between PM and welfare effects. In the evaluation of the welfare-based evidence (CHAPTER 13), the PM ISA focuses specifically on the nonecological welfare effects of PM (i.e., visibility, materials effects, and climate) because the ecological effects are assessed in the ISA for Oxides of Nitrogen, Oxides of Sulfur and Particulate Matter – Ecological Criteria as a result of these criteria pollutants being inter-related through complex chemical and physical atmospheric processes and all contributing to nitrogen (N) and sulfur (S) deposition (U.S. EPA, 2018). However, in the assessment of effects on materials the PM ISA summarizes soiling and deterioration of materials attributable to PM and related nitrogen (N) and sulfur (S) components because of the difficulty associated with isolating the effects of gaseous and particulate N and S wet deposition and because the ISA for Oxides of Nitrogen, Oxides of Sulfur and Particulate Matter – Ecological Criteria focuses only on ecological effects (U.S. EPA, 2018).

Key to interpreting the health and welfare effects evidence is understanding the sources, chemistry, and distribution of PM in the ambient air (CHAPTER 2). It is these atmospheric relationships and processes that influence human exposure (CHAPTER 3) and the uptake of inhaled PM in the respiratory tract (CHAPTER 4). The uptake of PM and its deposition in the body directly influences the biological mechanisms by which PM could potentially result in a health effect (CHAPTER 5, CHAPTER 6, CHAPTER 7, CHAPTER 8, CHAPTER 9, CHAPTER 10, and CHAPTER 11). Further, the ISA aims to characterize the independent effect of PM (i.e., $PM_{2.5}$, $PM_{10–2.5}$, and UFP) on health (CHAPTER 5, CHAPTER 6, CHAPTER 7, CHAPTER 8, CHAPTER 9, CHAPTER 10, and CHAPTER 11). The ISA also informs policy-relevant issues (Section 1.6 and CHAPTER 5, CHAPTER 6, CHAPTER 7, CHAPTER 8, CHAPTER 9, CHAPTER 10, CHAPTER 11, and CHAPTER 12), such as (1) potential copollutant confounding (Section 1.5.1); (2) timing of effects (i.e., averaging time of exposure metric and lag at which associations are observed in epidemiologic studies (Section 1.5.2); (3) PM concentration-response relationship(s), and evaluation of potential thresholds for effects (Section 1.5.3); (4) PM components and sources and relationships with health effects (Section 1.5.4); and (5) populations or lifestages at increased risk for health effects related to PM exposure (Section 1.5.5).

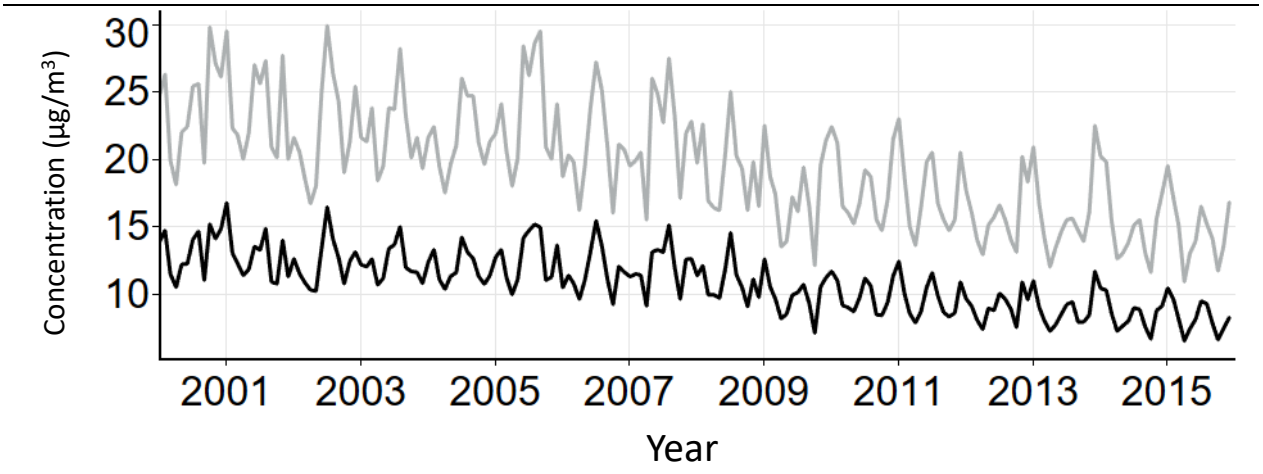
Sources and Exposure to PM

The main objective of the ISA is to characterize health and welfare effects related to ambient PM exposure. This requires understanding PM sources, atmospheric formation, measurement methods, and concentrations. Additionally, with respect to characterizing the health effects of PM it requires understanding the factors that affect both exposure to ambient PM and the uncertainty in estimating exposure. These factors include unmeasured variability in $PM_{2.5}$, $PM_{10–2.5}$, and UFP concentrations and size distributions, exposure to copollutants, and uncharacterized PM composition.

Particulate matter is comprised of components that are directly emitted (primary PM) as well as formed through atmospheric chemical reactions involving gaseous precursors (secondary PM) (Section 2.3). Both primary and secondary PM contribute substantially to overall PM mass in ambient air. Within an urban environment most primary $PM_{2.5}$ emissions are from anthropogenic sources, and include some combination of industrial activities, motor vehicles, cooking, and fuel combustion. However, in many locations secondary PM formed from the precursors sulfur dioxide (SO_2), oxides of nitrogen (NO_X), ammonia (NH_3), and volatile organic compounds (VOCs), accounts for the majority of $PM_{2.5}$ mass. Direct emissions of primary $PM_{2.5}$ have decreased slightly (~9% since 2002) over the past decade, along with a substantial decrease in emissions since 2006 of the major $PM_{2.5}$ precursors SO_2 and NO_X, 65% and 30%, respectively. $PM_{10–2.5}$ is almost entirely primary in origin, composed largely of crustal material, sea salt, and biological material. National average $PM_{10–2.5}$ concentrations have changed little over the past decade. Ambient UFPs originate from two distinct processes, primary particles directly emitted from specific sources like motor vehicles and new particle formation by photochemical processes under favorable atmospheric conditions.

There are well-established federal reference methods (FRM) and national monitoring networks for $PM_{2.5}$, PM_{10}, and $PM_{10–2.5}$ (Section 2.4). Recent monitoring initiatives include the implementation of the National Core multipollutant monitoring network, which includes $PM_{2.5}$ and $PM_{10–2.5}$ measurements along with a suite of other pollutants, a new near road monitoring network that includes $PM_{2.5}$ monitors at 36 sites, and the first routine monitoring of particle number count at 23 sites. Satellite-based measurements in conjunction with chemical transport models have also become increasingly used for estimating $PM_{2.5}$ concentrations. In general, the fraction of PM_{10} accounted for by $PM_{2.5}$ is higher in the eastern U.S. than in the western U.S. Compared to $PM_{2.5}$, $PM_{10–2.5}$ concentrations are more spatially variable. The limited amount of available UFP measurements data indicated that the highest UFP concentrations occur in the winter and near roads with heavy traffic, often over short time periods. Overall, UFP concentrations are more spatially variable than $PM_{2.5}$. As Figure 2-22 shows, national average $PM_{2.5}$ concentrations decreased by about 5 $\mu g/m^3$ from 2000 to 2015. Much of this decrease is accounted for by a corresponding decrease in sulfate concentrations, especially in the eastern U.S., attributed to reduced SO_2 emissions. Sulfate concentrations are mainly associated with $PM_{2.5}$ and have historically been highest in summer. The reduction in $PM_{2.5}$ and sulfate concentrations has coincided with shifts from summer, as the season with the highest national average concentration, to a more even

distribution of $PM_{2.5}$ concentrations between summer and winter, and to an increase in the contribution of $PM_{10–2.5}$ to PM_{10} concentrations.



Black = mean, gray = 90th percentile.
Source: Permission pending, Chan et al. (2018).

Figure ES-2 Long-term trend in national monthly and annual average $PM_{2.5}$ concentrations (µg/m³) from 2000−2015.

Fixed-site monitoring is frequently used for obtaining $PM_{2.5}$ exposure surrogates in both short-term and long-term exposure epidemiologic studies (Section 3.3), given that spatial variability in $PM_{2.5}$ concentration tends to be lower than for other size fractions. Fixed-site monitoring for $PM_{10–2.5}$ has been performed by different methods. It is important to consider the method used in order to characterize errors and uncertainties in the data that are related both to the monitoring method and the proximity of the individual receptor to the monitor because $PM_{10–2.5}$ is typically more spatially variable than $PM_{2.5}$. Condensation particle counter (CPC) is most commonly used to measure UFP. However, some portion of the UFP size distribution may be omitted using CPC, since they do not typically measure particles smaller than 10 nm. UFP also tends to be more spatially variable than $PM_{2.5}$, contributing to uncertainties in exposure assignments.

Modeling approaches, such as spatial interpolation methods, land use regression, dispersion models, and chemical transport models (CTMs), have for years provided estimates of exposure concentration where no measurements are available. More recently, hybrid models drawing input from CTMs, satellite observations of aerosol optical density, surface measurements of PM concentration, and land use variables have become available. Most studies using hybrid methods are applied to model $PM_{2.5}$ and have out-of-sample cross-validations with $R^2 > 0.8$. Models are employed less frequently to estimate

$PM_{10-2.5}$ and UFP exposure concentration, despite $PM_{10-2.5}$ and UFP typically being more spatially variable than $PM_{2.5}$. This is related in part to less availability of input data.

When particles enter a building envelope, they may be lost during the process of infiltration to indoor, to produce an infiltration factor (F_{inf}) < 1 (Section 3.4). F_{inf} varies with season, window opening, building age, wind speed and particle size distribution (with F_{inf} lower for $PM_{10-2.5}$ and UFP compared with $PM_{2.5}$). When examining the influence of estimated exposure concentrations on health effect estimates in a time-series study of short-term PM exposure, use of a fixed-site monitor in lieu of a microenvironmental model that accounted for infiltration produced considerably attenuated health effect estimates, which resulted in an underestimation of the health effect. Infiltration of PM through a building envelope may change the temporal variability of the indoor PM concentration time-series, resulting in reduced correlation between the health effect of interest and the estimated exposure concentration. In the examination of how exposure concentration estimates influence health effect estimates in an epidemiologic study of long-term PM exposure, simulating indoor concentrations produced unbiased health effect estimates.

In summary, exposure error tends to produce underestimation of health effects in epidemiologic studies of PM exposure, although bias in either direction can occur. Recent improvements in estimating spatial resolution of the $PM_{2.5}$ concentration surface have reduced bias and uncertainty in health effects estimates. $PM_{10-2.5}$ and UFP concentrations tend to be more spatially variable than $PM_{2.5}$ concentrations, but data are either unavailable or less often available to fit or validate hybrid models for those size fractions. As a result, there is typically less uncertainty in health effect estimates derived from both monitored and modeled exposure estimates for $PM_{2.5}$ compared with either $PM_{10-2.5}$ or UFP.

Dosimetry of Inhaled PM

Particle dosimetry characterizes the intake, deposition, and retention of PM in the respiratory tract (CHAPTER 4). The basic understanding of particle dosimetry has not changed since the last review. Quantification of the fraction of inhaled particles reaching the lung and the small fraction of deposited particles that enter the blood, distribute around the body, and accumulate in organs and tissues has improved. Understanding the dosimetry of particles is crucial to providing evidence that supports whether it is biologically plausible that PM exposure can lead to a range of health effects spanning multiple organ systems.

A variety of factors influence the amount of inhaled particles deposited and retained in the respiratory tract and include exposure concentration and duration, activity and breathing conditions (e.g., nasal vs. oronasal route and minute ventilation), and particle properties (e.g., particle size, hygroscopicity, and solubility in airway fluids and cellular components). Inhalability is particularly important for between species extrapolation since it decreases more rapidly as particle size increases in rodents (commonly used in laboratory studies) compared to humans. In people, the fraction of oral versus nasal breathing is influenced by age, activity level, sex, disease status (e.g., allergies, upper respiratory

infections), and perhaps body mass index, which ultimately contributes to the fraction of particles inhaled and reaching the lower respiratory tract.

Recent evidence shows that in both humans and rodents, a small fraction of gold nanoparticles depositing in the peripheral lung may move into circulation. The fraction of deposited particles that move into circulation is dependent on particle size and is in the range of 0.2% or less for particles between 5 nm and 200 nm, but may reach a few percent for smaller particles. The translocated particles are distributed around the body and may be retained in other organs or eliminated via urine. Some more limited data show that particles may also reach the fetus in a size dependent manner. Although translocation in humans has only been demonstrated for gold nanoparticles and to some degree for titanium dioxide, the translocation of several types of nanoparticles has been demonstrated in rodents. The importance of compound type on particle translocation has not yet been ascertained. These studies suggest that, following deposition in the lung, a small fraction of ambient particles under 200 nm may translocate into circulation.

Health and Welfare Effects of PM Exposure

This ISA integrates information on PM exposure and health effects from epidemiologic, controlled human exposure, and toxicological studies to determine the causal nature of relationships between exposure to PM of various size fractions (i.e., $PM_{2.5}$, $PM_{10–2.5}$, and UFPs) and broad health effect categories. For most health effect categories, except for reproductive and developmental effects, effects are evaluated separately for short-term exposures (i.e., hours up to approximately one month) and long-term exposures (i.e., one month to years). For welfare effects the ISA evaluates evidence as it pertains to the welfare effects of visibility impairment, climate effects, and effects on materials. A consistent and transparent framework [Preamble to the ISA (U.S. EPA, 2015), Table II] is applied to classify the health and welfare effects evidence according to a five-level hierarchy:

1. Causal relationship
2. Likely to be a causal relationship
3. Suggestive of, but not sufficient to infer, a causal relationship
4. Inadequate to infer the presence or absence of a causal relationship
5. Not likely to be a causal relationship

The causality determinations presented in Table ES-1, reflect those PM size fraction, exposure duration, and broad health category combinations for which a "*causal relationship*" or "*likely to be causal relationship*" was concluded in this ISA. The conclusions presented are informed by recent findings in combination with the evidence detailed in the 2009 PM ISA. Important considerations include: (1) determining whether laboratory studies of humans and animals, in combination with epidemiologic studies, inform the biological mechanisms by which PM can impart health effects and provide evidence demonstrating that PM exposure can independently cause a health effect; (2) determining whether there is consistency in epidemiologic evidence across various geographic locations, populations, and methods

used to estimate PM exposure; (3) evaluating epidemiologic studies that examine potential influence of factors (i.e., confounders) that could bias associations observed with PM exposure; (4) determining the coherence of findings integrated across controlled human exposure, epidemiologic, and toxicological studies; and (5) making judgments regarding the influence of error and uncertainty on the relationship between PM exposure and health effects in the collective body of available studies. Table ES-2 details the causality determinations for the welfare effects.

Table ES-1 Summary of "causal relationship" and "likely to be causal relationship" causality determinations for PM exposure and health effects from the current draft PM ISA and corresponding causality determinations from the 2009 PM ISA.

Size Fraction	Health Effect Category[a] and Exposure Duration	Causality Determination	
		2009 PM ISA	Current Draft PM ISA
$PM_{2.5}$	Respiratory Effects—Short-term exposure Section 5.1.12, Table 5-18	Likely to be a causal relationship	Likely to be a causal relationship
	Respiratory Effects—Long-term exposure Section 5.2.13, Table 5-28	Likely to be a causal relationship	Likely to be a causal relationship
	Cardiovascular Effects—Short-term exposure Section 6.1.16, Table 6-33	Causal relationship	Causal relationship
	Cardiovascular Effects—Long-term exposure Section 6.2.18, Table 6-52	Causal relationship	Causal relationship
	Nervous System Effects—Long-term exposure Section 8.2.9, Table 8-20	Not evaluated	Likely to be a causal relationship
	Cancer—Long-term exposure Section 10.2.6, Table 10-8	Suggestive of, but not sufficient to infer, a causal relationship	Likely to be a causal relationship
	Total mortality—Short-term exposure Section 11.1.12, Table 11-4	Causal relationship	Causal relationship
	Total mortality—Long-term exposure Section 11.2.7, Table 11-8	Causal relationship	Causal relationship

Table ES-1 (Continued): Summary of "Causal Relationship" and "Likely to be Causal Relationship" causality determinations for PM exposure and health effects from the current draft PM ISA and corresponding causality determinations from the 2009 PM ISA.

Size Fraction	Health Effect Category[a] and Exposure Duration	Causality Determination	
		2009 PM ISA	Current Draft PM ISA
UFP	Nervous System Effects—Long-term exposure Section 8.6.7, Table 8-34	Not evaluated	Likely to be a causal relationship

ISA = Integrated Science Assessment; PM = particulate matter; $PM_{2.5}$ = fine particulate matter; UFP = ultrafine particles.

Previous causality determinations taken from the 2009 PM ISA (U.S. EPA, 2009).

[a]An array of outcomes is evaluated as part of a broad health effect category: physiological measures (e.g., airway responsiveness), clinical outcomes (e.g., hospital admissions), and cause-specific mortality. Total mortality includes all nonaccidental causes of mortality and is informed by findings for the spectrum of morbidity effects (e.g., respiratory, cardiovascular) that can lead to mortality. The sections and tables referenced include a detailed discussion of the evidence that supports the causality determinations and the $PM_{2.5}$ and UFP concentrations with which health effects have been associated.

Health Effects of $PM_{2.5}$ Exposure

Across the PM size fractions evaluated within this ISA, the most substantial scientific evidence indicating relationships between short- and long-term PM exposure is for $PM_{2.5}$. The causality determinations for $PM_{2.5}$ reflect the total body of scientific evidence, building off the conclusions presented in the 2009 PM ISA. The following sections detail those exposure duration and broad health effect categories where this ISA concluded a "*causal*" or "*likely to be causal*" causality determination, reflecting the highest degree to which the evidence reduces chance, confounding, and other biases in the exposure—health effect relationship. Those health effect categories where there is still a large degree of uncertainty or limited examination of the relationship between $PM_{2.5}$ exposure and health effects resulting in the causality determination of "*suggestive of, but not sufficient to infer, a causal relationship*" and "*inadequate to determine the presence or absence of a causal relationship*" are summarized in Chapter 1, Table 1-5.

Respiratory Effects

As in the 2009 PM ISA, the current ISA concludes there is a "*likely to be causal relationship*" between *short-term $PM_{2.5}$ exposure and respiratory effects* (Section 5.1). Recent epidemiologic studies continue to provide strong evidence for a relationship between short-term $PM_{2.5}$ exposure and several respiratory-related endpoints, including asthma exacerbation, chronic obstructive pulmonary disease (COPD) exacerbation, and combined respiratory-related diseases, particularly from studies examining emergency department visits and hospital admissions. The consistent, positive associations observed for asthma and COPD emergency department visits and hospital admissions are further supported by evidence of increased symptoms and medication use in response to short-term $PM_{2.5}$ exposure, which is

indicative of asthma and COPD exacerbations. Animal toxicological studies of short-term $PM_{2.5}$ exposure provide coherence and biological plausibility for asthma and COPD exacerbations by demonstrating asthma-related responses in an animal model of allergic airways disease and enhanced lung injury and inflammation in an animal model of COPD. Animal toxicological evidence also demonstrates altered host defense, greater susceptibility to bacterial infection, respiratory irritant effects, and other effects. This broad body of experimental evidence indicating $PM_{2.5}$-related respiratory effects in healthy populations generally provides biological plausibility for respiratory effects in association with short-term $PM_{2.5}$ exposure, but does not inform the relationship with asthma or COPD exacerbation. In addition, controlled human exposure studies provide minimal evidence of effects due to short-term $PM_{2.5}$ exposure, such as decrements in lung function and pulmonary inflammation. Recent epidemiologic studies build upon the limited number of studies that previously examined potential copollutant confounding and indicate that $PM_{2.5}$ associations with asthma exacerbation, combined respiratory-related diseases, and respiratory mortality remain relatively unchanged in copollutant models with gaseous pollutants (i.e., O_3, NO_2, SO_2, with more limited evidence for CO) and other particle sizes (i.e., $PM_{10–2.5}$). Animal toxicological studies further support an independent effect of $PM_{2.5}$ on respiratory health by demonstrating asthma- and COPD-related responses in animal models of disease. Evidence of consistent, positive associations between $PM_{2.5}$ and respiratory mortality demonstrate a continuum of respiratory-related effects.

Both the 2009 PM ISA, and the current ISA concluded there is a "*likely to be causal relationship*" between *long-term $PM_{2.5}$ exposure and respiratory effects* (Section 5.2). There is strong evidence from multiple cohorts that varied in study location, exposure assessment methods, and time periods examined that demonstrated an effect of long-term $PM_{2.5}$ exposure on lung development (i.e., lung function growth). Additional, although more limited, evidence from epidemiologic studies indicates associations between long-term $PM_{2.5}$ exposure and asthma development in children, asthma prevalence in children, childhood wheeze, and pulmonary inflammation. Animal toxicological studies demonstrating impaired lung development resulting from pre- and post-natal $PM_{2.5}$ exposure and the development of an allergic phenotype along with an increase in airway responsiveness following long-term $PM_{2.5}$ exposure provide biological plausibility for these findings. Animal toxicological studies also demonstrate $PM_{2.5}$ exposure-induced oxidative stress, inflammation, and morphological changes in both upper and lower airways. There is limited assessment of potential copollutant confounding of respiratory morbidity outcomes, but recent animal toxicological studies partially address the independence of $PM_{2.5}$ effects by demonstrating $PM_{2.5}$ induced oxidative stress, inflammation, and morphologic changes. This broad body of experimental evidence indicating $PM_{2.5}$-related respiratory effects in healthy populations generally provides biological plausibility for respiratory effects in association with long-term $PM_{2.5}$ exposure. Additional epidemiologic evidence, indicates an acceleration of lung function decline in adults, as well as consistent evidence for respiratory mortality and cause-specific respiratory mortality, providing evidence of a continuum of effects in response to long-term $PM_{2.5}$ exposure. The relationship between long-term $PM_{2.5}$ exposure and respiratory effects is further supported by epidemiologic studies demonstrating improvements in lung function growth and bronchitic symptoms in children and improvement in lung function in adults in association with declining $PM_{2.5}$ concentrations.

Cardiovascular Effects

Consistent with the 2009 PM ISA, this ISA concludes there is a "*causal relationship*" between *short-term $PM_{2.5}$ exposure and cardiovascular effects* (Section 6.1). The strongest evidence comes from epidemiologic studies that reported consistent, positive associations between short-term $PM_{2.5}$ exposure and cardiovascular-related emergency department visits and hospital admissions particularly for ischemic heart disease (IHD) and heart failure (HF), as well as cardiovascular-related mortality. Recent examinations of potential copollutant confounding generally indicate that the associations observed with $PM_{2.5}$ and cardiovascular effects in single pollutant models remain relatively unchanged in copollutant models, providing evidence that the observed associations with $PM_{2.5}$ are not artefacts due to confounding by another air pollutant. The independence of a $PM_{2.5}$ cardiovascular effect is further supported by recent experimental studies. Recent controlled human exposure studies expand upon previous findings and demonstrate $PM_{2.5}$-induced changes in endothelial function and blood pressure, which is coherent with animal toxicological studies demonstrating the same effects. Moreover, experimental evidence demonstrating decreased cardiac contractility and left ventricular pressure is coherent with epidemiologic studies observing positive associations between ambient $PM_{2.5}$ and ED visits and hospital admissions for HF. Thus, the collective body of experimental evidence supports and provides biological plausibility for epidemiologic studies reporting associations particularly between short-term $PM_{2.5}$ exposure and IHD and HF outcomes, as well as a range of other cardiovascular-related effects (e.g., arrhythmia, thrombosis) that can result in more severe outcomes possibly leading to death.

The 2009 PM ISA, as well as the current PM ISA, concluded there is a "*causal relationship*" between *long-term $PM_{2.5}$ exposure and cardiovascular effects* (Section 6.2). Epidemiologic studies of multiple recent U.S.-based cohorts along with reanalyses of these cohorts provide strong evidence of consistent, positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality. These studies used a variety of exposure assessment and statistical techniques and examined various spatial domains (e.g., 1 × 1 km grid cells, census tract, etc.) in many locations where mean annual average $PM_{2.5}$ concentrations are ≤12 μg/m^3. Recent epidemiologic studies of cardiovascular morbidity have greatly expanded upon the body of evidence available at the completion of the 2009 PM ISA by focusing on populations with distinct demographic characteristics (e.g., post-menopausal woman, male doctors, etc.) and extensively considering potential confounders (e.g., socioeconomic status [SES]). While an extended analysis of the Women's Health Initiative (WHI) cohort strengthened the initial observation of a relationship between long-term $PM_{2.5}$ exposure and coronary events among post-menopausal women, additional cohorts of women similar to the WHI cohort did not report consistent, positive associations with coronary heart disease (CHD), myocardial infarction or stroke. Longitudinal studies examining the progression of atherosclerosis in relation to long-term exposure to $PM_{2.5}$ reported inconsistent results that were dependent upon the vascular bed examined, but there was evidence of $PM_{2.5}$-associated coronary artery calcification, a strong predictor of CHD, within a study focusing on the progression of atherosclerosis in a healthy population, i.e., Multi-Ethnic Study of Arthrosclerosis and Air Pollution (MESA—Air). A limited number of epidemiologic studies examining other cardiovascular effects,

provide some evidence of associations with HF, blood pressure, and hypertension as well as subclinical cardiovascular biomarkers. Recent studies also reduce the uncertainty associated with potential copollutant confounding by reporting that associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality remained relatively unchanged or increased in copollutant models adjusted for O_3, NO_2, SO_2, and $PM_{10-2.5}$. Evidence from animal toxicological studies further supports a direct $PM_{2.5}$ effect on the cardiovascular system and provides coherence with effects observed in epidemiologic studies. For example, animal toxicological studies demonstrating atherosclerotic plaque progression in mice is coherent with epidemiologic studies of atherosclerosis, while animal toxicological studies reporting increased coronary artery wall thickness, decreased cardiac contractility and output, and changes in blood pressure are coherent with epidemiologic studies of HF. Furthermore, when considering the collective body of evidence there are biologically plausible pathways by which long-term exposure to $PM_{2.5}$ could lead to a continuum of effects potentially resulting in death.

Nervous System Effects

The 2009 PM ISA did not make a causality determination for long-term $PM_{2.5}$ exposure and nervous system effects due to the paucity of data available. Since the 2009 PM ISA, the literature base has greatly expanded and the combination of animal toxicological and epidemiologic evidence supports a "*likely to be causal relationship*" between *long-term $PM_{2.5}$ exposure and nervous system effects* (Section 8.2). Animal toxicological studies provide evidence for a range of nervous system effects including neuroinflammation and oxidative stress, neurodegeneration, cognitive effects, and effects on neurodevelopment. Epidemiologic studies, although fewer in number, generally support associations between long-term $PM_{2.5}$ exposure and changes in brain morphology, cognitive decrements, and dementia. Both experimental and epidemiologic evidence is well substantiated and coherent, supporting a pathway involving neuroinflammation in specific regions of the brain (i.e., the hippocampus, cerebral cortex and hypothalamus) and morphologic changes in the brain indicative of neurodegeneration. Overall, the lack of consideration of copollutant confounding introduces some uncertainty in the interpretation of the epidemiologic studies but this uncertainty is addressed, in part, by the direct evidence of effects provided by experimental animal studies. In addition to the nervous system effects primarily observed in adults, there is initial and limited epidemiologic evidence of neurodevelopmental effects, specifically autism spectrum disorder (ASD), which is supported by an animal toxicological study demonstrating $PM_{2.5}$-induced inflammatory and morphologic changes in regions of the brain consistent with ASD.

Cancer

The 2009 PM ISA concluded that evidence was "*suggestive of a causal relationship*"[30] between *long-term $PM_{2.5}$ exposure and cancer* (Section 10.2). Building upon the decades of research on whole PM

[30] Since the 2009 PM ISA, the causality determination language has been updated and this category is now stated as "suggestive of, but not sufficient, to infer a causal relationship".

exposures and evidence presented in the 2009 PM ISA, recent experimental and epidemiologic evidence indicating genotoxicity, epigenetic effects (i.e., hypo- and hyper-methylation of DNA), and increased carcinogenic potential due to $PM_{2.5}$ exposure, along with strong epidemiologic evidence for increases in lung cancer incidence and mortality supports a "*likely to be causal relationship*" between long-term $PM_{2.5}$ exposure and cancer. $PM_{2.5}$ exhibits various characteristics of carcinogens, as shown in studies demonstrating genotoxic effects (e.g., DNA damage), epigenetic alterations, oxidative stress, and electrophilicity. Studies of cancer development have often focused on whole PM exposures[31], not individual PM size fractions, or individual components often found to encompass $PM_{2.5}$ (e.g., hexavalent chromium, arsenic). Ames *Salmonella*/mammalian-microsome mutagenicity assays of $PM_{2.5}$ and $PM_{2.5}$ extracts demonstrate that PM contains mutagenic agents. In vitro and in vivo toxicological studies demonstrate the potential for $PM_{2.5}$ exposure to result in DNA damage, which is supported by limited human evidence. Cytogenic effects (e.g., chromosomal aberrations), and differential expression of genes potentially relevant to genotoxicity or cancer pathogenesis have also been demonstrated. There is also limited evidence for cellular and molecular changes that could lead to genomic instability as well as for the carcinogenic potential of $PM_{2.5}$, as demonstrated by enhanced tumor formation in animals treated with urethane. The experimental and epidemiologic evidence of genotoxicity, epigenetic effects, and carcinogenic potential provides biological plausibility for the results from multiple epidemiologic studies conducted in diverse cohorts in terms of geographic coverage and population demographics reporting primarily consistent, positive associations between long-term $PM_{2.5}$ exposure and lung cancer incidence and mortality, particularly in never smokers. In the limited assessment of potential copollutant confounding, $PM_{2.5}$-lung cancer incidence and mortality associations were found to be relatively unchanged in models with O_3.

Mortality

As in the 2009 PM ISA, the current ISA concludes there is a "*causal relationship*" between *short-term $PM_{2.5}$ exposure and total (nonaccidental) mortality* (Section 11.1). Recent multicity studies conducted in the U.S., Canada, Europe, and Asia in combination with the single- and multicity studies evaluated in the 2009 PM ISA continue to provide evidence of consistent, positive associations between short-term $PM_{2.5}$ exposure and total mortality. The positive associations reported across studies reflect both traditional analyses using ambient monitors as well as analyses conducted in both urban and rural locations that use new exposure assignment techniques and rely on multiple sources of $PM_{2.5}$ data (e.g., ambient monitors, statistical models, and satellite images). Recent studies also expand upon the assessment of potential copollutant confounding and indicate that $PM_{2.5}$-mortality associations are relatively unchanged in copollutant models with gaseous pollutants and $PM_{10–2.5}$. The positive associations reported for total mortality are supported by positive associations for cause-specific mortality (i.e., cardiovascular- and respiratory-related mortality). The consistent and coherent evidence across

[31] Whole PM exposures represent exposures that contain both PM and gaseous pollutants.

scientific disciplines for cardiovascular morbidity, particularly ischemic events and HF (CHAPTER 6), and to a lesser degree for respiratory morbidity, with the strongest evidence for exacerbations of COPD and asthma (CHAPTER 5), provide biological plausibility for cause-specific mortality and ultimately total mortality. Recent studies also further reduce chance, confounding, and other biases in the relationship between short-term $PM_{2.5}$ exposure and total mortality.

Both the 2009 PM ISA and the current ISA concludes there is a "*causal relationship*" between *long-term $PM_{2.5}$ exposure and total (nonaccidental) mortality* (Section 11.2). Additional reanalyses and extensions of the American Cancer Society and Harvard Six Cities cohorts as well as new cohorts consisting of Medicare participants, people that live in Canada, or people employed in a specific job (e.g., teacher, nurse, etc.) further support a positive association between long-term $PM_{2.5}$ exposure and total mortality, particularly in areas with annual mean concentrations <20 $\mu g/m^3$, and in some cases below 12 $\mu g/m^3$. Positive associations persist regardless of the exposure assignment approach used (i.e., ambient monitors or the combination of monitoring, modeling, and satellite data) and in copollutant models, particularly with O_3 and more limited evidence for NO_2 and $PM_{10-2.5}$. The evidence for total mortality is supported by positive associations for cause-specific mortality, including cardiovascular, respiratory, and lung cancer mortality. The coherence of effects across scientific disciplines for cardiovascular morbidity, particularly for CHD, stroke and atherosclerosis, and respiratory morbidity for the development of COPD, contribute to the biological plausibility for mortality due to long-term $PM_{2.5}$ exposure. Additionally, recent studies demonstrating increases in life expectancy due to decreases in long-term $PM_{2.5}$ concentrations further support a relationship between long-term $PM_{2.5}$ exposure and total mortality.

Health Effects of UFP Exposure

Since the completion of the 2009 PM ISA recent studies further explored the relationship between UFP exposure and health effects. The interpretation of epidemiologic study results is complicated by most studies relying on a single monitor to measure UFPs, which is inadequate as has been reflected in some monitoring campaigns that demonstrate a high degree of spatial variability in UFP concentrations and that the size distribution of UFPs changes with distance from source (Section 2.5). Additionally, experimental studies often include size ranges up to 200 nm or higher, which complicates the examination of coherence and biological plausibility of UFP-related health effects. These uncertainties in addition to the inconsistency across studies in the characterization of UFP with respect to size distribution and exposure metric contributed to causality determinations that did not exceed "*suggestive of, but not sufficient to infer, a causal relationship*" for most exposure and health effect category combinations.

Nervous System Effects

Due to the few studies that examined long-term UFP exposure and nervous system effects, the 2009 PM ISA did not make a causality determination; however, it was hypothesized that ambient UFPs may reach the brain via olfactory transport based on a few animal toxicological studies of

laboratory-generated UFPs. Since then, additional strong animal toxicological evidence of neurotoxicity and altered neurodevelopment, in combination with initial evidence suggesting potential translocation of UFPs into the brain via olfactory transport and from a single epidemiologic study indicating effects on attention and memory support a "*likely to be causal relationship*" between *long-term UFP exposure and nervous system effects* (Section 8.6). Animal toxicological studies provide consistent evidence of brain inflammation and oxidative stress in multiple regions of the brain, morphologic changes that are characteristic of neurodegeneration and Alzheimer's disease. Additionally, there is evidence of neurodevelopmental effects, including behavioral, neuroinflammatory, and morphological changes consistent with ASD. The animal toxicological study results are supported by an epidemiologic study reporting evidence of decrements on tests of attention and memory in children. However, epidemiologic studies of long-term UFP exposure are sparse due to difficulties in capturing the spatial variation in long-term UFP concentrations that can result in substantial exposure measurement error.

Policy-Relevant Considerations for Health Effects Associated with Particulate Matter Exposure

This section describes issues relevant for considering the potential significance of impacts of ambient PM, particularly $PM_{2.5}$, exposure on public health (Section 1.6)[32], including potential copollutant confounding of $PM_{2.5}$-health effects associations, the relationship between $PM_{2.5}$ exposure and the timing of health effects, the shape of the concentration-response (C-R) relationship, whether $PM_{2.5}$ components and sources are more closely associated with health effects than $PM_{2.5}$ mass, and the identification of populations and lifestages potentially at increased risk of a $PM_{2.5}$-related health effect.

Recent epidemiologic studies greatly expand upon the evidence informing whether associations observed between short- and long-term $PM_{2.5}$ exposure and health are confounded by other pollutants observed in the air pollution mixture. The examination of potential copollutant confounding in studies of respiratory and cardiovascular effects are primarily limited to studies of emergency department visits and hospital admissions. Across studies of short-term $PM_{2.5}$ exposure and respiratory and cardiovascular effects and mortality, correlations between $PM_{2.5}$ and gaseous (i.e., SO_2, NO_2, CO, and O_3) and particulate pollutants (i.e., $PM_{10-2.5}$) varied across studies, with low-to-moderate correlations (i.e., <0.7). Collectively, studies of short-term $PM_{2.5}$ exposure that examined potential copollutant confounding indicated that associations remained relatively unchanged in copollutant models, and in instances where associations were attenuated they remained positive. Far fewer studies examined potential copollutant confounding and long-term $PM_{2.5}$ exposure, but there has been an expansion of studies focusing on mortality. Studies focusing on respiratory (i.e., lung function and asthma development) and cardiovascular effects (i.e., cardiovascular mortality), along with lung cancer incidence and mortality, provide initial evidence that associations with $PM_{2.5}$ are relatively unchanged in copollutant models with primarily traffic-related pollutants (i.e., NO_2, NO_X, and CO) and O_3. For mortality, the most extensive

[32] Section 1.6 in Chapter 1 integrates the evidence across all health chapters, but each health chapter has individual discussions on the topics discussed within this section.

analyses occurred for O_3, with more limited assessments of other pollutants, but overall associations were reported to remain unchanged in copollutant models for total (nonaccidental) mortality, cardiovascular, and respiratory mortality.

An important question that informs different aspects of the PM NAAQS is the timing of observed effects due to short-term $PM_{2.5}$ exposure, specifically the averaging time of the exposure metric in epidemiologic studies and the lag days over which health effects are observed. Some recent epidemiologic studies focusing on respiratory- and cardiovascular-related emergency department visits and hospital admissions, cardiovascular effects (e.g., ST-elevation, myocardial infarction, and out-of-hospital cardiac arrest), and mortality examined associations between subdaily exposure metrics and the widely used 24-hour average exposure metric. Across the studies evaluated, the available evidence does not indicate that sub-daily averaging periods for $PM_{2.5}$ are more closely associated with health effects than the 24-hour average exposure metric. In addition to examining potential differences in associations by averaging time of the exposure metric, recent epidemiologic studies expanded the assessment of examining the timing of effects by systematically examining lag days by focusing on whether there is evidence of an immediate (e.g., lag 0−1 days), delayed (e.g., lag 2−5 days), or prolonged (e.g., lag 0−5 days) effect of PM on health. Epidemiologic studies examining potential differences in associations in relation to short-term $PM_{2.5}$ exposure focused on respiratory- and cardiovascular-related emergency department visits and hospital admissions as well as mortality. While recent studies provided evidence of associations in the range of 0−5 days for respiratory effects, there was evidence of an immediate effect for cardiovascular effects and mortality (i.e., 0−1 days) with some initial evidence of associations occurring over longer exposure durations (e.g., 0−4 days).

An examination of the C-R relationship between short- and long-term $PM_{2.5}$ exposure and health effects can inform both the shape of the C-R curve and whether there is a threshold (i.e., concentration level) below which there is no evidence of an effect of $PM_{2.5}$ on health. Studies of short-term $PM_{2.5}$ exposure and health are limited to studies of respiratory-related emergency department visits and hospital admissions, and mortality. Epidemiologic studies of respiratory disease and asthma emergency department visits and hospital admissions focusing on the shape of the C-R curve provide initial evidence of a linear relationship with less certainty at concentrations below 10 $\mu g/m^3$. However, studies focusing on whether the $PM_{2.5}$ association changes at different concentration ranges (i.e., cut-point analyses) provide some evidence of potential nonlinearities in the C-R relationship. Epidemiologic studies of mortality greatly expand upon the evidence evaluated in the 2009 PM ISA where C-R analyses were limited to studies of PM_{10}. Evidence from U.S. studies examining short-term $PM_{2.5}$ exposure and mortality indicate a linear relationship at concentrations as low as 5 $\mu g/m^3$ with cut-point analyses providing no evidence of a threshold. For long-term $PM_{2.5}$ exposure, most of evidence on the shape of the C-R curve and whether a threshold exits comes from studies of mortality with some initial recent evidence from studies of respiratory and cardiovascular effects, as well as lung cancer mortality and incidence. Epidemiologic studies of long-term $PM_{2.5}$ exposure and mortality used a variety of statistical approaches and cut-point analyses, which support a linear, no-threshold relationship for total

(nonaccidental) mortality, especially at lower ambient $PM_{2.5}$ concentrations, with confidence in some studies in the range of 5−8 μg/m^3. Additionally, there is initial evidence indicating that the slope of the C-R curve may be steeper (supralinear) at lower concentrations for cardiovascular mortality. Evaluation of the C-R relationship is more limited for respiratory and cardiovascular effects, but overall initial assessments support a linear relationship specifically at long-term $PM_{2.5}$ concentrations ranging from 10 to 12 μg/m^3 and 5−10 μg/m^3, respectively.

Recent epidemiologic and experimental studies extensively build upon those studies evaluated in the 2009 PM ISA that examined relationships between exposure to $PM_{2.5}$ components and sources and health effects. As detailed in the Preface, this ISA focuses on specific study criteria to thoroughly evaluate whether there is evidence that an individual component(s) and/or source(s) is more closely related to health effects than PM mass. Across the health effects categories evaluated in this ISA, most studies that examine PM sources and components focused on $PM_{2.5}$. In studies examining both short- and long-term exposure a variety of health effects were examined ranging from subclinical (e.g., changes in lung function, respiratory symptoms) to more overt e.g., emergency department visits, hospital admissions, and mortality). Across exposure durations and health effects categories it was concluded that many $PM_{2.5}$ components and sources are associated with many health effects, and the evidence does not indicate that any one source or component is consistently more strongly related with health effects than $PM_{2.5}$ mass.

Lastly, an important consideration in evaluating whether the NAAQS provides public health protection with an adequate margin of safety is assessing whether there are specific populations or lifestages at increased risk of a PM-related health effect. While the ISA provides substantial evidence of health effects due to short- and long-term exposure to $PM_{2.5}$ across populations with diverse characteristics (e.g., children, older adults, people with pre-existing cardiovascular diseases, etc.), an evaluation of whether any of these populations are at increased risk of a PM-related health effect relies on evidence from specific types of studies that can directly inform this question as detailed in Section 1.6 and CHAPTER 12. Based on the framework for characterizing the evidence for populations potentially at increased risk of an air pollutant-related health effect detailed in the 2013 O_3 ISA (U.S. EPA, 2013), this ISA concludes there is adequate evidence that children are at increased risk of a $PM_{2.5}$-related health effect based off strong evidence of impaired lung function growth and additional evidence of decrements in lung function and asthma development. Additionally, there is adequate evidence that nonwhite people are at increased of $PM_{2.5}$-related health effects based on studies of long-term $PM_{2.5}$ exposure and mortality and studies demonstrating differential exposure by race. There was also suggestive evidence that populations with pre-existing cardiovascular and respiratory disease, that are overweight or obese, with genetic variants in genes in the glutathione pathway and oxidant metabolism, or that are of low SES are at increased risk for $PM_{2.5}$-related health effects.

PM Exposure and Welfare Effects

Compared to the evaluation of the health effects evidence, the evaluation of the welfare effects evidence focuses broadly on PM and not individual size fractions or exposure durations. Additionally, the evaluation, as noted previously, focuses on the welfare effects of visibility impairment, climate effects, and effects on materials due to the ecological effects of PM being evaluated in the ISA for Oxides of Nitrogen, Oxides of Sulfur and Particulate Matter–Ecological Criteria (U.S. EPA, 2018).

Table ES-2 Summary of causality determinations for relationships between PM exposure and welfare effects from the 2009 and current draft PM ISA.

Welfare Effect Category	Causality Determination	
	2009 PM ISA	Current Draft PM ISA
Visibility Impairment Section 5.1.12, Table 5-18	Causal relationship	Causal relationship
Climate Effects Section 5.2.13, Table 5-28	Causal relationship	Causal relationship
Effects on Materials Section 6.1.16, Table 6-33	Causal relationship	Causal relationship

ISA = Integrated Science Assessment; PM = particulate matter.
Previous causality determinations taken from the 2009 PM ISA (U.S. EPA, 2009).

As noted in Table ES-2, this ISA concludes a "causal relationship" between PM visibility impairment, climate effects, and effects on materials which is consistent with the 2009 PM ISA. For visibility impairment (Section 13.2), the relationship between PM and light extinction has been well characterized. The rapid decline in $PM_{2.5}$ sulfate that has occurrent from 2002−2012 (i.e., −4.6% per year in rural areas and −6.2% per year in urban areas) has contributed to improvements in visibility in many areas, but an increasing amount of light extinction is now due to nitrate and organic matter. There have been no recent visibility preference studies; however, a recent meta-analysis demonstrates that scene-dependent haze metrics better account for preference compared to only using the deciview scale as a metric. For climate (Section 13.3), there is substantial evidence indicating that PM affects the radiative forcing of the climate system, both through direct scattering and absorption of radiation, and indirectly, by altering cloud properties. However, it is important to note there are still substantial uncertainties with respect to key processes linking PM and climate, specifically clouds and aerosols because of the scale between PM-relevant cloud processes and the resolution of state-of-the-art models and the indirect impacts and feedbacks in the climate system due to an initial radiative effect due to PM. Lastly, for effects on materials (Section 13.4), most of the evidence has often focused on examining PM impacts on stone

used for historic monuments and buildings. Recent evidence further expands the understanding of soiling and corrosion process for glass and metals, and demonstrates that atmospheric soiling can impact energy efficiency of photovoltaic systems and some buildings.

Scientific Considerations and Key Findings of the Health and Welfare Effects Evidence

As summarized in the Preface (Section P.3), the Preamble to the ISAs (U.S. EPA, 2015) describes the process by which the U.S. EPA evaluates the strengths and limitations in the scientific evidence using a weight-of-evidence framework to form causality determinations within the ISAs. There are five different causality determinations, which may be used to characterize evidence with each determination delineated by the degree to which chance, confounding, and other biases affect interpretation of the scientific evidence (Table P-2). As documented by the extensive evaluation of evidence throughout the subsequent chapters of this ISA, the U.S. EPA carefully considers uncertainties in the evidence, and the extent to which recent studies have addressed or reduced uncertainties from previous assessments, as well as the strengths of the evidence. Uncertainties considered in the epidemiologic evidence, for example, include the potential for confounding by copollutants or covarying factors and exposure error. The U.S. EPA evaluates many other important considerations (not uncertainties) such as coherence of evidence from animal and human studies, evaluation of different PM components, heterogeneity of risk estimates, and the shape of concentration-response relationships. All aspects are evaluated in drawing scientific conclusions and making causality determinations, and where there is clear evidence linking PM with effects with minimal remaining uncertainties, the U.S. EPA makes a determination of a *causal* or *likely to be causal* relationship.

Key findings of the health effects evidence spanning each of the PM size fractions and welfare effects evaluated in this ISA are summarized below and in Chapter 1 (Section 1.7). These highlights encapsulate the evidence that informed consideration of strengths and limitations and development of causality determinations. For the health (i.e., respiratory and cardiovascular effects, and mortality due to short- and long-term $PM_{2.5}$ exposure) or welfare effects categories for which *causal* or *likely to be causal* determinations were made, recent findings were found to reduce or fully address previous uncertainties in the evidence and increase the strength of U.S. EPA's scientific conclusions. For other PM-effect relationships, the key findings highlighted below indicate where there is strength in the evidence, but uncertainties remain, resulting in causality determinations of *suggestive of, but not sufficient to infer, a causal relationship* or in some cases *inadequate to infer the presence or absence of a causal relationship*, both of which reflect there is limited evidence to evaluate both strengths and weaknesses.

Health Effects Evidence: Key Findings

A large body of scientific evidence spanning many decades clearly demonstrates there are health effects attributed to both short- and long-term PM exposure, with the strongest evidence for a relationship between some health effects and $PM_{2.5}$. Generally, for most health effects and exposures to $PM_{10-2.5}$ and UFPs, there are more limitations and uncertainties across scientific disciplines (i.e., atmospheric chemistry, exposure science, and both epidemiology and experimental sciences), complicating the interpretation of the evidence. The collective body of evidence for each of the PM size fraction, exposure, and health outcome category combinations evaluated in this ISA was carefully considered and assessed, including the inherent strengths, limitations, and uncertainties in the overall body of evidence such as the available methods, models and data used within and across studies. This full assessment of the current state of the science for $PM_{2.5}$, $PM_{10-2.5}$, and UFPs resulted in the causality determinations detailed in Table 1-4. Through identification of the strengths and limitations in the evidence this ISA may help in the prioritization of research efforts to support future PM NAAQS reviews. Examples of the key findings in the health effects evidence considered in this PM ISA include:

$PM_{2.5}$

- There are many recent epidemiologic studies conducted in diverse geographic locations, encompassing different population demographics, and using a variety of exposure assignment techniques, that continue to report consistent positive associations between short- and long-term $PM_{2.5}$ exposure and respiratory and cardiovascular effects and mortality. This evidence continues to support the large body of previously published epidemiologic studies reporting positive $PM_{2.5}$ associations with respiratory and cardiovascular effects and mortality and in some cases strengthens and extends the evidence base for other health effects.
- New $PM_{2.5}$ exposure assignment methods that utilize several sources of available data (i.e., satellite observations, model predictions, and ambient monitors) in epidemiologic studies better allow for the inclusion of less urban areas. These methods are well validated by $PM_{2.5}$ monitors in areas with moderate-to-high population density. Although fewer monitors are available for model validation in sparsely populated rural areas compared with urban areas, $PM_{2.5}$ concentrations are typically lower and more spatially homogeneous in rural areas, resulting in the need for fewer validation sites.
- The large number of animal toxicological and controlled human exposure studies provide coherence and biological plausibility for effects observed, particularly respiratory, cardiovascular, and mortality in epidemiologic studies of short- and long-term $PM_{2.5}$ exposure.
- Both animal toxicological and controlled human exposure studies, using concentrated ambient particle (CAP) exposures, provide evidence of a direct effect of PM exposure on various health effects.
- Epidemiologic studies that conducted copollutant analyses show that associations remain relatively unchanged when adjusting for gaseous pollutants and other particle size fractions (e.g., $PM_{10–2.5}$), addressing a key uncertainty identified in the 2009 PM ISA.
- Recent epidemiologic studies indicate that the observed heterogeneity in risk estimates is not attributed solely to differences in the composition of $PM_{2.5}$, but also reflects city-specific exposure conditions (e.g., housing and commuting characteristics).

- Evidence continues to support a linear, no-threshold concentration—response relationship, but with less certainty in the shape of the curve at lower concentrations (i.e., below about 8 $\mu g/m^3$).
- For health effects where it was concluded that the evidence is suggestive of, but not sufficient to infer, a causal relationship (including short- and long-term $PM_{2.5}$ exposure and metabolic effects, male and female reproduction and fertility, pregnancy and birth outcomes, and short-term exposures and nervous system effects) epidemiologic and experimental studies report inconsistent evidence of an association/effect or there are relatively few studies focusing on the health effect of interest.

$PM_{10–2.5}$

- Routine national monitoring of $PM_{10-2.5}$ was initiated in 2011. $PM_{10-2.5}$ concentrations are more spatially and temporally variable than $PM_{2.5}$. Although some $PM_{10–2.5}$ data are available across the nation, micro-to-neighborhood scale data are not widely available, adding uncertainty to the interpretation of results from epidemiologic studies, especially for long-term exposure studies that rely on spatial contrasts to examine associations with health effects.
- Epidemiologic studies that examined associations between short- and long-term $PM_{10–2.5}$ exposure and various health effects use multiple methods to estimate concentrations, complicating the comparison of results across studies.
- Depending on the health effect, few or no experimental studies examined the relationship between short- and long-term exposure to $PM_{10–2.5}$ and health effects. The few studies conducted provide inconsistent evidence of effects due to $PM_{10–2.5}$ exposures contributing to limited coherence and biological plausibility.
- The causality determinations for all health outcome categories for short- and long-term $PM_{10-2.5}$ exposure were either *suggestive of, but not sufficient to infer, a causal relationship* or *inadequate to infer the presence or absence of a causal relationship*, indicating limitations and uncertainties in the evidence base.

UFPs

- There is no national ambient monitoring network in place to measure UFP concentrations, thus there is limited information on UFP exposures within the U.S.
- There are a limited number of epidemiologic studies that examined short- or long-term UFP exposure and various health effects.
- It is difficult to assess the results across epidemiologic studies due to the different size ranges of UFPs examined, the exposure metrics used, and spatial and temporal variability of UFP concentrations.
- There is strong and consistent animal toxicological evidence linking long-term UFP exposure to nervous system effects, which directly informed the *likely to be causal relationship* conclusion. This evidence is in contrast to the limited evidence base for other health effects.
- For all other health effect categories, animal toxicological studies and controlled human exposure studies provide limited, and in some instances inconsistent, evidence of effects due to short- or long-term UFP exposure contributing to limited coherence and biological plausibility.
- There is evidence of translocation of UFPs to the brain via the olfactory nerve, but it is unclear whether this translocation occurs in humans as well as in animals. There is also uncertainty surrounding the mechanisms and degree to which particles translocate from the respiratory tract

to the brain, however, translocation of particles to the brain may not be required for UFP-related nervous system effects.

- For health effects where it was concluded that the evidence is *inadequate to infer the presence or absence of a causal relationship*, few or no epidemiologic and experimental studies examined the relationship between short- or long-term UFP exposures.

Welfare Effects Evidence: Key Findings

A large body of scientific evidence spanning many decades also demonstrates there are welfare effects attributed to PM. This collective body of evidence contributed to the causality determinations detailed in Chapter 13 of this ISA for each of the nonecological welfare effects evaluated (see Table 1-4). Examples of the key findings in the welfare effects evidence considered in this PM ISA include:

- Recent studies further confirm evidence from previous assessments supporting the strong relationship between PM and the nonecological welfare effects of visibility impairment, effects on the climate, and materials damage.
- For visibility impairment and materials damage there is extensive evidence demonstrating the relationship between PM and light extinction and PM impacts on stone, respectively.
- While there is substantial evidence indicating that PM affects the climate system, specifically through radiative forcing, there are still substantial uncertainties in key processes, such as the relationship between clouds and aerosols and the indirect impacts and feedbacks in the climate system due to the radiative effect of PM.

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CHAPTER 1 INTEGRATED SYNTHESIS

Overall Conclusions of the Particulate Matter (PM) Integrated Science Assessment (ISA)

- Recent evidence spanning the scientific disciplines (i.e., atmospheric chemistry, exposure science, dosimetry, epidemiology, controlled human exposure, and animal toxicology) builds upon evidence detailed in the 2009 PM ISA and reaffirms that for short- and long-term $PM_{2.5}$ exposure there is a "*causal relationship*" for cardiovascular effects and total (nonaccidental) mortality and a "*likely to be causal relationship*" for respiratory effects.
- Recent experimental and epidemiologic evidence supports a "*likely to be causal relationship*" for long-term $PM_{2.5}$ exposure and nervous system effects.
- Recent evidence, primarily from studies of lung cancer incidence and mortality, in combination with the decades of research on the mutagenicity and carcinogenicity of PM supports a "*likely to be causal relationship*" between long-term $PM_{2.5}$ exposure and cancer.
- Recent evidence from primarily animal toxicological studies supports a "*likely to be causal relationship*" for long-term ultrafine particle (UFP) exposure and nervous system effects.
- Remaining uncertainties and limitations in the scientific evidence contribute to a "*suggestive of, but not sufficient to infer,* a *causal relationship*" and "*inadequate to infer the presence or absence of a causal relationship*" for all other exposure, size fraction, and health effects combinations.
- Recent evidence builds upon and reaffirms that there is a "*causal relationship*" between PM and the nonecological welfare effects: visibility impairment, climate effects, and materials effects.
- The assessment of PM sources and components confirms and continues to support the conclusion from the 2009 PM ISA: *Many $PM_{2.5}$ components and sources are associated with many health effects, and the evidence does not indicate that any one source or component is more strongly related with health effects than $PM_{2.5}$ mass*.
- Many populations (e.g., healthy, diseased, etc.) and lifestages (e.g., children, older adults, etc.) have been shown to be at-risk of a health effect in response to short- or long-term PM exposure, particularly $PM_{2.5}$. However, of the populations and lifestages examined, current scientific evidence indicates that only some populations may be at *disproportionately increased risk* of a $PM_{2.5}$-related health effect, including nonwhite populations, children, people with specific genetic variants in genes in the glutathione pathway, people who are overweight or obese, people with pre-existing cardiovascular and respiratory diseases, and people of low socioeconomic status (SES).

1.1 Introduction

1.1.1 Purpose

The subsequent chapters of this ISA provide a detailed evaluation and characterization of the current state of the science with respect to the health and nonecological welfare effects[33] due to exposure to particulate matter (PM). The overall scope of the ISA, which governs the types of studies considered in the evaluation of the scientific evidence, is detailed in the Preface. Aspects specific to evaluating studies of PM that form the basis of the causality determinations detailed within this ISA are described in the Appendix. The main chapters of the ISA provide both the scientific basis for causality determinations[34] and policy-relevant scientific information that supports the review of the National Ambient Air Quality Standards (NAAQS) for PM. The purpose of this CHAPTER 1 is not to summarize each of the chapters, but to synthesize the key findings on each topic considered in characterizing PM exposure and relationships with health and welfare effects. This ISA draws forward and integrates evidence evaluated in prior assessments including the 2009 PM ISA (U.S. EPA, 2009) and earlier assessments e.g., 2004 PM Air Quality Criteria Document (AQCD) (U.S. EPA, 2004) and 1996 PM AQCD (U.S. EPA, 1996).

1.1.2 Organization of the ISA

The ISA consists of the Preface (legislative requirements and history of the primary and secondary PM NAAQS; and purpose and overview of the ISA along with the overall scope, and process for evaluating evidence), Executive Summary, and thirteen chapters. CHAPTER 1 synthesizes the scientific evidence that best informs the policy-relevant questions detailed within the *Integrated Review Plan for the Primary National Ambient Air Quality Standards for Particulate Matter* (PM IRP; (U.S. EPA, 2016)) that frame this review of the primary (health-based) and secondary (welfare-based) PM NAAQS. CHAPTER 2 characterizes the sources, atmospheric processes related to PM formation, and trends in ambient PM concentrations, for specifically $PM_{2.5}$ (fine PM; PM with a nominal mean aerodynamic diameter less than or equal to 2.5 μm), $PM_{10–2.5}$ (thoracic coarse or coarse PM; PM with a nominal mean aerodynamic diameter greater than 2.5 μm and less than or equal to 10 μm), and ultrafine particles [UFPs, generally considered as particulates with a diameter less than or equal to 0.1 μm (typically based on physical size, thermal diffusivity or electrical mobility)]. CHAPTER 3 describes methods to estimate human exposure to PM and the impact of exposure measurement error on

[33] Hereafter welfare effects refers to nonecological welfare effects, unless otherwise noted. The ecological effects resulting from the deposition of PM and PM components are being considered in a separate assessment as part of the review of the secondary (welfare-based) NAAQS for oxides of nitrogen, oxides of sulfur, and PM (U.S. EPA, 2018)
[34] The general process for developing an ISA, including the framework for evaluating weight of evidence and drawing scientific conclusions and causal judgments, is described in a companion document, Preamble to the Integrated Science Assessments (U.S. EPA, 2015).

associations with health effects. CHAPTER 4 describes the dosimetry of the various size fractions of PM. CHAPTER 5, CHAPTER 6, CHAPTER 7, CHAPTER 8, CHAPTER 9, CHAPTER 10, and CHAPTER 11 evaluate and integrate epidemiologic, controlled human exposure, and animal toxicological evidence and characterize the biological plausibility for health effects related to short-term and long-term exposure to $PM_{2.5}$, $PM_{10–2.5}$, and UFPs for respiratory effects, cardiovascular effects, metabolic effects, nervous system effects, reproductive and developmental effects, cancer, and mortality, respectively. CHAPTER 12 evaluates the scientific evidence on populations and lifestages potentially at increased risk of a PM-related health effect. Lastly, CHAPTER 13 evaluates the scientific evidence for welfare effects, focusing specifically on the nonecological welfare effects of visibility impairment, climate effects, and effects on materials.

A key consideration in the health effects assessment is the extent to which evidence indicates that $PM_{2.5}$, $PM_{10–2.5}$, and UFPs exposures independently cause health effects. To that end, this chapter draws upon information about the sources, atmospheric chemistry, distribution, background sources of ambient PM, as well as exposure to ambient PM of different size fractions and identifies pollutants and other factors related to the distribution of or exposure to ambient PM that can potentially influence epidemiologic associations observed between health effects and $PM_{2.5}$, $PM_{10–2.5}$, and UFP exposures (Section 1.2). The chapter also summarizes information on the dosimetry of inhaled PM of different size fractions (Section 1.3). The discussions of the health effects evidence and causality determinations (Section 1.4) details the extent to which there is biological plausibility for the various PM exposure duration-health effects relationships evaluated, and provides an integrated summary of the epidemiologic and experimental (i.e., animal toxicological and controlled human exposure) evidence and whether it collectively supports independent relationships between $PM_{2.5}$, $PM_{10–2.5}$, or UFPs exposure and health effects.[35] This chapter also integrates evidence across the ISA for specific policy-relevant issues that are informative in the PM NAAQS review (Section 1.5), specifically: potential copollutant confounding (Section 1.5.1); the timing of effects, which includes the lag structure of associations and averaging time for exposure metrics (Section 1.5.2); the shape of the concentration-response relationship and whether a threshold exits (Section 1.5.3); and whether individual PM components or exposure metrics representative of PM sources are a better indicator for the PM-health effects relationship than PM mass (Section 1.5.4). Additionally, within the policy-relevant considerations discussion, this chapter summarizes the evidence as to whether specific populations or lifestages are at increased risk of a PM-related health effect, which is an important consideration in the context of the NAAQS and ensuring public health is protected with an adequate margin of safety (Section 1.5.5). This chapter also characterizes the welfare effects evidence and the role of PM, specifically non-ecological effects on visibility, climate, and materials (Section 1.6). Lastly, Section 1.7, summarizes the causality determinations for all PM size fraction, exposure duration, and health and welfare effects combinations evaluated within this ISA.

[35] When discussing epidemiologic evidence, as detailed in the Preface, risk estimates are for a 10 $\mu g/m^3$ increase in 24-hour average $PM_{2.5}$ and $PM_{10–2.5}$ concentrations and a 5 $\mu g/m^3$ increase in annual $PM_{2.5}$ and $PM_{10–2.5}$ concentrations.

1.2 From Emissions Sources to Exposure to Particulate Matter

The characterization of human exposure is key to understanding the relationships between ambient PM (i.e., $PM_{2.5}$, $PM_{10–2.5}$, and UFP) and health effects. Exposure to PM is influenced by a variety of factors including, but not limited to, time-activity patterns, building characteristics, and amount of PM in the ambient air. The latter is influenced by sources and atmospheric processes contributing to ambient PM concentrations that together can influence the spatial and temporal patterns of PM. These patterns have implications for variation in exposure in the population, the adequacy of methods used to estimate exposure, and in turn, the strength of inferences that can be drawn about the health and welfare effects related to PM exposure.

1.2.1 Emission Sources and Distribution of Ambient Concentrations

PM is well defined as a complex mixture of solid and liquid droplets that is often characterized by distinct size fractions, i.e., $PM_{2.5}$, $PM_{10–2.5}$, and UFPs. The characteristics of each PM size fraction can vary in terms of: sources and emissions, atmospheric processes that result in PM formation, variability in concentrations over time and space, and monitoring.

Observations and new developments in the characterization of ambient PM build on the conclusions reported in the 2009 PM ISA, as summarized in CHAPTER 2. In the 2009 PM ISA, a decreasing trend in $PM_{2.5}$ concentrations were reported between 1999−2007, and a decreasing trend in PM_{10} concentrations between 1988−2007. In addition, for the years 2005−2007, there was considerable variability in daily average concentrations of $PM_{2.5}$. PM size was also observed to vary with location, with a generally larger fraction of PM_{10} mass accounted for by $PM_{10–2.5}$ size in western cities (e.g., Phoenix and Denver) and by $PM_{2.5}$ mass in eastern U.S. cities (e.g., Pittsburgh and Philadelphia). Compared to the larger PM size fractions, there was more limited information on the regional and temporal variability of UFPs. The composition of $PM_{2.5}$ nationally was also observed to vary, with higher sulfate concentrations in the summer and in the eastern U.S., and higher particulate organic carbon (OC) concentrations in the western and southeastern U.S. Little information was available on $PM_{10–2.5}$ or UFP composition. In urban areas, $PM_{2.5}$, PM_{10}, and UFPs were all observed to peak during morning rush hour and exhibited an evening rush hour peak that was broader than the morning peak and extended into the overnight period, reflecting the collapse of the mixing layer after sundown. In terms of measuring PM, notable advances had taken place in real-time PM mass measurement methods, single particle aerosol mass spectrometry methods, organic speciation methods, and dichotomous samplers for distinguishing $PM_{2.5}$ and $PM_{10–2.5}$. Major PM sources identified included combustion of fossil fuel, either by stationary sources or by transportation for primary PM, and formation of sulfates from SO_2 emitted mainly by electric power generating units (EGUs). Progress was also noted in understanding the chemistry of new particle formation and of secondary organic aerosol (SOA) formation. Background PM typically accounts for a

small fraction of urban $PM_{2.5}$ or PM_{10}, but high PM concentrations can occur during episodic events like wildfires or dust storms.

Changes in ambient PM characteristics as well as new research developments have occurred since the 2009 PM ISA. Ambient annual average $PM_{2.5}$ concentrations in the U.S. on average were 3.4 $\mu g/m^3$ lower in the period from 2013−2015 than in the period from 2005−2007 decreased from a 3-year average of 12 $\mu g/m^3$ for 2013−2015 to 8.6 $\mu g/m^3$ for 2005−2007, continuing the downward trend in national ambient $PM_{2.5}$ concentrations. However, while $PM_{2.5}$ concentrations were observed to decline, national average $PM_{10-2.5}$ concentrations were similar in both time periods. While monthly national average $PM_{2.5}$ concentrations were higher in summer than in winter from 2002−2008, this pattern is reversed from 2012−2015, when monthly average $PM_{2.5}$ concentrations became higher in winter than in summer. A greater reduction in sulfate concentrations than other component concentrations resulted in smaller sulfate contributions to $PM_{2.5}$ mass in 2013−2015 compared to 2005−2007, especially in the Eastern U.S. At many locations sulfate has been replaced by organic material as the greatest contributor to $PM_{2.5}$ mass. Much of the organic material is SOA, and there has been continued progress in understanding SOA precursors, formation processes, and components. The declines in $PM_{2.5}$ and sulfate concentrations are consistent with a large reduction in SO_2 emissions, mainly from decreased EGU coal combustion. Monitoring network changes have provided a more extensive set of observations for understanding the contributions of $PM_{2.5}$ and $PM_{10-2.5}$ to PM_{10}. The decrease in $PM_{2.5}$ concentrations has resulted in smaller $PM_{2.5}/PM_{10}$ ratios in many locations. PM_{10} in the East and Northwest is in the range of 50−60% $PM_{2.5}$, while PM_{10} in the Western U.S. is generally less than 50% $PM_{2.5}$. Routine measurement of UFPs is in its beginning stages, with only a few monitors beginning to report data.

1.2.1.1 Sources and Emissions of PM

PM is comprised of components that are directly emitted (primary particles) as well as formed through atmospheric chemical reactions involving gaseous precursors (secondary particles). The sources of PM vary with PM size fraction.

$PM_{2.5}$ can be generated from both natural and anthropogenic sources., The greatest contributors to primary $PM_{2.5}$ at the national level are agricultural dust, dust resuspended through on-road activities, and fires (i.e., wildfires, prescribed fires, and agricultural fires; see Section 2.3.1.1: and Figure 2-2). On a national scale, anthropogenic emissions have been estimated to account for 40% of total primary $PM_{2.5}$ emissions and 16% of total PM_{10} emissions (U.S. EPA, 2017). However, this does not account for secondary PM, most of which is derived from anthropogenic precursors. On an urban scale, sources that emit $PM_{2.5}$ vary from city-to-city. Generally, anthropogenic sources account for nearly all urban primary $PM_{2.5}$ emissions, and they include some combination of industrial activities, motor vehicles, cooking, and fuel combustion, and often wood smoke as well as construction and road dust. (Section 2.3.1.2). These

urban anthropogenic primary sources and more regional secondary generation both contribute substantially to $PM_{2.5}$ mass in urban locations.

Source contributions to primary $PM_{2.5}$ emissions have changed over time. For example, changes in both gasoline and diesel emissions controls have led to reductions in primary $PM_{2.5}$ emitted from newer vehicles, and primary emissions from stationary fuel combustion, industrial activities, and nonroad vehicles have also decreased (Section 2.3.1.2). Natural and international sources are generally minor contributors to $PM_{2.5}$ in urban areas. In many locations secondary PM accounts for the majority of $PM_{2.5}$ mass. The major PM precursors that can ultimately contribute to $PM_{2.5}$ mass include sulfur dioxide (SO_2), oxides of nitrogen (NO_X), ammonia (NH_3), and volatile organic compounds (VOCs) (Section 2.3.2.1). SO_2 emissions are mainly from electricity generating units (EGUs, 67%) while NO_X is emitted by several combustion sources, including on-road vehicles (34%), off-road vehicles (21%), and EGUs (13%). NH_3 emissions are dominated by livestock waste (55%) and fertilizer application (26%), and VOCs, on a national scale, mainly biogenic in origin (70%) (Section 2.3.2.1). Emissions of some $PM_{2.5}$ precursors, and subsequently their overall contribution to $PM_{2.5}$ mass, have changed over time (Section 2.3.2.1). Since the 2009 PM ISA, SO_2 emissions have been reduced from 13.9 million metric tons (MMT) in 2006 to 4.8 MMT in 2014, representing a 65% reduction and the greatest reduction among all precursor emissions (Section 2.3.2.1). NO_X emissions were also substantially reduced during the same time, decreasing from 19.4 MMT in 2006 to 13.5 MMT in 2014, representing an overall reduction of 30%. NH_3 emissions, however, have remained relatively constant over time, with estimates of 3.8 MMT in 2006 and 3.9 MMT in 2014 (Section 2.3.2.1).

While $PM_{2.5}$ is comprised of both primary PM, generated mostly from combustion-related activities, and secondary PM from atmospheric chemical reactions of precursor emissions, $PM_{10–2.5}$ is almost entirely primary in origin. $PM_{10–2.5}$ is produced by surface abrasion or by suspension of sea spray or biological material (e.g., microorganisms, pollen, plant and insect debris) (Section 2.3.3). Major sources on a national scale are unpaved road dust and agricultural dust, and in urban areas paved road dust and construction dust are usually major sources. Dust events can also result from international transport, and some of the dust particles in these events fall into the $PM_{10–2.5}$ size range. Primary biological aerosol particles can also be an important contributor to $PM_{10–2.5}$, including fungal spores, bacteria, viruses, and plant debris.

Ambient UFPs originate from two distinct processes, primary particles directly emitted from specific sources and new particle formation (NPF), which occurs because of particular atmospheric conditions that allow for particle nucleation (Section 2.3.4). UFP and $PM_{2.5}$ primary sources are largely indistinguishable because UFP is usually emitted by the same sources as $PM_{2.5}$, and grow out of the ultrafine size range through coagulation or gas-to-particle condensation over a short duration to form particles within the $PM_{2.5}$ size range. (Section 2.3.4.1). However, differences in the impact of various sources while particles are still mostly in the UFP size range can lead to differences in sources of greatest concern in both size ranges. For example, freshly emitted motor vehicle exhaust often occurs on busy

urban streets in residential neighborhoods, while emissions from electric power generation occur further away from human activity, and particles are likely to grow out of the UFP size range to a greater extent before reaching populated areas. It typically takes between about half a day and three days before newly-formed particles grow larger than 100 nm in diameter. As a result, although UFP size increases from 10 nm to 25 nm within 100 m, vehicle-related PM components are still mainly in the UFP size range as far as 1 km from a major highway.

Although relatively limited information is available on a source-by-source basis to capture changes in UFP emissions over time, analyses of individual sources where new source requirements have been instituted allow for an assessment of source contributions to UFP emissions. Most new research on UFP emissions has been focused on automobile exhaust, in part because of some of the highest observed UFP concentrations have been observed in near-road environments. For example, new requirements on heavy-duty diesel highway engines that were phased in from 2007−2010 and focused on reducing PM and NO_X emissions have led to reductions in UFP number concentration (NC) of more than 90% compared to earlier diesel engine models (Section 2.3.4.1). Although these newer diesel highway engines generate, on average, a smaller amount of UFP emissions compared to earlier models, there can still be discrete periods of extremely high UFP formation. This is due to thermal desorption of adsorbed sulfates that build up within the exhaust catalyst system and then can be released in a single burst (Section 2.3.4.1). Motor vehicles are a leading source of UFP emissions especially near roadways and recently similar observations of high UFP levels downwind of airports have also been reported. However, stationary point sources are also important, particularly at further distances from roadways. Gasoline and diesel-powered highway vehicles, nonroad diesel engines, and industrial sources are likely the largest sources of UFP in populated areas, where relative contributions of mobile and stationary sources of UFP are likely to vary considerably depending on location, season, and time of day.

1.2.1.2 Atmospheric Processes and PM Formation

The atmospheric processes that result in PM formation, specifically oxidation reactions to form ammonium sulfate and ammonium nitrate, have been well characterized in previous assessments (U.S. EPA, 2009, 2004) (Section 2.3.2.2). As a result, recent research has focused primarily on the formation of SOA, and has shown that SOA is a sizeable contributor to $PM_{2.5}$ mass under a variety of atmospheric conditions (Section 2.3.2.3). New research has increased our understanding of how a substantial amount of SOA is produced by several important processes: reactions of the biogenic VOC isoprene; cloud processing; and further oxidation of gas phase products formed from atmospheric VOC oxidation. Additionally, PM formation from biogenic VOC reactions has been reported to be enhanced by anthropogenic influences, including NO_X and SO_2 precursor emissions. (Section 2.3.2.3). Compositional analyses have shown that organosulfates and organonitrates often account for a large fraction of SOA, up to 5−10% for organosulfates and up to 10−20% for organic nitrates (Section 2.3.2.3). Examination of atmospheric processes that lead to SOA formation has led to observations that atmospheric aging

(oxidation) of organic aerosols increases reactive oxygen species activity of ambient PM (Section 2.5.1.1.7). Reactive oxygen species (ROS) have been shown to contribute to cellular oxidative stress in respiratory tract cells (Section 5.1.1).

In addition to exploring SOA formation, recent studies have further examined particle nucleation. New instrumentation has made it possible to measure atmospheric molecular clusters and to directly observe the process of particle nucleation (Section 2.3.4). This research has also focused on identifying the chemical species important in the particle nucleation process. Previous research had focused mainly on the role of sulfate and water, with increasing evidence that organic species were also involved. More recent research identified the importance of additional species, including ammonia and amines as well as extremely low volatility organic compounds in particle nucleation. (Section 2.3.4.2).

1.2.1.3 Monitoring and Modeling of PM

Broadly, PM is measured through the following: well-established long-term national monitoring networks based on well-established monitoring methods; individual monitors established for a specific period for the purposes of characterizing air quality or conducting an epidemiologic study using a variety of established or experimental methods; and satellite measurements. Depending on the PM size fraction, the extent to which information is available on ambient concentrations will vary as a direct result of the monitoring capabilities currently available.

For $PM_{2.5}$ and PM_{10}, extensive national air monitoring networks have been established based on Federal Reference Methods (FRMs) for supporting air quality analyses for the purposes of monitoring for compliance with the PM NAAQS, measurement of spatial and temporal trends of air pollutants, and to support research to assess exposure and health risks from PM exposures (Section 2.4.6). Because PM itself is a complex mixture, additional monitoring networks have been established to capture information on $PM_{2.5}$ components. Specifically, the Chemical Speciation Network (CSN), and the Interagency Monitoring of Protected Visual Environments (IMPROVE) network, which was established for the specific purpose of understanding the relationship between PM composition and atmospheric visibility impairment, both monitor $PM_{2.5}$ components (Section 2.4.6).

Two new national monitoring networks provided additional monitoring of $PM_{2.5}$ and/or $PM_{10-2.5}$ (Section 2.4.6). The first national monitoring network was established as a result of the 2010 NO_2 NAAQS. This network instituted near-road monitors that were placed within 50 m of heavily trafficked roads in urban areas, and many of these near-road monitoring sites also conducted routine monitoring of $PM_{2.5}$. The NCore monitoring network was deployed starting in January 2011 and included measurements for $PM_{2.5}$ and $PM_{10-2.5}$. The $PM_{10-2.5}$ measurements were based on improved monitoring methods specified for $PM_{10-2.5}$ measurement methods to qualify as FRMs and Federal Equivalence Methods (FEMs), and compared to previously used methods that relied on taking the difference between PM_{10} and $PM_{2.5}$ FRM measurements (Section 2.4.6). The new $PM_{10-2.5}$ monitoring requirements are met by using

identical instrumentation for both $PM_{2.5}$ and PM_{10} except for the sampler cut-point; i.e., using the same sampler design, filter type, and filter face velocity for both $PM_{2.5}$ and $PM_{10–2.5}$ in the same sampler.

To date, most monitoring efforts with respect to PM focus on mass-based measurements of $PM_{2.5}$, PM_{10}, and $PM_{10–2.5}$. Recently, some monitors have been deployed to measure UFP concentrations. Routine network particle number concentration (NC) measurements were initiated at a few sites, mostly in New York state, which were made possible by the recent development of water-based condensation particle counters (CPCs) (Section 2.4.6). In other research, new CPCs have been developed, which are capable of measuring NC of particles with aerodynamic diameter 0.001 μm and larger, and these are especially useful for investigating the atmospheric nucleation of particles. (Section 2.4.3.1). Analysis of particle number count data from field studies shows that UFPs are likely to vary considerably among widely used methods, reflecting differences in the size ranges measured. While size ranges of ambient UFP measurements can vary depending on the monitor used, it is important to note that the ambient UFP size range varies from that used in experimental (i.e., animal toxicological and controlled human exposure) studies that rely on concentrated ambient particle (CAP) UFP exposures. Specifically, UFP CAPs result in particle size ranges up to 0.18−0.3 μm, which is larger than the nominal UFP size limit of less than 0.1 μm, which has previously been defined as the upper size cut as detailed in the 2009 PM ISA. Because the contribution to mass from particles less than 0.1 μm is relatively small, much of the mass may be associated with particles greater than 0.1 μm. However, as described in Section 2.4.3.1, the difference in particle number measurements between PM delivered with usual methods in controlled exposure studies and ambient UFP from which it originates is likely to be much less than the difference in mass (Section 2.4.3.3).

Some of the biggest developments since the 2009 PM ISA include the use of satellite-based measurements to estimate $PM_{2.5}$ concentrations and the continued evolution of chemical transport models (CTMs). Satellite-based measurements have become widely used and combined with modeled data and ground level measurements to extend spatial coverage and improve spatial resolution of $PM_{2.5}$ estimates (Section 2.4.5). Although satellite based $PM_{2.5}$ measurements allow for an expansion of the spatial coverage of epidemiologic studies, they are subject to measurement errors not encountered with FRM or other ground-based measurements, particularly due to data availability because of the inability to provide measurements during days with cloud or snow cover. This is because $PM_{2.5}$ is not directly measured and its estimation is based on computational algorithms involving a range of assumptions, such as vertical distribution and particle composition (Section 2.4.5). With respect to CTMs, advances have included the addition of biogenic VOC chemistry, organic aerosol aging, cloud chemistry, dry deposition, meteorological processes, wind-blown dust, and ammonia emissions. Collectively, these additions have resulted in demonstrable improvements in the prediction of seasonal variation and long-term changes in $PM_{2.5}$ concentrations (Section 2.4.7).

1.2.1.4 National PM Concentrations

Recent assessments of ambient PM concentrations have shown a general decline over time. $PM_{2.5}$ concentrations are generally lower than those reported in the 2009 PM ISA, decreasing from a national 3-year average of 12 μg/m^3 for 2005−2007 to 8.6 μg/m^3 for 2013−2015 (Section 2.5.1.1.1 and Section 2.5.2.1.1). Similar to the trend in $PM_{2.5}$ concentrations, national 3-year average PM_{10} concentrations have declined by 15% compared to those reported for 2005−2007, and are estimated at 21.1 μg/m^3 for 2013−2015, at least in part reflecting decreases in $PM_{2.5}$ concentrations. As detailed in Section 1.2.1.3, limited data are available from national monitors for $PM_{10-2.5}$ and UFP. As a result, it is difficult to assess trends in UFP and $PM_{10-2.5}$ concentrations over time (Section 2.5.1.1.5 and Section 2.5.2.1.3).

An examination of $PM_{2.5}$ composition trends further informs the overall reductions in $PM_{2.5}$ concentrations that have occurred over time. The biggest change in $PM_{2.5}$ composition that has occurred since the 2009 PM ISA, is the reduction in sulfate concentrations. Between 2000 and 2015 nationwide annual average sulfate concentration decreased by 17% at urban sites and 20% at rural sites. This change in sulfate concentrations is most evident in the eastern U.S., and has resulted in organic matter or nitrate now being the greatest contributor to $PM_{2.5}$ mass in most locations (Section 2.5.1.1.6). The observed decline in $PM_{2.5}$ sulfate concentrations can be attributed to a similar decline in SO_2 emissions. The overall reduction in sulfate concentrations likely contributed substantially to the decrease in national average $PM_{2.5}$ concentrations as well as the decline in the fraction of PM_{10} accounted for by $PM_{2.5}$, when compared to the years 2005−2007 (Section 2.5.1.1.6).

1.2.1.5 Spatial and Temporal Variability in PM Concentrations

Although there has been an overall reduction in national PM concentrations over time, there are distinct spatial and temporal patterns in PM concentrations. At a macro scale, $PM_{2.5}$ concentrations are generally higher and more spatially uniform in the eastern U.S. than in the western U.S. (Section 2.5.1.1.1). While $PM_{2.5}$ concentrations are generally higher in the eastern U.S., the highest reported concentrations are an exception to this trend, occurring in California. Especially high $PM_{2.5}$ concentrations are observed in the San Joaquin Valley, where multiple monitors recorded 3-year average concentrations greater than 14 μg/m^3, and in the Los Angeles basin, where 3-year average concentrations exceeded 12 μg/m^3 at several monitors. In the Eastern U.S., the highest $PM_{2.5}$ concentrations are in or near the Ohio Valley, extending eastward into Pennsylvania, where 3-year average concentrations for numerous monitors exceeded 10 μg/m^3. On a national scale there are distinct east and west patterns in long-term average $PM_{2.5}$ concentrations, but on an urban scale there is not a clear pattern of $PM_{2.5}$ spatial variability with some observations indicating relatively uniform concentrations while others depict a high degree of variability (Section 2.5.1.2.1).

Seasonal analyses have shown a change in the season with the highest $PM_{2.5}$ concentrations. Compared to the 2009 PM ISA, where the examination of seasonal $PM_{2.5}$ concentrations depicted higher concentrations in the summer, recent data indicate higher average $PM_{2.5}$ concentrations in the winter, which reflects lower SO_2 emissions and subsequently sulfate concentrations in the summer (Section 2.5.1.1.1 and Section 2.5.2.2.1). Within most urban areas, $PM_{2.5}$ exhibit a rush hour peak in the morning and evening (Section 2.5.2.3).

In general, the fraction of PM_{10} accounted for by $PM_{2.5}$ is higher in the eastern U.S. than in the western U.S. (Section 2.5.1.1.4). Compared to $PM_{2.5}$, $PM_{10–2.5}$ concentrations are more spatially variable (Section 2.5.1.2.3). Ninety-eighth percentile $PM_{10–2.5}$ concentrations greater than 40 $\mu g/m^3$ were observed in multiple locations in California, as well as in the southwestern states of Nevada, Arizona, New Mexico, Texas, and the central plains states of Oklahoma, Missouri, and Iowa, and the urban areas of St. Louis, MO, Cleveland, OH, and south Florida. While not directly comparable, PM_{10} concentrations, monitoring data for which are available for many more years, can inform, and are often consistent with, the observed spatial and temporal pattern of $PM_{10–2.5}$ concentrations. Compared to the 2004 AQCD (U.S. EPA, 2004), more PM_{10} in the eastern U.S. is now accounted for by $PM_{10–2.5}$ than before based on examining the fraction of PM_{10} comprised of $PM_{2.5}$. The $PM_{2.5}$ fraction of PM_{10} appears to have decreased from about 60−70% in –the 2004 PM AQCD to about 50−60% in 2013–2015 reported in this document, although the 2013−2015 observations are based on national network data and the 2004 data are based on a limited number of field study samples (Section 2.5.1.1.4). All U.S. regions display clear seasonal variations in $PM_{10–2.5}$ concentrations, with the lowest concentrations occurring around January and the highest occurring in the summer months (Section 2.5.2.2.2). Most $PM_{10–2.5}$ measurements have been based on 24-hour monitoring, however, considerably higher $PM_{10–2.5}$ concentrations have been observed using monitors capable of recording higher time resolution measurements, potentially indicating a tendency for intense $PM_{10–2.5}$ short-term episodes not captured by 24-hour monitoring (Section 2.5.1.1.3).

Data on the spatial and temporal variability in UFP concentrations is rather limited, particularly in the U.S. However, a single U.S. study that measured a full year of urban size-resolved particle number count measurements indicated about 90% of particles were smaller than 0.1 µm. (Section 2.5.1.1.5). The limited amount of available UFP measurements data indicated that the highest UFP concentrations occur in the winter and near roads with heavy traffic, often over short time periods (Section 2.5.1.2.4 and Section 2.5.2.2.3). Overall, UFP concentrations are more spatially variable than $PM_{2.5}$ (Section 2.5.1.2.4). Examinations of temporal variability show that UFP concentrations typically rise substantially in the morning and remain high into the evening hours when they reach their maximum, with distinct rush hour and early afternoon peaks. Additionally, there is evidence of seasonal impacts on the temporal variability of UFP concentrations, with high afternoon concentrations during warmer months possibly due to photochemical formation, and lower concentrations through the night (Section 2.5.1.1.5 and Section 2.5.2.2.3).

A detailed evaluation of the composition of $PM_{2.5}$, $PM_{10-2.5}$, and UFPs finds that each size fraction is dominated by a few components. For $PM_{2.5}$, there are clear geographic differences in its composition. In the eastern U.S., sulfate and organic matter are the highest contributors to total mass while in the western U.S. organic matter most often is the highest contributor, although sulfate, nitrate, and crustal material can also be abundant (Section 2.5.1.1.6). When examining the absolute concentrations of specific components, the highest nitrate concentrations are observed in the western U.S., particularly in California, but with some elevated concentrations in the upper Midwest. Seasonally, nitrate concentrations are much higher in the winter than summer in all locations (Section 2.5.1.1.6). Organic and elemental carbon concentrations are both more uniformly distributed in the eastern U.S., but more variable among western U.S. locations. The highest urban concentrations in the western U.S. occur during fall and winter (Section 2.5.1.1.6). Crustal material is a substantial contributor to $PM_{2.5}$ mass in dry areas of the western U.S., such as in Phoenix and Denver (Section 2.5.1.1.6). For $PM_{10-2.5}$, as noted previously concentrations are highest in southwestern U.S. and are observed to be largely dominated by crustal material, but organic material can also represent a substantial contribution to mass, as well as biological material like bacteria, viruses, fungal spores, pollen, and plant debris (Section 2.5.1.1.6). For UFPs there is still relatively limited information on its composition, but initial data indicate that urban UFPs are rich in organic and elemental carbon, while sulfate and ammonium are likely to be substantial contributors to UFPs in areas where new particle formation occurs (Section 2.5.1.1.6).

Background PM generally refers to PM that is formed by sources or processes that cannot be influenced by actions to control PM concentrations. Various background definitions have been used for NAAQS reviews. U.S. background concentration of a pollutant is the concentration resulting from natural primary and precursor sources everywhere in the world plus anthropogenic sources outside of the U.S., Canada, and Mexico. Similarly, North American background concentrations is the concentration resulting from natural primary and precursor sources everywhere in the world plus anthropogenic sources outside of the U.S., Canada, and Mexico. U.S. background sources of PM include wind erosion of natural surfaces, volcanic production, wildfires, sea salt, biological material like pollen and spores, SOA produced by oxidation of biogenic hydrocarbons, and international transport. Background PM can be episodic, as in the case of volcanic eruptions, forest fires, and dust storms or more consistent, as in the case of a relatively constant, low level contributions from natural and intercontinental sources outside of major events. Nationally, it has been estimated that wildfire smoke contributes between 10% and 20% of primary $PM_{2.5}$ emissions per year, and intercontinental transport contributes 0.05 to 0.15 $\mu g/m^3$ to annual average $PM_{2.5}$ concentrations in the U.S., but that this contribution varies by region and season. On average, natural sources including soil dust and sea salt have been estimated to account for approximately 10% of U.S. urban $PM_{2.5}$ (Section 2.5.4).

1.2.1.6 Summary

Since the 2009 PM ISA there are new developments and observations in the characterization of ambient PM. For $PM_{2.5}$, these include observations of a steep decline in SO_2 precursor concentrations, replacement of sulfate with organic matter as the greatest contributor to $PM_{2.5}$ mass in many locations in the eastern U.S., and a substantial decrease in national average $PM_{2.5}$ concentration. A large body of new research has also refined the overall understanding of SOA formation processes. Improvements in CTM methods have resulted in demonstrable improvements in the prediction of seasonal variation and long-term changes in $PM_{2.5}$. Extensive new network monitoring for $PM_{10–2.5}$ has greatly increased the amount of data available for assessing relative amounts of $PM_{2.5}$ and $PM_{10–2.5}$, showing that $PM_{10–2.5}$ as a fraction of PM_{10} has increased in the eastern U.S. as sulfate and $PM_{2.5}$ have decreased, and that in many western locations the contribution of $PM_{10–2.5}$ to PM_{10} exceeds the contribution of $PM_{2.5}$ to PM_{10}. This new monitoring effort has further informed the understanding of seasonal and regional differences in $PM_{10–2.5}$ concentrations. Recent studies focusing on UFPs, largely supports observations in the 2009 PM ISA, but new areas of emphasis include instrumentation for measuring particles as small as 1 nm and the initiation of long-term monitoring in a few U.S. locations, which will facilitate future research. However, network data are still sparse, and there is still far less information regarding patterns of spatial and temporal variability of UFP in comparison to $PM_{2.5}$ or $PM_{10–2.5}$. Differences in monitoring methods and the lack of a consistent definition also make comparison of UFP data difficult between different field studies or methods.

1.2.2 Assessment of Human Exposure

Findings from the recent exposure assessment literature build on evidence presented in the 2009 PM ISA for the assessment of PM exposures. The 2009 PM ISA found that spatial variability of $PM_{10–2.5}$ and UFP at micro-to-neighborhood scales was greater than that of $PM_{2.5}$, and primary $PM_{2.5}$ components, such as EC, exhibited greater spatial variability than $PM_{2.5}$ components produced through atmospheric chemical reactions, such as NO_3^- or SO_4^{2-}. Regional variability in PM composition was also noted and thought to result from differences among sources in different parts of the country. Models, such as land use regression (LUR), were discussed as tools intended to characterize spatially variable components or size fractions, but limitations in the LUR's ability to adequately capture spatial variability were identified in several papers reviewed. Additionally, variability in the PM size distribution, PM composition, and infiltration was identified across regions as factors that could influence individual exposure to PM. Unmeasured variability in ambient PM concentration, size fractions, and composition were noted to cause potential uncertainty in estimates of exposure concentrations and health effect estimates. The recent literature advances the state of exposure science by presenting innovative methodologies to estimate PM exposure, detailing new and existing measurement and modeling methods, and further informing the influence of exposure measurement error due to new and existing exposure concentration estimation methods on associations between PM and health effects reported in the epidemiologic study literature.

New evidence supports older findings that appropriate surrogates for exposure concentration may depend on PM size distribution, because spatial variability in PM concentrations varies with particle size (Section 3.4.3.2). Multiple techniques have recently been developed or improved to assign PM exposure concentrations in epidemiologic studies. These methods include personal monitors, data averaging across monitors, interpolation methods, LUR models, spatiotemporal models, CTMs, dispersion models, microenvironmental models, and satellites (Section 3.3). Fixed-site monitors also continue to be used frequently to estimate exposure concentration. Each method has strengths and limitations. Accordingly, errors and uncertainties in the exposure assessment methods can add bias and uncertainty to health effect estimates from epidemiologic studies on the health effects of PM exposure.

Ambient PM data from individual sites continue to be used widely in health studies as a surrogate for PM exposure concentration, because fixed-site monitors provide a continuous record of ambient PM concentrations over many years (Section 3.3.1.1). For $PM_{2.5}$, the concentration profile tends to be more homogeneous across the urban or neighborhood scale, ambient concentrations estimated at fixed-site monitors may reflect exposure concentrations. However, the higher degree of spatial variability in ambient $PM_{10–2.5}$ and UFP across an urban area may not be captured by a fixed-site monitor. As a result, uncharacterized variability in a time-series of exposure concentrations across space, resulting from use of fixed-site monitoring data, in a time-series epidemiologic study of $PM_{10–2.5}$ or UFP exposure may tend to attenuate health effect estimates (Section 3.4.5.1). For long-term exposure studies, bias may occur in either direction depending on whether the fixed-site monitor is over- or underestimating ambient $PM_{10–2.5}$ or UFP exposure concentration for the population of interest (Section 3.4.5.2). In all study types, use of fixed-site monitoring ambient $PM_{10–2.5}$ or UFP concentrations in lieu of the true exposure is expected to widen confidence intervals beyond what would be obtained if the true exposure were used. Personal monitors directly measure PM exposure, but they produce a relatively limited data set, making them most suitable for panel epidemiologic studies (Section 3.4.5.1.2). Without accompanying geographic positioning system (GPS) or time-activity diary data, it is impossible to distinguish ambient PM exposure from exposure to PM of nonambient origin in these studies.

Models of PM concentration can be used to develop exposure surrogates for individuals and large populations when personal exposure measurements are unavailable (Section 3.3.2). Recent developments have been made to advance techniques for spatiotemporal modeling, which typically combine universal kriging with variables describing land use, population characteristics, emissions, and geographic features (Section 3.3.2.3). GIS-based spatiotemporal models of concentration that are used as exposure surrogates have produced out-of-sample cross-validation (i.e., out-of-sample $R^2 > 0.8$) for $PM_{2.5}$ and its components, some of which have more spatially varying concentration fields than $PM_{2.5}$ mass concentration. Overly-smoothed exposure concentration surfaces from spatiotemporal models have been shown to bias the health effect estimate towards the null (i.e., underestimating the true health effect) with decreased probability that the confidence intervals contain the true health effect, particularly when the actual spatial variability is much higher than what is represented by the model (Section 3.4.5.2). Bias correction and bootstrap calculation of standard errors have been shown to improve health effect estimate prediction

from spatiotemporal models when the exposure estimates have a classical-like error structure. A study of $PM_{2.5}$ mass and components, including EC, OC, Si, and S, where the exposure model errors had a Berkson structure, did not exhibit improvement of the health effect estimate when bootstrap simulation of the standard error was applied. When the exposure estimates have a Berkson-like error structure, health effect estimate predictions would only be expected to improve when model covariates are chosen so that the statistical distribution of the modeled exposure concentrations is close to the distribution of the true exposure concentrations.

Recent developments have been made for mechanistic models, such as dispersion models and CTMs, to simulate the transport, dispersion, and (in the case of CTMs) atmospheric chemistry of ambient PM (Section 3.3.2.4). Hybrid approaches to combine exposure concentration predictions from CTMs with those from fixed-site monitoring data or dispersion models have grown since the 2009 PM ISA. CTMs are limited in their spatial resolution, which is typically at length scales of 4 km or 12 km (and sometimes down to 1 km). Data fusion techniques merge CTMs with dispersion model results or fixed-site monitoring data. They are designed to estimate spatial variability of exposure concentrations at the subgrid scale, typically through a hierarchical modeling framework. These models have good cross-validation and have the potential to reduce exposure measurement error and resulting bias and uncertainty in health effect estimates produced by epidemiologic models of long-term exposure to PM, even for spatially-varying size fractions and components.

Several advancements to data fusion techniques have been made since the 2009 PM ISA to merge aerosol optical density (AOD) observations from satellite images with surface-level PM measurements from fixed-site monitors (Section 3.3.3). Regression models have been developed to calibrate the AOD observations to surface measurements of $PM_{2.5}$, and $PM_{2.5}$ exposure concentrations have then been estimated from those models in locations where surface measurements are unavailable. Land use or other geographical variables incorporated in these models have been shown to improve cross-validation and reduce error in estimates of exposure concentrations, and increasing the number of monitors used to fit the model has reduced bias and uncertainty in the exposure estimates. Hence, hybrid modeling approaches combining satellite data with fixed-site monitoring data and LUR or spatiotemporal modeling results have the potential to reduce bias and uncertainty in health effect estimates reported in epidemiologic studies of short- and long-term exposure to $PM_{2.5}$. Satellite data techniques have not typically been applied to model spatially-variable UFP, $PM_{10-2.5}$, or $PM_{2.5}$ component exposure concentration fields. Epidemiologic studies where PM exposure concentration is derived from a hybrid satellite-LUR model have reported larger magnitude health effect estimates with increasing spatial resolution (i.e., dividing the spatial domain into many smaller areas in which concentration is modeled) of the exposure concentration surfaces. If the effect estimate derived from the hybrid model was shown by cross-validation to be more accurate than a low-resolution model, then this finding suggests that low spatial resolution (i.e., a spatial domain with a small number of large areas in which concentration is modeled) of the PM exposure concentration surface may cause bias of the health effect estimate towards the null to underestimate the true health effect in a long-term exposure study (Section 3.4.5.2).

Among the methods evaluated, only personal monitoring and microenvironmental modeling account for indoor exposure to ambient PM (Section 3.3.1.2). Particles are deposited during the process of infiltration to indoor or vehicle microenvironments, to produce an infiltration factor (F_{inf}) <1 (Section 3.4.1.1). As described in the 2009 PM ISA, F_{inf} varies with season, window opening, building age, wind speed and particle size distribution (with F_{inf} lower for $PM_{10–2.5}$ compared with $PM_{2.5}$). Recent studies have reported lower F_{inf} for UFP compared with F_{inf} for $PM_{2.5}$, potentially reflecting diffusion-driven surface deposition losses for UFP during the infiltration process. In a study of the influence of exposure estimates on health effect estimates in a time-series epidemiologic study of PM exposure, use of a fixed-site monitor in lieu of a microenvironmental model that accounted for infiltration produced considerably attenuated health effect estimates (Section 3.4.5.1). Infiltration of PM through a building envelope may change the temporal variability of the indoor PM concentration time-series, resulting in reduced correlation between the health effect of interest and the estimated exposure concentration. In a study of the influence of modeled exposure concentrations on health effect estimates in an epidemiologic study of long-term average PM exposure, simulating indoor concentrations produced unbiased health effect estimates. Furthermore, the health effect estimate was biased towards the null with inflated confidence intervals after omitting a term for infiltration in a LUR or spatiotemporal model. Bias towards the null leads to underestimation of the true health effect (Section 3.4.5.2).

Exposure to copollutants may result in some confounding of the PM health effect estimate if exposure to the copollutants and their relationships to the health effect of interest are both correlated with PM exposure (Section 3.4.3). Median correlations of 24-hour ambient $PM_{2.5}$ with concentrations of some ambient gases (CO, NO_2, O_3) from the U.S. EPA Air Quality System (AQS) during 2013−2015 were as high as Pearson $R = 0.5$, although correlation varied with season (highest for O_3 in summer and for CO and NO_2 in winter). The upper end of the distribution of correlations approached one for these gases. Copollutant correlation data for short-term concentration measurements from the literature since the 2009 PM ISA were consistent with the AQS data. For $PM_{10–2.5}$, median correlations of 24-hour ambient concentrations during the same time period were as high as Pearson $R = 0.4$ but with upper correlations typically below Pearson $R = 0.7–0.8$. Median correlations between $PM_{2.5}$ and $PM_{10–2.5}$ range between 0.2 and 0.5, with higher values in summer and fall. Data for UFP correlations were very limited, but they indicate correlations as high as Pearson $R = 0.5$ for NO_2 and NO_X. Sites with moderate-to-strong correlations ($R > 0.4$) may introduce a greater degree of confounding into epidemiologic results, depending on the relationship between the copollutants and the health effect of interest.

Some epidemiologic studies of the health effects of PM exposure have examined potential associations between health effects and exposure to PM components (Section 3.4.4) since the 2009 PM ISA. An examination of the composition of $PM_{2.5}$ using data from AQS found that the highest Pearson correlations between $PM_{2.5}$ mass and $PM_{2.5}$ component concentrations occurred for OC, SO_4^{2-}, EC, and NO_3^-. A large percentage of $PM_{2.5}$ mass concentration is a product of atmospheric chemistry. The recent peer-reviewed literature showed high correlations of $PM_{2.5}$ mass concentrations with concentrations of secondary SO_4^{2-} and NO_3^- as well as primary V and Zn. Similarly, high correlations between the

quasi-ultrafine $PM_{0.25}$ and V were observed in recent studies for $PM_{0.25}$ exposure concentrations, and correlations near Pearson $R = 1$ during the winter support the notion that heating oil combustion plays a role in these associations. For $PM_{10-2.5}$, the largest correlation was for Si, possibly in dust. Median correlations reported from AQS and the literature for $PM_{10-2.5}$ with all other $PM_{10-2.5}$ components were Pearson $R < 0.5$, indicating that $PM_{10-2.5}$ is not strongly associated with combustion. Generally, $PM_{2.5}$ components reflect the secondary nature of their production, the $PM_{0.25}$ components reflect combustion, and $PM_{10-2.5}$ components reflect mechanical generation.

In summary, exposure error tends to produce underestimation of health effects in epidemiologic studies of PM exposure, although bias in either direction can occur. There are new developments in assessment of PM exposure, including hybrid spatiotemporal models that incorporate satellite observations of AOD, land use variables, surface monitoring data from FRMs, and/or CTMs. Improvements in spatial resolution of the $PM_{2.5}$ concentration surface have reduced bias and uncertainty in health effects estimates. However, high correlations with some gaseous copollutants necessitate evaluation of the impact of confounding on health effects estimates, using two-pollutant models to ascertain robustness of epidemiologic study results. $PM_{10-2.5}$ and UFP concentrations tend to be more spatially variable than $PM_{2.5}$ concentrations, and data are either unavailable or less often available to fit or validate hybrid models for those size fractions. As a result, there is typically less uncertainty in health effect estimates derived from both monitored and modeled exposure estimates for $PM_{2.5}$ compared with $PM_{10-2.5}$ and UFP.

1.3 Dosimetry of PM

Particle dosimetry refers to the characterization of deposition, translocation, clearance, and retention of particles and their components within the respiratory tract and extra-pulmonary tissues. The dose from inhaled particles deposited and retained in the respiratory tract is governed by several factors. These factors include exposure concentration and duration, activity and breathing conditions (e.g., nasal vs. oronasal route and minute ventilation), and particle properties (e.g., particle size, hygroscopicity, and solubility in airway fluids and cellular components). Basic information related to the mechanisms of particle deposition and clearance and the influence of disease severity on these mechanisms has not changed over the last several PM NAAQS reviews. Compared to prior reviews, species similarities and differences in the amounts of inhaled PM reaching the lower respiratory tract is now better understood and quantified. Additionally, some older literature on route of breathing in humans, that was not included in prior reviews, has come to light and shows differences in route of breathing as a function of age and sex. New data on particle translocation across the olfactory mucosa into the brain and from the alveolar epithelium into the blood also now allows for improved estimates of the importance of these processes in humans.

To be deposited in the respiratory tract, particles need to first be inhaled. Inhalability refers to the fraction of particles that can enter the upper respiratory tract (i.e., the head) during inhalation and is dependent on the aerodynamic diameter of the particle (d_{ae}). A commonly used occupational criterion of particle inhalability in humans based on the d_{ae} of particles, predicts that as d_{ae} increases from 1−10 µm, inhalability decreases from ~97 to ~77%, plateauing at 50% for particles ~40 µm in diameter (Section 4.1.5). The occupational criterion is for relatively high wind speeds (>1 m/s). In calm air, inhalability decreases toward zero with increasing d_{ae} above about 20 µm for nasal and 30 µm for oral breathing. There is evidence for much lower particle inhalability in infants than adults. In rodents, inhalability decreases more rapidly than in humans, from 80 to 44%, as d_{ae} of particles increases from 2.5 to 10 µm especially for faster breathing rates. Inhalability and nasal deposition are particularly important considerations influencing how much PM makes it into the lower respiratory tract of rodents relative to humans (Section 4.1.6).

The route of breathing, breathing pattern (volume and rate), and particle size are among the factors affecting the amount of PM that enters the body and may subsequently deposit in the respiratory tract. With increasing physical activity, there is an increase in minute ventilation and a shift from nasal to oronasal breathing, and depending on the size fraction of PM inhaled, potentially greater PM penetration into the lower respiratory tract (i.e., the lungs). Even at rest, differences have been observed by age, sex, disease status, and body mass index in the fraction of oral versus nasal breathing (Section 4.1.3). Children inhale a larger fraction of air through their mouth than adults, and males tend inhale a larger fraction of air through their mouth than females (across all ages). Individuals with allergies or upper respiratory infections experience increased nasal resistance, and thus, an increased fraction of oral breathing. Obesity, especially in boys, may also contribute to increased nasal resistance and an increased oral fraction of breathing relative to normal weight children. Due to their increased amount of oral breathing, these individuals may be expected to have greater PM penetration into the lower respiratory tract than healthy, normal weight adults. Children may also be expected to have a greater intake dose of PM per body mass than adults. Route of breathing is instrumental in determining the amount of PM inhaled and also impacts the size of particles that can reach the lower respiratory tract. In humans, the fraction of a breath entering through the mouth increases the fraction of particles reaching the lower respiratory tract (Figure 4-3). In contrast, rodents are obligatory nasal breathers and only a small percentage of larger particles (i.e., >3 µm) reaches the lower respiratory tract (Figure 4-4).

Particle deposition in the respiratory tract occurs predominantly by diffusion, impaction, and sedimentation (Section 4.2). Total respiratory tract particle deposition can reach nearly 100% in humans for particles smaller than approximately 0.01 µm (via diffusion) and greater than 10 µm (via sedimentation and impaction), but is minimal for particles between 0.3 to 0.7 µm. The nose and mouth represent the first line of defense against particles depositing in the lower respiratory tract, with roughly 100% of particles 10 µm or greater depositing in the human nose. Inter-species differences in the inhalability and nasal deposition of particles has also been shown to affect the size of particles that can enter the respiratory tract and the percentage of particles deposited in various regions. While larger

particles tend to deposit in the nose in humans, in rodents almost 100% of particles >5 µm are deposited in the nose. Additionally, oronasal breathing in humans contributes to greater penetration of coarse particles into the lower respiratory tract, whereas rats breath only nasally. There are also differences between children and adults in terms of breathing patterns and ventilation, indicating that children may receive a higher dose per lung surface area of ambient PM in the lower respiratory tract. Respiratory disease can lead to differences in both total deposition and deposition patterns relative to the disease-free lung. In general, the PM dose rate is increased by lung disease, but depends on the severity of and type of disease.

For any given particle size, the pattern of poorly soluble particle deposition influences clearance by partitioning deposited material between regions of the respiratory tract (Section 4.3). While particles depositing in the mouth are generally swallowed or removed by expectoration, particles deposited in the posterior nasal passages or tracheobronchial (TB) airways are moved by mucociliary transport towards the nasopharynx and swallowed. In the alveolar region clearance occurs mainly via macrophage phagocytosis. Clearance is more rapid in rodents than humans and has been shown to decrease with age beyond adulthood. Human studies have shown that ultrafine carbon particles do not rapidly or significantly translocate from the lungs into the circulation (Section 4.3.3.2). However, a new human study has demonstrated some translocation of nano-sized gold particles from the lungs into circulation. The finding of material in the blood in this new human study, but not prior human studies may, in part, be a matter of an increased signal to noise afforded in this new methodology and/or an indication that there is a difference in particle translocation from the lung depending on the inhaled particle type. Animal studies using poorly soluble nano-sized gold and iridium (Ir) particles have provided more extensive evidence of translocation into blood and secondary organs. The estimated urinary elimination by 24 hours post-inhalation of the gold nanoparticles is nearly identical between humans and rats. Soluble materials deposited in the respiratory tract can enter the blood more rapidly than insoluble materials. Recent evidence across species indicates that particles of varying composition, particle size (less than 200 nm diameter), and solubility can also translocate to the brain via the olfactory bulb. It remains unclear, though, whether translocation to the olfactory bulb and brain regions varies by species and whether certain species are more predisposed to this translocation route.

There is a dosimetric basis for several particle sampling conventions used to quantify airborne PM concentrations. The U.S. EPA has size-selective sampling conventions for fine particles indicated by $PM_{2.5}$ and PM_{10} as an indicator for the purposes of regulating the thoracic coarse particles (i.e., the inhalable particles that remain if $PM_{2.5}$ particles are removed from a sample of PM_{10}; aka $PM_{10–2.5}$). $PM_{2.5}$ is not well representative [nor was it intended to be] of the occupational definition of respirable particles which has a 50% cut-point at 4 µm versus 2.5 µm for the $PM_{2.5}$ sampler (Figure 4-2). The selection of $PM_{2.5}$ for the NAAQS was mainly to delineate the atmospheric fine (combustion derived, aggregates, acid condensates, secondary aerosols) and coarse (crustal, soil-derived dusts) PM modes and for consistency with community epidemiologic health studies reporting various health effects associated with $PM_{2.5}$ but not on dosimetric considerations as was the case for the respirable particle sampler convention. Although

the respirable sampling convention has a dosimetric basis, it is reflective of the total PM mass concentration to which the alveolar region may be exposed not the PM mass deposition or dose. PM_{10} is often referred to as the thoracic fraction of inhalable particles and there is an occupational sampling convention for thoracic particles both of which have a 50% cut-point at about 10 µm (Figure 4-2). However, it should be recognized that the fraction of inhaled 10 µm particles reaching the thorax is <20% for most activity levels and breathing habits. Breathing completely through the mouth, fraction of inhaled 10 µm particles reaching the thorax approaches 40%. Thus, using a 50% cut-point at 10 µm provides a conservative (protective) overestimate of thoracic particles.

1.4 Evaluation of the Health Effects of PM

This ISA evaluates relationships between an array of health effects and short-term and long-term exposures to PM (i.e., $PM_{2.5}$, $PM_{10–2.5}$, and UFPs) in epidemiologic, controlled human exposure, and animal toxicological studies. In assessing the overall evidence, strengths and limitations of individual studies were evaluated based on scientific considerations detailed in the Appendix. Short-term exposures are defined as those with durations of hours up to one month, with most studies examining effects related to exposures in the range of 24 hours to 1 week. Long-term exposures are defined as those with durations of more than 1 month to years. As detailed in the Preface, the evaluation of the health effects evidence focuses on exposures conducted at concentrations of PM that are relevant to the range of human exposures across ambient microenvironments (up to 2 mg/m^3, which is one to two orders of magnitude above ambient concentrations), and (1) include a composite measure of PM[36] or (2) apply some approach to assess the direct effect of a specific PM size-fraction when the exposure of interest is a source-based mixture (e.g., diesel exhaust, gasoline exhaust, wood smoke). Drawing from evidence related to the biological plausibility of PM-related health effects and the broader health effects evidence described in detail in Chapters 5−11, information on dosimetry in CHAPTER 4 and Section 1.4, as well as issues regarding exposure assessment and potential confounding described in CHAPTER 3 and Section 1.3, the subsequent sections and accompanying table (Table 1-2) summarize the key evidence that informed the causality determinations for relationships between PM exposure and health effects, specifically those relationships where a "*causal*" or "*likely to be causal*" relationship has been concluded (Table 1-1). Those relationships between PM and health effects where a "*suggestive of, but not sufficient to infer*" or "*inadequate*" causality determination has been concluded are noted in Table 1-7, but more fully discussed in the respective health effects chapters.

[36] Composite measures of PM may include mass, volume, surface area, or number concentration.

Table 1-1 "Causal" and "likely to be causal" causality determinations for short- and long-term PM exposure.

Size Fraction	Health Effects Category	Exposure Duration	Causality Determination	Section
$PM_{2.5}$	Respiratory	Short-term	Likely to be causal	1.4.1.1.1
		Long-term	Likely to be causal	1.4.1.1.2
	Cardiovascular	Short-term	Causal	1.4.1.2.1
		Long-term	Causal	1.4.1.2.2
	Nervous System	Long-term	Likely to be causal	1.4.1.3.1
	Cancer	Long-term	Likely to be causal	1.4.1.4.1
	Mortality	Short-term	Causal	1.4.1.5.1
		Long-term	Causal	1.4.1.5.2
UFP	Nervous System	Long-term	Likely to be causal	1.4.3.1

1.4.1 Health Effects of $PM_{2.5}$

Substantial scientific evidence exists across disciplines (i.e., animal toxicology, controlled human exposure, and epidemiology), with additional support from studies examining biological plausibility, showing that both short- and long-term $PM_{2.5}$ exposure can result in a range of health effects, from changes in circulating biomarkers to mortality. However, the overall confidence in the $PM_{2.5}$ exposure – health effects relationship varies depending on the exposure duration (i.e., short- or long-term) and broad health category (e.g., cardiovascular effects, respiratory effects) examined. Across the broad health effects categories examined, the evidence supporting biological plausibility varies, but generally includes modulation of the autonomic nervous system and inflammation as part of the pathways leading to overt health effects. Discussions of subsequent events that could occur due to deposition of inhaled $PM_{2.5}$ in the respiratory tract are detailed in the biological plausibility sections of each health chapter and summarized in the following sections when detailing the health effects evidence.

1.4.1.1 Respiratory Effects

Recent scientific evidence continues to support a "*likely to be causal relationship*" between both short- and long-term $PM_{2.5}$ exposure and respiratory effects, which is consistent with the conclusions of

the 2009 PM ISA. These causality determinations are based on the consistency of findings within disciplines, coherence among evidence from controlled human exposure, epidemiologic, and toxicological studies, and biological plausibility for respiratory effects, such as asthma exacerbation, development of asthma, COPD exacerbation, and respiratory mortality.

1.4.1.1.1 Respiratory Effects Associated with Short-Term $PM_{2.5}$ Exposure

Epidemiologic studies provide strong evidence for overt respiratory effects, including respiratory-related emergency department visits and hospital admissions and respiratory mortality due to short-term $PM_{2.5}$ exposure, but there is more limited evidence of respiratory effects from experimental studies to provide coherence. Collectively this evidence supports a "*likely to be causal relationship*" between short-term $PM_{2.5}$ exposure and respiratory effects, which is consistent with the conclusions of the 2009 PM ISA (Table 1-2). This conclusion is based on multiple recent epidemiologic studies demonstrating generally consistent, positive associations with emergency department visits for asthma and combined respiratory-related diseases, as well as with respiratory mortality. Evidence from animal toxicological studies, although limited, is supportive of and provides biological plausibility for the associations observed in the epidemiologic studies.

Recent epidemiologic studies continue to provide strong evidence for a relationship between short-term $PM_{2.5}$ exposure and several respiratory-related endpoints, including asthma exacerbation (Section 5.1.2.1), COPD exacerbation (Section 5.1.4.1), and combined respiratory-related diseases (Section 5.1.6), particularly from studies examining emergency department visits and hospital admissions. The consistent positive associations between short-term $PM_{2.5}$ exposure and asthma and COPD emergency department visits and hospital admissions are supported by epidemiologic studies demonstrating associations with other respiratory-related effects such as symptoms and medication use that are indicative of asthma and COPD exacerbations (Section 5.1.2.2 and Section 5.1.4.2). The collective body of epidemiologic evidence for asthma exacerbation is more consistent in children than in adults. Epidemiologic studies examining the relationship between short-term $PM_{2.5}$ exposure and respiratory mortality provide evidence of consistent positive associations, demonstrating a continuum of effects (Section 5.1.9).

Building off the studies evaluated in the 2009 PM ISA, recent epidemiologic studies expand the assessment of potential copollutant confounding. There is some evidence that $PM_{2.5}$ associations with asthma exacerbation, combined respiratory-related diseases, and respiratory mortality remain relatively unchanged in copollutant models with gaseous pollutants (i.e., O_3, NO_2, SO_2, with more limited evidence for CO) and other particle sizes (i.e., $PM_{10–2.5}$) (Section 5.1.10.1). The uncertainty related to whether there is an independent effect of $PM_{2.5}$ on respiratory health, is partially addressed by findings of animal toxicological studies. Specifically, short-term exposure to $PM_{2.5}$ enhanced asthma-related responses in an animal model of allergic airways disease and enhanced lung injury and inflammation in an animal model of COPD (Section 5.1.2.4.3 and Section 5.1.4.4.2). Although there is a broad body of experimental

evidence demonstrating respiratory effects due to short-term $PM_{2.5}$ exposure it is not entirely coherent with the results of epidemiologic studies. However, the experimental evidence does provide biological plausibility for some respiratory-related endpoints. This includes limited evidence of altered host defense and greater susceptibility to bacterial infection as well as consistent evidence of respiratory irritant effects. Animal toxicological evidence for other respiratory effects is inconsistent. Additionally, controlled human exposure studies conducted in people with asthma or COPD show minimal respiratory effects due to short-term $PM_{2.5}$ exposure, such as decrements in lung function and pulmonary inflammation.

1.4.1.1.2 Respiratory Effects Associated with Long-Term $PM_{2.5}$ Exposure

Epidemiologic studies provide strong evidence for effects on lung development, with additional evidence for the development of asthma in children due to long-term $PM_{2.5}$ exposure. Evidence from animal toxicological studies, although limited in number, supports the findings of these epidemiologic studies. There is also epidemiologic evidence for a decline in lung function in adults. Collectively this evidence supports a "*likely to be causal relationship*" between long-term $PM_{2.5}$ exposure and respiratory effects, which is consistent with the conclusions of the 2009 PM ISA (Table 1-2).

Recent epidemiologic studies continue to support an association between long-term $PM_{2.5}$ exposure and several respiratory-related endpoints in children and adults. In children, studies in multiple cohorts provide strong evidence for decrements in lung function growth (Section 5.2.2.1.1). Robust and persistent effects were observed across study locations, exposure assessment methods, and time periods. An animal toxicological study demonstrating impaired lung development resulting from pre- and post-natal $PM_{2.5}$ exposure provides biological plausibility for these findings (Section 5.2.2.1.2). Results of prospective cohort studies in children also provide some evidence for asthma development in children, and are supported by studies of asthma prevalence in children, childhood wheeze, and pulmonary inflammation (Section 5.2.3). Biological plausibility is provided by an animal toxicological study of long-term $PM_{2.5}$ exposure demonstrating the development of an allergic phenotype and increase in airway responsiveness (Section 5.2.3.3.2). There is limited evidence of increased bronchitic symptoms and hospitalization in children with asthma in relation to long-term $PM_{2.5}$ exposure (Section 5.2.7). In adults, long-term $PM_{2.5}$ exposure was associated with an acceleration of lung function decline (Section 5.2.2.2.2). Consistent evidence was observed for respiratory mortality and cause-specific respiratory mortality for COPD and infection (Section 5.2.10), providing evidence of a continuum of effects in response to long-term $PM_{2.5}$ exposure.

Although still limited in number, recent epidemiologic studies further examine potential copollutant confounding. There is some evidence that $PM_{2.5}$ associations with respiratory mortality remained robust in models with some gaseous pollutants (Section 5.2.10); however, there is limited assessment of potential copollutant confounding when examining respiratory morbidity outcomes. The uncertainty related to the independence of $PM_{2.5}$ effects is partially addressed by findings of animal

toxicological studies. Long-term exposure to $PM_{2.5}$ resulted in oxidative stress, inflammation, and morphologic changes in both upper and lower airways (Section 5.2.8), in addition to the asthma-related and lung development-related effects mentioned above. Epidemiologic studies examining the effects of declining $PM_{2.5}$ concentrations provide additional support for a relationship between long-term $PM_{2.5}$ exposure and respiratory health by demonstrating improvements in lung function growth and bronchitic symptoms in children and improvement in lung function in adults in association with declining $PM_{2.5}$ concentrations (Section 5.2.11). However, the limited examination of copollutant confounding in studies of declining $PM_{2.5}$ concentrations is a notable uncertainty given the corresponding decline in other pollutants over the time-period of the evaluated studies.

1.4.1.2 Cardiovascular Effects

Consistent with the conclusions of the 2009 PM ISA, more recently published scientific evidence further strengthens that there is a "*causal relationship*" between both short- and long-term $PM_{2.5}$ exposure and cardiovascular effects. These causality determinations are based on the consistency of findings within disciplines, coherence among evidence from controlled human exposure, epidemiologic, and toxicological studies, and biological plausibility for cardiovascular effects, such as reduced myocardial blood flow, altered vascular reactivity, myocardial infarctions, and cardiovascular mortality.

1.4.1.2.1 Cardiovascular Effects Associated with Short-Term $PM_{2.5}$ Exposure

Strong evidence from epidemiologic studies demonstrating associations between cardiovascular emergency department visits and hospital admissions in combination with evidence for $PM_{2.5}$-induced cardiovascular effects from controlled human exposure and animal toxicological studies confirms and extends the conclusion of a "*causal relationship*" between short-term $PM_{2.5}$ exposure and cardiovascular effects from the 2009 PM ISA (Table 1-2). This conclusion is based on multiple high-quality epidemiologic studies demonstrating associations with cardiovascular effects such as ischemic heart disease (IHD) and heart failure (HF) related emergency department visits and hospital admissions, as well as cardiovascular mortality. The epidemiologic evidence is primarily supported by experimental studies demonstrating endothelial dysfunction, changes in blood pressure, and alterations in heart function in response to short-term $PM_{2.5}$ exposure. Additional evidence from epidemiologic, controlled human exposure, and animal toxicological studies also provides ample evidence of biologically plausible pathways by which short-term exposure to $PM_{2.5}$ can result in overt cardiovascular effects.

Consistent with the 2009 PM ISA, the strongest evidence comes from epidemiologic studies that reported consistent positive associations between short-term $PM_{2.5}$ exposure and cardiovascular-related emergency department visits and hospital admissions particularly for IHD and HF, as well as cardiovascular-related mortality. While the evidence is generally consistent across the copollutants

evaluated, the evidence was especially consistent for air pollutants that are not typically associated with traffic (i.e., ozone, SO_2, $PM_{10–2.5}$). In some instances, associations in copollutant models were attenuated, but this was only observed for the traffic-related pollutants (i.e., NO_2, CO), which generally had higher correlations with $PM_{2.5}$ than other copollutants. This recent evidence generally indicates that the associations observed with $PM_{2.5}$ and cardiovascular effects in single pollutant models remain relatively unchanged in copollutant models, indicating that the observed associations with $PM_{2.5}$ are not artefacts due to confounding by another air pollutant (Section 6.1.14.1). These epidemiologic studies reduce a key uncertainty identified in the 2009 PM ISA by providing evidence that gaseous pollutants are not likely to confound the $PM_{2.5}$-cardiovascular relationship.

The independence of $PM_{2.5}$ effects is further addressed by findings of recent controlled human exposure and animal toxicological studies. The most consistent evidence from controlled human exposure studies is for a $PM_{2.5}$ effect on endothelial function. More specifically, in contrast to the previous review where a single controlled human exposure study did not find changes in endothelial function following short-term $PM_{2.5}$ exposure, multiple recent controlled human exposure studies that examined endothelial function reported that $PM_{2.5}$ impaired at least some measure of vessel dilation following reactive hyperemia or pharmacological challenge relative to filtered air exposure. Given the relationship between endothelial function and blood pressure, these results are coherent with controlled human exposure studies that reported changes in blood pressure following short-term $PM_{2.5}$ exposure. The results of these controlled human exposure studies are also coherent with evidence from animal toxicological studies demonstrating endothelial dysfunction and changes in blood pressure or the renin angiotensin system following short-term $PM_{2.5}$ exposure. Moreover, changes in endothelial function and blood pressure reported in experimental studies are consistent with time-series and case-crossover epidemiologic studies reporting associations between short-term $PM_{2.5}$ exposure and IHD, as well as with limited epidemiologic panel study evidence of associations with blood pressure. In addition, animal toxicological studies demonstrating that short-term $PM_{2.5}$ exposure results in decreased cardiac contractility and left ventricular pressure are coherent with epidemiologic studies reporting associations between short-term $PM_{2.5}$ exposure and HF.

Collectively, the evidence from controlled human exposure, animal toxicological and epidemiologic panel studies provide a biologically plausible pathway by which short-term $PM_{2.5}$ exposure could result in cardiovascular effects such as an emergency department visits, hospital admission, or mortality. This proposed pathway (Section 6.1.1) begins with pulmonary inflammation and/or activation of sensory nerves in the respiratory track. It progresses to autonomic nervous system imbalance and/or systemic inflammation that can potentially affect cardiovascular endpoints such as endothelial function, HRV, hemostasis, and/or BP. Changes in the aforementioned cardiovascular endpoints may then lead to the development of arrhythmia, thrombosis, and/or acute myocardial ischemia, potentially resulting in outcomes such as myocardial infarction, IHD, HF, and possibly death.

Overall, across the scientific disciplines, recent studies extend and support the previous evidence for a continuum of cardiovascular-related health effects following short-term exposure to $PM_{2.5}$. These effects range from relatively modest increases in biomarkers related to inflammation, to subclinical cardiovascular endpoints such as endothelial dysfunction, the overt outcomes of emergency department visits and hospital admissions, specifically for IHD and HF, and ultimately cardiovascular-related mortality.

1.4.1.2.2 Cardiovascular Effects Associated with Long-Term $PM_{2.5}$ Exposure

Multiple recent and previously available epidemiologic studies that extensively control for potential confounders provide strong evidence of positive associations with cardiovascular mortality, which in combination with supporting evidence from recent studies examining cardiovascular morbidity reaffirms the conclusion of a "*causal relationship*" between long-term $PM_{2.5}$ exposure and cardiovascular effects in the 2009 PM ISA (Table 1-2). This conclusion is based on recent U.S. and Canadian cohort studies demonstrating consistent, positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality with more limited evidence from studies examining long-term $PM_{2.5}$ exposure and cardiovascular morbidity.

Epidemiologic studies consisting of U.S.-based cohorts and subsequent analyses of these cohorts, provided the basis of the conclusions in the 2009 PM ISA. These studies in combination with recent cohort studies, continue to demonstrate consistent, positive associations and support a strong relationship between long-term $PM_{2.5}$ exposure and cardiovascular mortality. The results of these recent cohort studies are consistent across various spatial extents, exposure assessment techniques, and statistical techniques in locations where mean annual average concentrations are near or below 12 $\mu g/m^3$ (Section 6.2.10).

The body of literature examining the relationship between long-term $PM_{2.5}$ exposure and cardiovascular morbidity has greatly expanded since the 2009 PM ISA. Recent epidemiologic studies examining cardiovascular morbidity endpoints consist of several large U.S. cohort studies each focusing on populations with distinct demographic characteristics (e.g., post-menopausal woman, male doctors, etc.) and extensive consideration of potential confounders. These studies have reported heterogeneous results, with several high-quality studies that adjusted for important covariates, including socioeconomic status (SES), reporting positive associations for cardiovascular morbidity endpoints. The strong associations reported between long-term $PM_{2.5}$ exposure and coronary events (e.g., coronary heart disease [CHD] and stroke) among post-menopausal women in the Women's Health Initiative (WHI) cohort, highlighted in 2009 PM ISA, were strengthened in an extended analysis that considered individual and neighborhood level SES. Recent analyses of other cohorts of women (i.e., Nurses' Health Study, California Teachers Study) that were comparable to WHI in that they considered menopausal status or hormone replacement therapy did not show consistent positive associations with CHD, myocardial infarction or stroke. Longitudinal studies demonstrated that changes in the progression of atherosclerosis

in relation to long-term exposure to $PM_{2.5}$ were variable across cohorts and found to depend, in part, on the vascular bed in which atherosclerosis was evaluated. However, within a study focusing on the progression of atherosclerosis in a healthy population, i.e., Multi-Ethnic Study of Arthrosclerosis and Air Pollution (MESA-Air), an association was observed between long-term $PM_{2.5}$ exposure and coronary artery calcification (CAC), which is a strong predictor of CHD (Section 6.3.4). A small number of studies report positive associations between long-term $PM_{2.5}$ exposure and HF, blood pressure and hypertension. Longitudinal epidemiologic analyses also support the observation of positive associations with markers of systemic inflammation, coagulation and endothelial dysfunction. These HF studies are coherent with animal toxicological studies demonstrating decreased contractility and cardiac output, and increased coronary artery wall thickness following long-term $PM_{2.5}$ exposure (Section 6.2.4.2). Moreover, animal toxicological studies finding a relationship between long-term exposure to $PM_{2.5}$ and changes in BP in rats and mice are coherent with epidemiologic studies reporting positive associations between long-term exposure to $PM_{2.5}$ and hypertension. Similarly, evidence of atherosclerotic plaque progression in a genetically susceptible mouse model is consistent with epidemiologic studies reporting associations between atherosclerosis and long-term $PM_{2.5}$ exposure.

The current body of evidence also reduces uncertainties identified in the 2009 PM ISA related to potential copollutant confounding and the shape of the concentration-response relationship for CVD effects following long-term $PM_{2.5}$ exposure. Generally, most of the $PM_{2.5}$ effect estimates relating long-term $PM_{2.5}$ exposure and cardiovascular mortality remained relatively unchanged or increased in copollutant models adjusted for O_3, NO_2, SO_2, and $PM_{10-2.5}$ (Section 6.2.15). In addition, most of the results from analyses examining the C-R function for cardiovascular mortality supported a linear, no-threshold relationship for cardiovascular mortality, especially at mean annual $PM_{2.5}$ concentrations ≤ 12 $\mu g/m^3$ (Section 6.2.10). Some studies reported that the slope of the concentration-response function tended to be steeper at lower concentrations, especially for IHD mortality, suggesting a supralinear concentration-response relationship. A limited number of cardiovascular morbidity studies examined the shape of the concentration-response relationship and generally reported steeper concentration-response functions at lower concentrations (starting at ~10 $\mu g/m^3$) with the slope of the concentration-response function decreasing at higher $PM_{2.5}$ concentrations (Section 6.2.16).

Evidence from animal toxicological and epidemiologic studies also provide biologically plausible pathways by which long-term $PM_{2.5}$ exposure could lead to cardiovascular effect such as CHD, stroke, and CVD-related mortality (Section 6.2.1). These pathways initially involve autonomic nervous system changes and/or systemic inflammation that can potentially effect endpoints related to vascular function, altered hemostasis, hypertension, atherosclerotic plaque progression, and arrhythmia. Changes in cardiovascular endpoints such as these may then lead to IHD, HF, and possibly death.

Overall, there is consistent evidence from multiple, high-quality epidemiologic studies that long-term exposure to $PM_{2.5}$ is associated with cardiovascular mortality. Associations with CHD, stroke and atherosclerosis progression were observed in several recent high-quality epidemiologic studies

providing coherence with the mortality findings. Results from copollutant models generally support the independence of the $PM_{2.5}$ associations. Additional evidence of the direct effect of $PM_{2.5}$ on the cardiovascular system is provided by experimental studies in animals demonstrating effects including atherosclerosis plaque progression, changes in cardiac contractility and BP.

1.4.1.3 Nervous System Effects

1.4.1.3.1 Nervous System Effects Associated with Long-Term $PM_{2.5}$ Exposure

The 2009 PM ISA evaluated a small number of experimental animal studies pertaining to the effects of long-term exposures to $PM_{2.5}$ on the nervous system. The literature base has greatly expanded with recent studies providing new information that strengthens the lines of evidence indicating that long-term $PM_{2.5}$ exposure can lead to effects on the brain associated with neurodegeneration (i.e., neuroinflammation and reductions in brain volume), as well as cognitive effects in older adults (Table 1-2). Specifically, animal toxicological studies provide evidence for a range of nervous system effects including neuroinflammation and oxidative stress, neurodegeneration, cognitive effects, and effects on neurodevelopment. The epidemiologic evidence is more limited but multiple studies generally support associations between long-term $PM_{2.5}$ exposure and changes in brain morphology, cognitive decrements and dementia. The consistency and coherence of the evidence across disciplines as it relates to region-specific brain inflammation, morphologic changes in the brain, cognitive effects and dementia in adult populations supports that there is a "*likely to be causal relationship*" between long-term $PM_{2.5}$ exposure and nervous system effects, which is the first time a causality determination has been made for long-term $PM_{2.5}$ exposure and nervous system effects.

There is strong evidence that long-term exposure to $PM_{2.5}$ can modulate the autonomic nervous system leading to downstream consequences including cardiovascular effects (Section 6.2.1). In addition, the pathway involving neuroinflammation in specific regions of the brain (i.e., the hippocampus, cerebral cortex and hypothalamus) and morphologic changes in the brain indicative of neurodegeneration, is well substantiated and coherent across experimental animal and epidemiologic studies (Section 8.2.3, Section 8.2.4). Specifically, morphologic changes induced in the hippocampus of animals were accompanied by impaired learning and memory and there is consistent evidence from multiple, high quality, epidemiologic studies that long-term $PM_{2.5}$ exposure is associated with reduced cognitive function (Section 8.2.5). Further, the presence of early markers of Alzheimer's disease pathology was demonstrated in animals following long-term exposure to $PM_{2.5}$ CAPs and associations with neurodegenerative changes in the brain (i.e., decreased brain volume) and Alzheimer's disease or all-cause dementia were observed in a limited number of epidemiologic studies (Section 8.2.6). Although the loss of dopaminergic neurons in the substantia nigra, which is a hallmark of Parkinson disease, was demonstrated in animals (Section 8.2.4), high quality epidemiologic studies do not report associations

with Parkinson disease (Section 8.2.6. Overall, the lack of consideration of copollutant confounding introduces some uncertainty in the interpretation of the epidemiologic studies but this uncertainty is addressed, in part, by the direct evidence of effects provided by experimental animal studies.

In addition to the findings described above, which are most relevant to adults, several recent studies of neurodevelopmental effects in children have also been conducted. Positive associations between long-term exposure to $PM_{2.5}$ during the prenatal period and autism spectrum disorder (ASD) were consistently observed across multiple epidemiologic studies (Section 8.2.7.2). However, several studies of performance on tests of cognitive function provided little support for an association. Overall, these epidemiologic studies of developmental effects are limited due to their lack of control for potential confounding by copollutants, the small number of studies, and uncertainty regarding critical exposure windows. Biological plausibility is provided for the ASD findings, by a study in animals that found inflammatory and morphologic changes in the corpus collosum and hippocampus, as well as ventriculomegaly in young animals following prenatal exposure to $PM_{2.5}$ CAPs.

1.4.1.4 Cancer

1.4.1.4.1 Cancer Associated with Long-Term $PM_{2.5}$ Exposure

Experimental and epidemiologic evidence indicating genotoxicity, epigenetic effects (i.e., hypo- and hyper-methylation of DNA), and increased carcinogenic potential due to $PM_{2.5}$ exposure, along with strong epidemiologic evidence for increases in lung cancer incidence and mortality, supports a "*likely to be causal relationship*" between long-term $PM_{2.5}$ exposure and cancer (Table 1-2). This causality determination represents a change from the "*suggestive of a causal relationship*"[37] determination reported in the 2009 PM ISA. The evidence base underlying this conclusion encompasses the decades of research on whole PM exposures and more recent research focusing specifically on $PM_{2.5}$.

$PM_{2.5}$ exhibits various characteristics of carcinogens, as shown in studies demonstrating genotoxic effects (e.g., DNA damage), epigenetic alterations, oxidative stress, and electrophilicity. The examination of the role of $PM_{2.5}$ in cancer development has often focused on whether whole PM, not specific size fractions, has mutagenic properties and whether exposure to whole PM results in genotoxicity or carcinogenicity. Additionally, it has been well characterized that some components of $PM_{2.5}$, specifically hexavalent chromium, nickel, arsenic, and PAHs are known human carcinogens. Extensive analyses of $PM_{2.5}$ and $PM_{2.5}$ extracts in the Ames *Salmonella*/mammalian-microsome mutagenicity assay demonstrate that PM contains mutagenic agents (Section 10.2.2.1). Additional in vitro and in vivo toxicological studies indicate the potential for $PM_{2.5}$ exposure to result in DNA damage,

[37] Since the 2009 PM ISA, the causality determination language has been updated and this category is now stated as "*suggestive of, but not sufficient to infer, a causal relationship*".

which is supported by limited human evidence (Section 10.2.2.2). Some studies have also demonstrated that $PM_{2.5}$ exposure can result in cytogenetic effects, specifically micronuclei formation and chromosomal aberrations (Section 10.2.2.3), as well as differential expression of genes potentially relevant to genotoxicity or other aspects of cancer pathogenesis (Section 10.2.2.4). Although inconsistently examined across studies, changes in cellular and molecular markers of genotoxicity and epigenetic alterations, which may lead to genomic instability, are demonstrated in response to $PM_{2.5}$ exposure. Further, the carcinogenic potential of $PM_{2.5}$ was demonstrated in an animal toxicological study in which chronic inhalation enhanced tumor formation that was initiated by exposure to urethane. (Section 10.2.4). Additionally, recent epidemiologic studies encompassing multiple cohorts that are diverse in terms of both geographic coverage and population characteristics, provide evidence of primarily consistent positive associations between long-term $PM_{2.5}$ exposure and lung cancer incidence and mortality, particularly in never smokers (Section 10.2.5.1). Experimental and epidemiologic evidence of genotoxicity, epigenetic effects, and carcinogenic potential provides biological plausibility for epidemiologic results of lung cancer incidence and mortality. Although limited in number, the assessment of potential copollutant confounding, particularly with O_3, indicates that $PM_{2.5}$ associations with lung cancer incidence and mortality are relatively unchanged in copollutant models (Section 10.2.5.1.3). There is limited evidence that long-term $PM_{2.5}$ exposure is associated with cancers in other organ systems; however, there is initial evidence that $PM_{2.5}$ exposure may reduce survival in individuals with cancer.

1.4.1.5 Mortality

Consistent with the conclusions of the 2009 PM ISA, more recently published scientific evidence reaffirms and further strengthens that there is a "*causal relationship*" between both short- and long-term $PM_{2.5}$ exposure and total mortality. These causality determinations are based on the consistency of findings across a large body of epidemiologic studies and coherence among evidence from controlled human exposure, epidemiologic, and toxicological studies, as well as biological plausibility for respiratory and cardiovascular morbidity effects by which short- and long-term $PM_{2.5}$ exposure could result in mortality.

1.4.1.5.1 Mortality Associated with Short-Term $PM_{2.5}$ Exposure

Strong recent and previously available epidemiologic evidence, in combination with evidence for biological plausibility for cause-specific mortality from studies that examined the relationship between short-term $PM_{2.5}$ exposure and cardiovascular and respiratory morbidity, collectively indicates there is a "*causal relationship*" between short-term $PM_{2.5}$ exposure and total (nonaccidental) mortality, which is consistent with the conclusions of the 2009 PM ISA (Table 1-2). This conclusion is based on multiple recent multi-city studies conducted in the U.S., Canada, Europe, and Asia that continue to provide evidence of consistent, positive associations between short-term $PM_{2.5}$ and total mortality, as well as

epidemiologic studies that use study design and/or statistical analyses that further reduce chance, confounding, and other biases.

Recent multi-city studies add to the body of evidence evaluated in the 2009 PM ISA and continue to support a positive association between short-term $PM_{2.5}$ exposure and total mortality with percentage increases in mortality ranging from 0.19−2.80% at lags of 0 to 1 day in studies where mean 24-hour average concentrations were primarily <20 $\mu g/m^3$ (Figure 11-1; Table 11-1). The positive associations observed across studies reflect traditional analyses using ambient monitors as well as analyses conducted in both urban and rural locations that use new exposure assignment techniques and rely on multiple sources of $PM_{2.5}$ data (e.g., ambient monitors, statistical models, and satellite images). Whereas the analysis of potential copollutant confounding was limited to single-city studies and studies of PM_{10} in the 2009 PM ISA, recent multi-city studies conducted in Europe and Asia focusing on $PM_{2.5}$ indicate that $PM_{2.5}$-mortality associations are relatively unchanged in copollutant models with gaseous pollutants and $PM_{10-2.5}$ (Section 11.1.4). These results from copollutant models further support an independent effect of $PM_{2.5}$ on mortality. The associations reported for total mortality are also supported by analyses demonstrating increases in cause-specific mortality, specifically for cardiovascular and respiratory mortality which comprise ~33 and ~9%, respectively, of total mortality (NHLBI, 2017) (Figure 11-2). The consistent and coherent evidence across scientific disciplines for cardiovascular morbidity, particularly ischemic events and heart failure (CHAPTER 6), and to a lesser degree for respiratory morbidity, with the strongest evidence for exacerbations of COPD and asthma (CHAPTER 5), provide biological plausibility for cause-specific mortality and ultimately total mortality. The relationship between short-term $PM_{2.5}$ exposure and total mortality is additionally supported by analyses that examined the concentration-response (C-R) relationship that continue to provide evidence of a linear, no-threshold relationship, although studies have not conducted extensive systematic evaluations of alternatives to linearity (Section 11.1.10).

1.4.1.5.2 Mortality Associated with Long-Term $PM_{2.5}$ Exposure

Strong recent and previously available epidemiologic evidence from cohorts in the U.S., Canada, and Europe demonstrates that there is a "*causal relationship*" between long-term $PM_{2.5}$ exposure and total mortality, which is consistent with the conclusions of the 2009 PM ISA (Table 1-2). This conclusion is based on multiple cohorts that continue to provide evidence of consistent, positive associations, as well as continued characterization of the relationship between long-term $PM_{2.5}$ exposure and total (nonaccidental) mortality through analyses that further reduce chance, confounding, and other biases. Additional evidence indicating coherence of effects across scientific disciplines for cardiovascular and respiratory morbidity and metabolic disease provides biological plausibility for cause-specific mortality, and supports the causal relationship with total mortality.

Additional reanalyses and extensions of the American Cancer Society (ACS) and Harvard Six Cities (HSC) cohorts as well as new cohorts consisting of Medicare participants, people that live in

Canada, or people employed in a specific job (e.g., teacher, nurse, etc.) further support a positive association between long-term $PM_{2.5}$ exposure and total mortality, particularly in areas with annual mean concentrations <20 μg/m^3, and in some cases below 12 μg/m^3 (Figure 11-17 and Figure 11-18). Across studies, positive associations were consistently observed regardless of the exposure assignment approach employed, with some studies relying on ambient monitors while others used modeled or remote sensing data or hybrid methods that combine two or more data sources. Recent studies have conducted analyses to examine potential copollutant confounding and indicate that associations between long-term $PM_{2.5}$ exposure and total mortality are relatively unchanged in copollutant models particularly with O_3, with more limited evidence for NO_2, and $PM_{10-2.5}$ (Section 11.2.3; Figure 11-20, Figure 11-21). The evidence for total mortality is further supported by analyses of cause-specific mortality, which report positive associations with cardiovascular, respiratory, and lung cancer mortality. The coherence of effects across scientific disciplines for cardiovascular morbidity, particularly for CHD, stroke and atherosclerosis, and respiratory morbidity for the development of COPD, contribute to providing biological plausibility for mortality due to long-term $PM_{2.5}$ exposure. Recent studies extensively examined the C-R relationship between long-term $PM_{2.5}$ exposure and total mortality, specifically in several U.S. and Canadian cohorts, and collectively continue to support a linear, no-threshold C-R relationship (Section 11.2.4; Table 11-7).

A recent series of studies evaluates the relationship between long-term exposure to $PM_{2.5}$ and mortality by examining the temporal trends in $PM_{2.5}$ concentrations and changes in life expectancy, testing the hypothesis that decreases in $PM_{2.5}$ concentrations would be associated with increases in life expectancy (Section 11.2.2.6). These studies reported that decreases in long-term $PM_{2.5}$ concentrations were associated with an increase in life expectancy across the U.S. for multiple time periods examined.

Table 1-2 Key Evidence contributing to "causal" and "likely to be causal" causality determinations for $PM_{2.5}$ exposure and health effects evaluated in the current draft Integrated Science Assessment for Particulate Matter.

Key Evidence	Health Effect Category[a] and Causality Determination	$PM_{2.5}$ Concentrations Associated with Effects
Respiratory Effects and Short-Term $PM_{2.5}$ Exposure (Section 5.1.12): Likely to be Causal Relationship *No change in causality determination from the 2009 PM ISA; new evidence further supports the previous determination.*		
Section 5.1.12 Table 5-18	Epidemiologic evidence, consisting mainly of hospital admissions and emergency department visits, strongly supports a relationship with asthma exacerbation, COPD exacerbation, and combinations of respiratory-related diseases. Evidence for associations with respiratory symptoms and medication use are coherent with other findings for asthma exacerbation and COPD exacerbation. Some epidemiologic studies examined copollutant confounding and reported that results are robust in models with gaseous pollutants (i.e., O_3, NO_2, SO_2, and with more limited evidence for CO) and other particle sizes (i.e., $PM_{10-2.5}$), especially for asthma exacerbation, aggregated respiratory conditions, and respiratory mortality. There is a large body of experimental evidence, some of which is coherent with epidemiologic study results, demonstrating respiratory effects due to short-term $PM_{2.5}$ exposure. These experimental studies provide evidence for biologically plausible pathways by which $PM_{2.5}$ exposure can impart a respiratory effect. Specifically, animal toxicological studies provide biological plausibility for asthma exacerbation, COPD exacerbation and respiratory infection and some evidence of an independent effect of $PM_{2.5}$ on respiratory endpoints. Controlled human exposure studies provide minimal evidence of respiratory effects, specifically decrements in lung function and pulmonary inflammation. Consistent positive associations with respiratory mortality provide evidence of a continuum of effects.	Mean ambient concentrations from epidemiologic studies for: *Hospital Admissions and Emergency Department Visits for Asthma, COPD, Respiratory Infections and Combinations of Respiratory-related Diseases:* U.S. and Canada: 4.7−24. 6 μg/m³ Europe: 8.8−27.7 μg/m³ Asia: 11.8−69.9 μg/m³ *Respiratory mortality:* U.S. and Canada: 7.9−19.9 μg/m³ Europe: 8.0−27.7 μg/m³ Asia: 11.8−69.9 μg/m³ Concentrations from animal toxicological studies for: *Allergic airway disease:* 442−596 μg/m³

Table 1-2 (Continued): Key Evidence contributing to "causal" and "likely to be causal" causality determinations for $PM_{2.5}$ exposure and health effects evaluated in the current draft Integrated Science Assessment for Particulate Matter.

Key Evidence	Health Effect Category[a] and Causality Determination	$PM_{2.5}$ Concentrations Associated with Effects
Section 5.1.12 Table 5-18 (continued)		*COPD:* 171−1,200 µg/m³ *Altered host defense:* 100−350 µg/m³
Respiratory Effects and Long-Term $PM_{2.5}$ Exposure (Section 5.2.13): Likely to be Causal Relationship *No change in causality determination from the 2009 PM ISA; new evidence further supports the previous determination.*		
Section 5.2.13 Table 5-28	Epidemiologic evidence strongly supports a relationship with decrements in lung function growth in children. Additional epidemiologic evidence supports a relationship with asthma development in children, with increased bronchitic symptoms in children with asthma, with an acceleration of lung function decline in adults, and with respiratory mortality and cause-specific respiratory mortality for COPD and respiratory infection. Some epidemiologic studies examined copollutant confounding and reported that results are robust in models with O_3, NO_2, and CO, especially for respiratory mortality. There is limited experimental evidence for these respiratory effects due to long-term $PM_{2.5}$ exposure. However, animal toxicological studies provide biological plausibility for decrements in lung function and asthma development in children, and reduce uncertainty regarding the independent effect of $PM_{2.5}$ for these endpoints. Animal toxicological studies also provide evidence for a wide variety of other biological effects, such as oxidative stress, inflammation and morphologic changes. Epidemiologic studies examining the effects of declining $PM_{2.5}$ concentrations, strengthen the relationship between long-term $PM_{2.5}$ exposure and respiratory health by demonstrating improvements in lung function growth and reduced bronchitic symptoms in children and improved lung function in adults as a result of lower $PM_{2.5}$ concentrations. However, within these studies there is limited examination of copollutant confounding, which is a notable uncertainty due to the corresponding decline in concentrations of other pollutants.	Mean ambient concentrations from epidemiologic studies for: *Decrement in lung function growth:* 6–28 µg/m³ *Asthma development in children:* 5.2−16.5 µg/m³ *Bronchitic symptoms in children with asthma:* 9.9−13.8 µg/m³ *Accelerated lung function decline in adults:* 9.5−17.8 µg/m³ *Respiratory mortality:* 6.3−23.6 µg/m³ Concentrations from animal toxicological studies for: *Impaired lung development:* 16.8 µg/m³ *Development of allergic airway disease:* 100 µg/m³

Table 1-2 (Continued): Key Evidence contributing to "causal" and "likely to be causal" causality determinations for $PM_{2.5}$ exposure and health effects evaluated in the current draft Integrated Science Assessment for Particulate Matter.

Key Evidence	Health Effect Category[a] and Causality Determination	$PM_{2.5}$ Concentrations Associated with Effects
Cardiovascular Effects and Short-Term $PM_{2.5}$ Exposure (Section 6.1.16): Causal Relationship *No change in causality determination from the 2009 PM ISA; new evidence further supports the previous determination.*		
Section 6.1.16 Table 6-33	There is strong evidence for coherence of effects across scientific disciplines and biological plausibility for a range of cardiovascular effects in response to short-term $PM_{2.5}$ exposure. Consistent epidemiologic evidence from multiple, high-quality studies at relevant $PM_{2.5}$ concentrations provide evidence of increases in emergency department visits and hospital admissions for IHD and HF, as well as cardiovascular mortality in multi-city studies conducted in the U.S., Canada, Europe, and Asia. These associations remain positive, but in some cases are reduced with larger uncertainty estimates, in copollutant models with gaseous pollutants. Evidence from controlled human exposure studies provide coherent and consistent evidence for changes in various measures of endothelial dysfunction and generally consistent evidence of changes in blood pressure. These controlled human exposure studies are in agreement with animal toxicological studies also demonstrating endothelial dysfunction and changes in blood pressure or the renin angiotensin system. In addition, animal toxicological studies demonstrating that short-term $PM_{2.5}$ exposure results in decreased cardiac contractility and left ventricular pressure are coherent with epidemiologic studies reporting associations between short-term $PM_{2.5}$ exposure and HF.	Mean ambient concentrations from epidemiologic studies for: *IHD:* 5.8−18.6 μg/m³ *HF:* 5.8−18.0 μg/m^3 Concentrations from controlled human exposure studies: 24−325 μg/m^3 for 2 h Concentrations from animal toxicological studies: 178−190 μg/m^3

Table 1-2 (Continued): Key Evidence contributing to "causal" and "likely to be causal" causality determinations for $PM_{2.5}$ exposure and health effects evaluated in the current draft Integrated Science Assessment for Particulate Matter.

Key Evidence	Health Effect Category[a] and Causality Determination	$PM_{2.5}$ Concentrations Associated with Effects
Cardiovascular Effects and Long-Term $PM_{2.5}$ Exposure (Section 6.2.18): Causal Relationship *No change in causality determination from the 2009 PM ISA; new evidence further supports the previous determination.*		
Section 6.2.18 Table 6-52	Multiple high-quality epidemiologic studies continue to provide evidence of consistent, positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality at lower ambient concentrations. The cardiovascular mortality associations were observed across different exposure assignment and statistical methods, and were relatively unchanged in copollutant models with both gaseous (i.e., O_3, NO_2, SO_2) and particle (i.e., $PM_{10-2.5}$) pollutants. The evidence for cardiovascular mortality, is supported by a smaller body of epidemiologic studies that further explored associations between long-term $PM_{2.5}$ exposure and cardiovascular morbidity, and reported some evidence for increased risk of $PM_{2.5}$-related MI and stroke, specifically in individuals with a pre-existing cardiovascular disease or diabetes. Recent epidemiologic studies also present evidence for an effect of long-term $PM_{2.5}$ exposure on subclinical features of cardiovascular morbidity, particularly progression of atherosclerosis as reflected by associations with coronary artery calcification (CAC), with more limited evidence for other measures, such as carotid intima-media thickness (CIMT). Key evidence from long-term animal toxicological studies includes consistent evidence for changes in BP, as well as some evidence for decreases in measures of heart function (e.g., contractility and cardiac output) and cardiac remodeling. Moreover, as in the previous review, there is also some additional evidence for atherosclerotic plaque progression in a genetically susceptible mouse model.	Mean ambient concentrations from epidemiologic studies for: *Cardiovascular mortality*: 4.1−17.9 μg/m^3 *Coronary events*: 13.4 μg/m^3 *CAC*: 14.2 μg/m^3 *CHD and Stroke (in those with pre-existing disease)*: 13.4−23.9 μg/m^3 Concentrations from animal toxicological studies for: *Blood pressure*: 85−375 μg/m^3 (up to 15 weeks)
Nervous System Effects and Long-Term $PM_{2.5}$ Exposure (Section 8.2.9): Likely to be Causal Relationship *Not evaluated in the 2009 PM ISA; new evidence showing brain inflammation and oxidative stress, neurodegeneration, cognitive effects, and neurodevelopmental effects.*		
Section 8.2.9 Table 8-20	There is evidence that long-term exposure to $PM_{2.5}$ can modulate the autonomic nervous system leading to downstream consequences including cardiovascular effects (Section 6.2.1). A second pathway involving neuroinflammation and morphologic changes in the brain indicative of neurodegeneration, is well substantiated and coherent across experimental animal and epidemiologic studies. The evidence relating to Parkinson disease, and neurodevelopmental effects was more limited. Consideration of copollutant confounding was generally lacking in the epidemiologic studies but the uncertainty in the interpretation of study findings was addressed, in part, by the direct evidence of effects provided by experimental animal studies.	Mean annual concentrations from epidemiologic studies for: *Brain volume:* 11.1−12.2 μg/m^3 *Cognition:* 8.5 (5-yr avg)–14.9 μg/m^3 *Autism:* 14.0−19.6 μg/m^3

Table 1-2 (Continued): Key Evidence contributing to "causal" and "likely to be causal" causality determinations for $PM_{2.5}$ exposure and health effects evaluated in the current draft Integrated Science Assessment for Particulate Matter.

Key Evidence	Health Effect Category[a] and Causality Determination	$PM_{2.5}$ Concentrations Associated with Effects
Section 8.2.9 Table 8-20 (continued)		Concentrations from animal toxicological studies for: *Brain inflammation/Oxidative stress:* 65.7−441.7 μg/m^3 *Neurodegenerative changes:* 94.4 μg/m^3 *Neurodevelopment:* 92.7 μg/m^3
Cancer and Long-Term $PM_{2.5}$ Exposure (Section 10.2): Likely to be Causal Relationship *Change in causality determination from the 2009 PM ISA (suggestive of a causal relationship) due to increased evidence of genotoxicity, carcinogenicity, and epigenetic effects for $PM_{2.5}$ and lung cancer incidence and mortality.*		
Section 10.2.6 Table 10-8	Primarily positive associations from multiple, high-quality studies for increases in lung cancer incidence and mortality. This evidence is supported by analyses focusing on never smokers and limited evidence of associations with histological subtypes of lung cancer found in never smokers. Across studies that examined lung cancer incidence and mortality potential confounding by smoking status and exposure to SHS was adequately controlled. A limited number of studies examined potential copollutant confounding, but associations were relatively unchanged in models with O_3 with more limited assessment of other gaseous pollutants and particle size fractions. Experimental and epidemiologic studies provide evidence for a relationship between $PM_{2.5}$ exposure and genotoxicity, epigenetic effects, and carcinogenic potential. Uncertainties exist due to the lack of consistency in specific cancer-related biomarkers associated with $PM_{2.5}$ exposure across both experimental and epidemiologic studies; however, $PM_{2.5}$ exhibits several characteristics of carcinogens. This provides biological plausibility for $PM_{2.5}$ exposure contributing to cancer development. Additionally, there is limited evidence of cancer occurring in other organ systems, but there is some evidence that $PM_{2.5}$ exposure may detrimentally impact survival from any type of cancer.	Mean annual concentrations from epidemiologic studies for: *Lung cancer incidence and mortality*: U.S. and Canada: 6.3−23.6 μg/m^3 Europe: 6.6−31.0 μg/m^3 Asia: 33.7 μg/m^3 Concentrations from animal toxicological studies for: *Carcinogenic potential:* 17.66 μg/m^3

Table 1-2 (Continued): Key Evidence contributing to "causal" and "likely to be causal" causality determinations for $PM_{2.5}$ exposure and health effects evaluated in the current draft Integrated Science Assessment for Particulate Matter.

Key Evidence	Health Effect Category[a] and Causality Determination	$PM_{2.5}$ Concentrations Associated with Effects
Total Mortality and Short-Term $PM_{2.5}$ Exposure (Section 11.1.12): Causal Relationship *No change in causality determination from the 2009 PM ISA; new evidence further supports the previous determination.*		
Section 11.1.12 Table 11-4	There is consistent epidemiologic evidence from multiple, high quality studies of increases in total (nonaccidental) mortality in multi-city studies conducted in the U.S., Canada, Europe, and Asia at ambient concentrations often below 20 μg/m^3. The associations observed were relatively unchanged in copollutant models with gaseous pollutants and $PM_{10-2.5}$, which is consistent with copollutant analyses for cardiovascular and respiratory mortality, but copollutant analyses were limited to studies conducted in Europe and Asia. Biological plausibility for the epidemiologic evidence for total mortality is provided by the strong cardiovascular morbidity evidence, particularly for ischemic events and heart failure, while support for biological plausibility is more limited from the respiratory morbidity evidence, with the strongest evidence for exacerbations of COPD and asthma. Although alternatives to linearity have not been systematically evaluated, recent mortality studies continue to support a linear, no-threshold C-R relationship.	Mean 24-h avg concentrations from epidemiologic studies for: *Total Mortality*: U.S. and Canada: 4.37−17.97 μg/m^3 Europe: 13−27.7 μg/m^3 Asia: 11.8−69.9 μg/m^3

Table 1-2 (Continued): Key Evidence contributing to "causal" and "likely to be causal" causality determinations for $PM_{2.5}$ exposure and health effects evaluated in the current draft Integrated Science Assessment for Particulate Matter.

Key Evidence	Health Effect Category[a] and Causality Determination	$PM_{2.5}$ Concentrations Associated with Effects
Total Mortality and Long-Term $PM_{2.5}$ Exposure (Section 11.2.7): Causal Relationship *No change in causality determination from the 2009 PM ISA; new evidence further supports the previous determination.*		
Section 11.2.7 Table 11-8	There is consistent epidemiologic evidence from multiple, high-quality studies of increases in total (nonaccidental) mortality from extended follow-ups of the American Cancer Society (ACS) cohort and Harvard Six Cities (HSC) cohort, as well as multiple studies focusing on a Medicare cohort, Canadian cohorts, and North American employment cohorts. The consistent increases in total mortality are observed across different exposure metrics based on ambient measurements, models, remote sensing, or hybrid methods that combine two or more of these methods, providing additional support for the mortality associations due to long-term $PM_{2.5}$ exposure reported in the 2009 PM ISA that relied on exposure metrics from ambient monitors. The consistent epidemiologic evidence for total mortality is supported by positive associations for cardiovascular, respiratory, and lung cancer mortality. Biological plausibility for total mortality is provided by the strong cardiovascular morbidity evidence, particularly for CHD, stroke, and atherosclerosis, while there is more limited evidence for biological plausibility from the respiratory morbidity evidence, with some evidence for development of COPD. Extensive epidemiologic evidence provides additional support for a linear, no-threshold concentration-response (C-R) relationship. A recent series of studies demonstrates that decreases in long-term $PM_{2.5}$ concentrations were associated with an increase in life expectancy across the U.S. for multiple time periods examined.	Mean annual concentrations from epidemiologic studies for: *Total mortality*: ACS/HSC Cohorts: 11.4−23.6 $\mu g/m^3$ Medicare Cohort: 8.12−12.0 $\mu g/m^3$ Canadian Cohorts: 8.7−9.1 $\mu g/m^3$ Employment Cohorts: 12.7−17.0 $\mu g/m^3$

CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; SHS = second hand smoke.

[a]A large spectrum of outcomes is evaluated as part of a broad health effect category including physiological measures (e.g., airway responsiveness, lung function), clinical outcomes (e.g., respiratory symptoms, hospital admissions), and cause-specific mortality. Total mortality includes all nonaccidental causes of mortality and is informed by the nature of the evidence for the spectrum of morbidity effects (e.g., respiratory, cardiovascular) that can lead to mortality. The sections and tables referenced include a detailed discussion of the available evidence that informed the causality determinations.

1.4.2 Health Effects of $PM_{10-2.5}$

At the completion of the 2009 PM ISA, substantial uncertainties remained in the evaluation of the health effects due to short- and long-term $PM_{10-2.5}$ exposures (U.S. EPA, 2009). This was due to a variety of factors including the inability of particles within the $PM_{10-2.5}$ size range to reach the lower respiratory tract of rodents due to nasal deposition (see Figure 4-4) and instead relying on intra-tracheal instillation to assess health effects, and epidemiologic studies relying on multiple methods of varying quality to estimate $PM_{10-2.5}$ concentrations (e.g., direct measurement through dichotomous samplers, difference between collocated PM_{10} and $PM_{2.5}$ monitors, difference between county-wide average PM_{10} and $PM_{2.5}$ when monitors were not collocated), which had not been systematically compared and potentially contributed to different degrees of exposure measurement error. Limited availability of data and higher spatial variability of $PM_{10-2.5}$ compared with $PM_{2.5}$ also contributed to uncertainty about the representativeness of the $PM_{10-2.5}$ concentrations as a surrogate for exposure.

Recent epidemiologic and experimental studies continue to examine the relationship between short- and long-term $PM_{10-2.5}$ exposure and health effects; however, the uncertainties in the evidence identified in the 2009 PM ISA have, to date, still not been addressed. Specifically, within the epidemiologic studies, there is evidence of positive associations across the various health effects evaluated, but the methods used to estimate $PM_{10-2.5}$ concentrations and subsequently assign exposures to $PM_{10-2.5}$ have not been systematically evaluated in the peer-reviewed literature (see Section 3.3.1.1). Overall, this contributes to uncertainty with respect to the spatial and temporal correlations in $PM_{10-2.5}$ concentrations across methods, which may add to uncertainties in $PM_{10-2.5}$ exposure surrogates given the larger spatial and temporal variability in $PM_{10-2.5}$ concentrations compared to $PM_{2.5}$ (see Section 2.5.1.2.3). Evidence from experimental studies in humans combined with evidence from epidemiologic panel studies and limited evidence from animal toxicological studies continues to provide some evidence to support biologically plausible pathways by which $PM_{10-2.5}$ could impart a variety of health effects. Overall, the uncertainties surrounding the evidence providing biological plausibility for health effects related to $PM_{10-2.5}$ exposure and the methods used to assign $PM_{10-2.5}$ exposure in epidemiologic studies collectively contributed to causality determinations across health effects categories of "*suggestive of, but not sufficient to infer, a causal relationship*" or "*inadequate to infer the presence or absence of a causal relationship*" (Table 1-7).

1.4.3 Health Effects of UFPs

At the completion of the 2009 PM ISA, relatively few studies examined the health effects attributed to short- and long-term UFP exposures. Across broad health categories there was limited and often inconsistent evidence of effects. There was some evidence of cardiovascular and respiratory effects due to UFP CAPs from controlled human exposure and animal toxicological studies with more evidence

from studies of diesel exhaust, but in the diesel exhaust studies it was not possible to determine if the effect observed was due to UFPs, gaseous components, or a combination of the two. Additionally, there were broader uncertainties that spanned atmospheric chemistry, exposure assessment, and epidemiology due to limited information on the spatial and temporal variability in UFP concentrations; the lack of a UFP monitoring network in the U.S.; and insufficient data on the composition of UFPs. These uncertainties were further reflected in epidemiologic studies as a result of most studies relying on a single monitor to estimate UFP exposure.

Recent studies have further explored the relationship between short- and long-term UFP exposure and health effects; however, the assessment of study results across experimental and epidemiologic studies is complicated by the size distribution examined in each discipline and the nonuniformity in the exposure metric examined (i.e., the particle size range and indicators [e.g., particle number concentration (NC), surface area concentration (SC), and mass concentration (MC)]) (see Preface). Specifically, experimental studies include size ranges up to 200 nm or higher. Epidemiologic studies often focus on various size ranges below 100 nm. However, if an epidemiologic study is focusing on NC it can include larger particle sizes, but it has been shown that 67−90% of NC represents particles <100 nm (Section 2.4.3.1).

Although there is some evidence of positive but imprecise associations across epidemiologic studies examining a range of health effects (e.g., cardiovascular and respiratory effects, and mortality), study results are difficult to interpret. This is due to most studies' reliance on a single monitor, which is inadequate as has been reflected in some monitoring campaigns that demonstrate a high degree of spatial variability in UFP concentrations and that the size distribution of UFPs changes with distance from source (Section 2.5.1). As noted above, examining coherence and biological plausibility of UFP-related health effects is complicated by the larger size distribution of UFPs examined in experimental studies compared with the size distribution examined in epidemiologic studies. Based on these overarching uncertainties and inconsistency across studies in the characterization of UFP with respect to size distribution and exposure metric, across most health effects categories the evidence collectively contributed to causality determinations that did not exceed "*suggestive of, but not sufficient to infer, a causal relationship*" (Table 1-7).

1.4.3.1 Nervous System Effects Associated with Long-Term UFP Exposure

The limited findings reported in the 2009 PM ISA indicated that subchronic exposure to UFP CAPs resulted in pro-inflammatory changes in the cortical region of the brains of mice and it was hypothesized that ambient UFP may reach the brain via olfactory transport based on studies demonstrating this mechanism using laboratory generated UFPs. The recent literature has greatly expanded, demonstrating overt neurological changes and providing some evidence suggesting potential translocation of UFPs via olfactory transport. Animal toxicological studies provide evidence for several

nervous system effects due to long-term UFP exposure including brain inflammation and oxidative stress, morphologic changes, and behavioral effects. Epidemiologic evidence is limited to a single study providing initial evidence of effects on attention and memory, but more broadly uncertainties remain with respect to effects due to long-term UFP exposure, specifically due to the uncharacterized temporal and spatial variability in UFP concentrations. Overall, the strong animal toxicological evidence of neurotoxicity and altered neurodevelopment supports a "*likely to be causal relationship*" between long-term UFP exposure and nervous system effects, which represents the first time a causality determination has been made for long-term UFP exposure and nervous system effects (Table 1-3).

Multiple toxicological studies of long-term UFP exposure conducted in adult animals provide consistent evidence of brain inflammation and oxidative stress in the whole brain, hippocampus, and cerebral cortex (Section 8.6.3). Studies also found morphologic changes, specifically neurodegeneration in specific regions of the hippocampus and pathologic changes characteristic of Alzheimer's disease, and initial evidence of behavioral effects in adult mice (Section 8.6.4 and Section 8.6.5). Toxicological studies examining pre- and post-natal UFP exposures provide extensive evidence for behavioral effects, altered neurotransmitters, neuroinflammation, and morphologic changes (Section 8.6.6.2). Persistent ventriculomegaly was observed in male, but not female mice, exposed postnatally to UFP (Section 8.6.6). Epidemiologic evidence is limited to a study of school children that provides support for the experimental results. This study, which did not consider copollutant confounding, reported an association between long-term exposure to UFP, which was measured at the school, and decrements on tests of attention and memory. In general, epidemiologic studies of long term exposure to UFP are sparse because there are challenges in capturing the spatial variation in long-term UFP concentrations that can result in substantial exposure measurement error (Section 8.6.7).

Table 1-3 Key Evidence contributing to a "likely to be causal" causality determination for UFP exposure and health effects evaluated in the current draft Integrated Science Assessment for Particulate Matter.

Key Evidence	Health Effect Category[a] and Causality Determination	UFP Concentrations Associated with Effects
Nervous System Effects and Long-Term UFP Exposure (Section 8.6.7): Likely to be Causal Relationship *Not evaluated in the 2009 PM ISA; new evidence showing brain inflammation and oxidative stress, neurodegeneration, cognitive effects, and neurodevelopmental effects.*		
Section 8.6.7 Table 8-34	Animal toxicological studies provide strong evidence for nervous system effects due to long-term UFP exposure including neuroinflammation, neurodegeneration, and altered neurodevelopment. Multiple toxicological studies conducted in adult animals provided consistent evidence of inflammation and oxidative stress in the whole brain, hippocampus, and cerebral cortex, as well as more limited evidence for neurodegeneration, Alzheimer's disease-related pathology, and behavioral effects. Experimental animal studies examining pre- and post-natal UFP exposures provide evidence for behavioral effects, altered neurotransmitters, neuroinflammation, and morphologic changes, including persistent ventriculomegaly. The epidemiologic evidence was limited to a study, that did not consider copollutant confounding, that provides initial evidence of that UFP may affect attention and memory in school children.	Concentrations from animal toxicological studies for: *Brain inflammation/Oxidative stress:* MC: 342−468 μg/m^3 NC: 140,000−254,000 particles/cm^3 *Neurodegenerative changes:* MC: 342−468 μg/m^3 NC: 140,000−254,000 particles/cm^3 *Cognitive and behavioral effects in adults:* MC: 342 μg/m^3 NC: 140,000 particles/cm^3 *Neurodevelopment:* 96.4−350 μg/m^3 NC: 180,000−200,000 particles/cm^3

MC = mass concentration; NC = number concentration.

[a]A large spectrum of outcomes is evaluated as part of a broad health effect category including physiological measures (e.g., airway responsiveness, lung function), clinical outcomes (e.g., respiratory symptoms, hospital admissions), and cause-specific mortality. The sections and tables referenced include a detailed discussion of the available evidence that informed the causality determinations.

1.5 Policy-Relevant Considerations

In the process of evaluating the current state of the science with respect to the effect of short- and long-term PM exposure on health, studies were identified that conducted analyses focused on addressing some of the main policy-relevant questions of this review, as detailed in the PM IRP (U.S. EPA, 2016), such as:

- Is there new evidence aimed at disentangling the effect of PM from the complex air pollution mixture to inform a direct effect of PM on health, specifically the assessment of potential copollutant confounding?
- Is there new evidence to inform the current indicators (i.e., $PM_{2.5}$ for fine particles and PM_{10} for thoracic coarse particles), averaging times (i.e., 24-hour average, annual average), and levels of the PM NAAQS?
- Is there new evidence on the shape of the concentration-response relationship and whether a threshold hold exists between PM exposure and various health outcomes (e.g., mortality, hospital admissions, etc.), especially for concentrations near or below the levels of the current PM NAAQS?
- Is there new evidence that individual PM component(s) or source(s) (e.g., industrial facilities, roads, atmospheric formation), are more strongly associated with health effects than PM mass, particularly for health effects for which there is sufficient evidence of a strong relationship (e.g., cardiovascular effects, mortality) with PM exposure?
- Is there new evidence indicating that specific populations or lifestages are at increased risk of a PM-related health effect compared to a referent population?

The following sections summarize the evidence that can inform consideration of these policy-relevant questions, specifically: potential copollutant confounding (Section 1.5.1), timing of effects (Section 1.5.2), concentration-response (C-R) relationship (1.5.3), PM components and sources (Section 1.5.4), and populations potentially at increased risk of a PM-related health effect (Section 1.5.5).

1.5.1 Potential Copollutant Confounding

Recent studies further evaluated the potential confounding effects of copollutants, both gaseous and particulate, on the relationship between short- and long-term $PM_{2.5}$ exposure and health effects. These studies build upon the evidence detailed in the 2009 PM ISA and continue to provide evidence indicating that associations with $PM_{2.5}$ are relatively unchanged in copollutant models. Evidence from epidemiologic studies, in combination with experimental studies detailed in previous chapters (i.e., Respiratory Effects-CHAPTER 5 and Cardiovascular Effects-CHAPTER 6) that examined exposure to PM (e.g., CAPs, resuspended PM, and whole mixtures in the presence and absence of a particle trap), demonstrate a direct effect of PM on health.

1.5.1.1 Short-term $PM_{2.5}$ Exposure

Building upon the studies evaluated in the 2009 PM ISA, recent epidemiologic studies have further examined whether copollutants confound associations between short-term $PM_{2.5}$ exposure and respiratory and cardiovascular effects and mortality. These studies continue to demonstrate $PM_{2.5}$-associations are relatively unchanged in copollutant models with both gaseous (i.e., O_3, NO_2, SO_2, and CO) and particulate (i.e., $PM_{10–2.5}$) pollutants.

The examination of potential copollutant confounding on the relationship between short-term $PM_{2.5}$ exposure and respiratory effects has been assessed most extensively through studies examining respiratory-related emergency department visits and hospital admissions, particularly for asthma, with more limited assessments of COPD and respiratory infection, and studies examining respiratory mortality (Section 5.1.10.1). Correlations between $PM_{2.5}$ and gaseous and particulate pollutants varied across studies, with low-to-moderate correlations (i.e., <0.7) observed for NO_2, SO_2, CO, and $PM_{10–2.5}$, and correlations spanning low-to-high for O_3. O_3 was most commonly examined, followed by NO_2, across the studies that assessed copollutant confounding, and $PM_{2.5}$ results were relatively unchanged in copollutant models. Although fewer studies focused on SO_2 and CO, the results from copollutant analyses were consistent with studies evaluated in the 2009 PM ISA, indicating that results are relatively unchanged in copollutant models. Recent studies that examined $PM_{10–2.5}$ further expand upon the initial results detailed in the 2009 PM ISA, and although results are consistent with observations from analyses of gaseous pollutants, there is greater uncertainty in these results due to the various methods employed across studies to estimate $PM_{10–2.5}$ concentrations.

While studies of respiratory-related emergency department visits and hospital admissions and respiratory mortality reported the strongest correlations between $PM_{2.5}$ and O_3, for cardiovascular effects moderate-to-strong correlations were reported for NO_2 and CO, with low to moderate correlations for O_3, SO_2, and $PM_{10–2.5}$. Across studies of various cardiovascular-related emergency department visits and hospital admissions and cardiovascular mortality, results were relatively unchanged in copollutant models, but there were some instances of attenuation of the $PM_{2.5}$ association in models with NO_2 and CO (Section 6.1.14.1). Overall, there was not an observed difference in the trend or pattern of copollutant model results across cardiovascular endpoints (e.g., aggregate CVD endpoints, IHD, heart failure, cardiovascular mortality). However, the few instances of attenuation were with traffic-related pollutants (i.e., NO_2, CO), which generally had higher correlations with $PM_{2.5}$ than the other copollutants. As a result, it is difficult to distinguish if the instances of observed attenuation in $PM_{2.5}$ associations are due to confounding or collinearity between pollutants.

Compared to epidemiologic studies that examined the potential confounding effects of copollutants on respiratory and cardiovascular effects, a more limited number of studies focused on mortality (Section 11.1.4). Recent multi-city studies conducted in Europe and Asia support the single- and multi-city studies examined in the 2004 PM AQCD and 2009 PM ISA that reported limited evidence of confounding by copollutants. Across studies examining both gaseous and particulate (i.e., $PM_{10–2.5}$)

pollutants, low-to-moderate correlations were reported with $PM_{2.5}$. Associations with $PM_{2.5}$ were relatively unchanged in copollutant models across the various study locations examined.

In addition to conducting traditional copollutant analyses, epidemiologic studies of respiratory (Section 5.1.10.1.1) and cardiovascular (Section 6.1.14.1.1) effects have also examined the role of PM within the broader air pollution mixture. These studies do not inform whether PM is independently associated with a respiratory effect, but they can assess whether days with higher $PM_{2.5}$ concentrations are more closely related to health effects. Studies of respiratory effects demonstrate that days where the air pollution mixture has high $PM_{2.5}$ concentrations often represent the days with the largest associations (in terms of magnitude) with a respiratory effect. Additionally, results indicate that risk estimates for a mixture are often similar, but in some cases larger, than those reported for $PM_{2.5}$ alone. However, for cardiovascular effects, generally, the evidence neither consistently or coherently indicated a stronger or weaker effect of combined exposure to $PM_{2.5}$ and another pollutant compared to exposure to $PM_{2.5}$ and other pollutants alone.

1.5.1.2 Long-term $PM_{2.5}$ Exposure

Epidemiologic studies focusing on long-term $PM_{2.5}$ exposure and health effects have traditionally provided a more limited assessment of the potential confounding effects of copollutants on $PM_{2.5}$ associations. Recent studies provide the initial evidence to inform copollutant confounding for some health outcomes, while in other instances (e.g., mortality) an assessment of copollutant confounding directly addresses a previously identified uncertainty in the scientific evidence.

Across the health effects evaluated within this ISA, relatively few studies examined the potential confounding effects of copollutants on the relationship between long-term $PM_{2.5}$ exposure and respiratory (Section 5.2.13), cardiovascular (Section 6.2.18), and cancer (Section 10.2.7), with a general lack of studies of assessing the role of copollutant confounding on observed associations with nervous system effects (Section 8.2.9). These studies often did not examine the full suite of gaseous pollutants, but tended to focus on traffic-related pollutants (i.e., NO_2, NO_X, and CO) and O_3, with some studies also examining $PM_{10-2.5}$. Across studies low-to-moderate correlations (i.e., $r < 0.7$) were often observed between copollutants and $PM_{2.5}$. Collectively, studies that examined the potential confounding effects of copollutants on the $PM_{2.5}$ association with respiratory (i.e., lung function and asthma development) and cardiovascular effects (i.e., cardiovascular mortality), along with lung cancer incidence and mortality, reported associations that were relatively unchanged in copollutant models, but these assessments were conducted in a limited number of studies.

Compared to other health effects, several studies of long-term $PM_{2.5}$ exposure and mortality examine potential copollutant confounding. Within studies that examined the potential confounding effects of copollutants on the relationship between long-term $PM_{2.5}$ exposure and mortality, the most extensive analyses occurred for O_3, with a limited number of studies examining NO_2, SO_2, $PM_{10-2.5}$, and

the air toxic, benzene. Studies that examined O_3 reported correlations that were generally moderate (ranging from $r = 0.49–0.73$), with a few studies reporting weak correlations ($r < 0.4$). Overall, associations remained relatively unchanged in copollutant models for total (nonaccidental) mortality, cardiovascular, and respiratory mortality (Figure 11-18). Studies focusing on copollutant models with NO_2, $PM_{10–2.5}$, SO_2 and benzene were examined in individual studies, and across these studies the $PM_{2.5}$-mortality association was relatively unchanged (Figure 11-19).

1.5.2 Timing of Effects

An important question to address when evaluating the scientific evidence demonstrating health effects due to short-term $PM_{2.5}$ exposure is the timing of observed effects. Studies have attempted to address this question through two primary avenues: (1) examining various averaging times of the exposure metric used to represent short-term exposure to $PM_{2.5}$ to determine whether PM averaged over time periods other than 24-hours are more closely associated with health effects; and (2) assessing whether the relationship between exposure and effect is biologically plausible by examining the lag days over which associations are observed.

1.5.2.1 Averaging Time

Most epidemiologic studies that examine the relationship between short-term $PM_{2.5}$ exposures and health effects rely primarily on an exposure metric that is averaged over 24-hours. Some recent studies, focusing on respiratory and cardiovascular effects and mortality, have examined whether there is evidence that subdaily exposure metrics are more closely related to health effects than the traditional 24-hour average metric.

Epidemiologic studies that examined both respiratory-related emergency department visits and hospital admissions as well as subclinical markers of respiratory effects explored associations with subdaily exposure metrics (Section 5.1.10.5). In studies of respiratory-related emergency department visits and hospital admissions, positive associations were not consistently observed with subdaily exposure metrics, and often there was no information on spatiotemporal variability of the subdaily metrics. Additionally, in a study that examined multiple subdaily averaging times and compared them to the 24-hour average exposure metric there was no difference in associations across metrics, but this was limited to a single study location. Panel studies also examined subdaily exposure metrics through personal monitoring, but associations were not consistently observed at these shorter averaging times for markers of pulmonary inflammation and changes in lung function.

A more limited number of studies examined subdaily exposure metrics and cardiovascular effects (Section 6.1.14.3). Studies of ST-elevation, myocardial infarction, out-of-hospital cardiac arrest, and cerebrovascular disease emergency department visits and hospital admissions reported positive

associations with subdaily exposure metrics, but the magnitude of the association tended to be larger when averaging over multiple hours up to one day (i.e., 24-hour average). These studies provide evidence that continues to support the use of a 24-hour average exposure metric.

A few studies examined subdaily $PM_{2.5}$ exposure metrics and associations with mortality, focusing on comparisons between the 24-hour average and an hourly peak exposure metric (Section 11.1.8.2). In these studies, positive associations were reported for both the 24-hour average and hourly peak exposure metric with the association often slightly larger in magnitude for the 24-hour average metric. Collectively, the available evidence does not indicate that subdaily averaging periods for $PM_{2.5}$ are more closely associated with health effects than the 24-hour average exposure metric.

1.5.2.2 Lag Structure of Associations

Often epidemiologic studies have examined associations between short-term $PM_{2.5}$ exposure and health effects over a series of single-day lags, multi-day lags, or by selecting lags *a priori*. Recent studies have expanded the assessment of examining the timing of effects by systematically examining lag days by focusing on whether there is evidence of an immediate (e.g., lag 0−1 days), delayed (e.g., lag 2−5 days), or prolonged (e.g., lag 0−5 days) effect of PM on health.

Epidemiologic studies of respiratory effects have primarily focused on examining the lag structure of associations for respiratory-related emergency department visits and hospital admissions, with most studies examining asthma with a more limited assessment for COPD and respiratory infection (Section 5.1.10.3). Across the studies that examined asthma, COPD, respiratory infections and combinations of respiratory-related diseases, the strongest association reported, in terms of magnitude and precision, is generally within a few days after exposure, but there is some evidence demonstrating the potential for a prolonged effect of $PM_{2.5}$ (i.e., lags ranging from 0−5 days). Recent studies of respiratory mortality provide additional insight on the lag structure of associations for respiratory-related effects due to short-term $PM_{2.5}$ exposure. Studies of respiratory mortality tend to support more immediate $PM_{2.5}$ effects (i.e., lags of 0 to 2 days), but initial evidence of stronger associations, in terms of magnitude and precision, at lags of 0−5 days. Collectively, the studies of respiratory morbidity and mortality that conducted systematic evaluations of $PM_{2.5}$ associations across a range of lags, provide evidence of effects within the range of 0–5 days after exposure.

Similar to respiratory effects, the majority of epidemiologic studies examining the lag structure of associations for cardiovascular effects focus on cardiovascular-related emergency department visits and hospital admissions. Studies of IHD, MI and cardiovascular-related outcomes emergency department visits and hospital admissions reported stronger associations for multi-day lags, but these effects tended to be in the range of 0−1 or 0−2 days. When examining cerebrovascular disease there was no evidence of an association at any of the lag days examined; however, when focusing on specific stroke types, particularly ischemic stroke there was evidence of immediate effects at lags of 0 and 1 day, which is consistent with

other cardiovascular outcomes. The immediate effects of $PM_{2.5}$ on cardiovascular morbidity outcomes, specifically those related to ischemic events, are consistent with the lag structure of associations observed in studies of cardiovascular mortality that report immediate effects (i.e., lag 0−1 day). There is some evidence indicating $PM_{2.5}$-cardviovascular mortality associations with exposures over longer durations, but this is not supported by studies examining single-day lags that encompass the same number of days.

An evaluation of recent epidemiologic studies of short-term $PM_{2.5}$ exposure and mortality found that studies either conducted analyses of single-day lags over many days or various iterations of multi-day lags (e.g., 0−1, 0−2, 0−3, etc.) (Section 11.1.8.1). Across studies, associations were largest in terms of magnitude and precision for total (nonaccidental) mortality at lags of 0 to 1 day, but there is some evidence that associations remain positive at multi-day lags up to 0−4 days. The combination of the multi- and single-day lag analyses provides further support of an immediate effect of short-term $PM_{2.5}$ exposure on mortality.

1.5.3 Concentration-Response (C-R) Relationship

In assessing the relationship-between short- and long-term PM exposure and health effects, an important consideration is whether the relationship is linear across the full range of ambient concentrations and whether there is a threshold concentration below which there is no evidence of an effect. As detailed in the 2004 AQCD and 2009 PM ISA, conducting C-R and threshold analyses is challenging due to the "(1) limited range of available concentration levels (i.e., sparse data at the low and high end); (2) heterogeneity of (at-risk) populations (between cities); and (3) influence of measurement error" (U.S. EPA, 2004). Recent studies that focus on the shape of the C-R curve expand upon the health effects evaluated in previous reviews and continue to provide evidence of a linear, no threshold, relationship between both short- and long-term $PM_{2.5}$ exposure and several respiratory and cardiovascular effects, and mortality, with some recent evidence indicating a steeper slope (i.e., supralinear curve) at lower concentrations for some outcomes (i.e., long-term $PM_{2.5}$ exposure and mortality). However, cut-point analyses that focus on whether risk changes at different concentration ranges provide some evidence of nonlinearity, specifically in the relationship between short-term $PM_{2.5}$ exposure and respiratory-related emergency department visits and hospital admissions. It is important to note that although recent studies have used many different statistical methods to examine the shape of the C-R relationship and generally provide evidence for a linear, no-threshold relationship, many of these studies have not systematically evaluated alternatives to a linear relationship.

1.5.3.1 Short-Term Exposure

Recent epidemiologic studies that examined the C-R relationship between short-term $PM_{2.5}$ exposure and health are limited to studies of respiratory-related emergency department visits and hospital

admissions (Section 5.1.10.6), and mortality (Section 11.1.10). Across studies that examined respiratory effects, different analytical methods have been employed to examine the C-R relationship, either explicitly examining the shape of the C-R curve and whether there is evidence of linearity across the full range of $PM_{2.5}$ concentrations, or through cut-point analyses that examine whether the risk of a $PM_{2.5}$-related respiratory effect changes within specified ranges of $PM_{2.5}$ concentrations. These studies primarily focused on asthma emergency department visits and hospital admissions, with some studies examining combinations of respiratory emergency department visits and hospital admissions. Studies that focused on the shape of the C-R curve provide initial evidence of a linear relationship for short-term $PM_{2.5}$ exposure and both respiratory disease and asthma hospital admissions and emergency department visits, with less certainty at concentrations below 10 $\mu g/m^3$. However, cut-point analyses provide some initial evidence indicating nonlinearity in the relationship (i.e., larger risk estimates at various quintiles when compared to the lowest quintile) between short-term $PM_{2.5}$ exposure and asthma emergency department visits and hospital admissions.

The examination of the C-R relationship for short-term PM exposure and mortality was initially limited to studies of PM_{10}. Recent epidemiologic studies focus on $PM_{2.5}$ and specifically the shape of the C-R curve at the low end of the $PM_{2.5}$ concentration distribution. Evidence from U.S. studies, which can examine the shape of the C-R curve at lower $PM_{2.5}$ concentrations compared to other countries, provide evidence indicating a linear relationship at concentrations as low as 5 $\mu g/m^3$. The observations from C-R analyses are further supported by cut-point analyses examining associations at different $PM_{2.5}$ concentrations as well as analyses that reported no evidence of a threshold. Overall, recent studies focusing on short-term $PM_{2.5}$ exposure and mortality support a linear, no threshold relationship at ambient $PM_{2.5}$ concentrations lower than those evaluated in the 2009 PM ISA.

1.5.3.2 Long-Term Exposure

The most extensive analyses of the C-R relationship between long-term PM exposure and a health outcome traditionally has been for $PM_{2.5}$ and mortality. Recent studies further expand and provide new insights on the relationship between long-term $PM_{2.5}$ exposure and mortality, and provide initial examinations of the C-R relationship for respiratory and cardiovascular effects, as well as lung cancer mortality and incidence.

While the assessment of the C-R relationship for long-term $PM_{2.5}$ exposure is more limited for most health outcomes, it has been extensively examined in studies of mortality (Section 11.2.4). Across studies a variety of statistical methods have been examined to assess whether there is evidence of deviations in linearity as well as cut point analysis that focus on examining risk at specific ambient concentrations (Table 11-7). These studies report results that generally support a linear, no-threshold relationship for total (nonaccidental) mortality, especially at lower ambient $PM_{2.5}$ concentrations, with confidence in some studies in the range of 5−8 $\mu g/m^3$. Additionally, there is initial evidence indicating

that the slope of the C-R curve may be steeper (supralinear) at lower concentrations for cardiovascular mortality.

Epidemiologic studies examining the C-R relationship for long-term $PM_{2.5}$ exposure and respiratory effects (Section 5.3.2.1.1) are limited in number and focus on asthma incidence and childhood wheeze. Studies of asthma incidence that examine the shape of the C-R curve and whether risk changes at different quartiles of $PM_{2.5}$ concentrations do not find any evidence for deviations in linearity and evidence of monotonically increasing risk, respectively. In an initial study of childhood wheeze, specifically repeated wheeze events, there is evidence of a linear C-R relationship with the greatest confidence at long-term $PM_{2.5}$ concentrations ranging from 10 to 12 $\mu g/m^3$.

A limited number of studies report initial assessments of the C-R relationship for long-term $PM_{2.5}$ concentrations and cardiovascular effects, specifically IHD incidence, coronary artery calcification (CAC), and hypertension (Section 6.2.16). For IHD incidence, there was evidence of a linear C-R relationship at concentrations below 15 $\mu g/m^3$, which is consistent with the shape of the curve when compared to the full range of $PM_{2.5}$ concentrations. Analyses of the relationship between long-term $PM_{2.5}$ exposure and CAC indicated both linear and nonlinear relationships, while there is initial evidence of a linear relationship between long-term $PM_{2.5}$ exposure and incidence of hypertension. A few studies that examined the relationship between long-term $PM_{2.5}$ exposure and lung cancer incidence and mortality also examined the shape of the C-R curve through assessments of linearity, and cut-point and threshold analyses (Section 10.2.5.1.4). These collective assessments provide initial evidence supporting a no-threshold, linear relationship across the range of $PM_{2.5}$ concentrations observed in the U.S., with confidence in some studies in the range of 5−10 $\mu g/m^3$.

1.5.4 PM Components and Sources

Building upon the initial evaluation conducted in the 2004 PM AQCD, the 2009 PM ISA conducted a formal evaluation of the relationship between exposures to PM components and sources and health effects. Through the evaluation of experimental and epidemiologic studies that focused on individual PM components as well as studies that used quantitative approaches aimed at reducing the correlation between components it was identified that many components and sources representative of combustion-related activities (e.g., motor vehicle emissions, coal combustion, oil burning, vegetative burning) are associated with a range of health effects. This assessment led to the 2009 PM ISA concluding that "many [components] of PM can be linked with differing health effects and the evidence is not yet sufficient to allow differentiation of those components or sources that are more closely related to specific health outcomes".

Building upon the evaluation of PM sources and components in the 2009 PM ISA, and as detailed in the Preface, this PM ISA systematically evaluated whether there was evidence that specific PM components or sources are more strongly associated with health effects than PM mass by focusing on

those studies that: (1) included a composite metric of PM (e.g., mass of $PM_{2.5}$ and/or $PM_{10–2.5}$, or in the case of ultrafine particles [UFP] mass, particle number, etc.) and PM components; (2) applied some approach to assess the particle effect (e.g., particle trap) of a mixture; or (3) conducted formal statistical analyses using source-based exposures that were not defined a priori (see Preface). Overall, these criteria allow for a thorough evaluation of whether there is evidence that an individual component(s) and/or source(s) is more closely related to health effects than PM mass. Across the health effects categories evaluated in this ISA, most studies that examine PM sources and components focus on $PM_{2.5}$. As such, the following sections summarize the current state of the science on $PM_{2.5}$ components and sources for those health effects categories where it was concluded that a "causal" or "likely to be causal" relationship exists, with details on the $PM_{2.5}$ components and sources evidence for the other health effects categories (e.g., Reproductive and Developmental Effects) in subsequent health chapters of this ISA.

Overall, recent studies continue to demonstrate that many $PM_{2.5}$ components and sources are associated with health effects ranging from subclinical (e.g., changes in heart function, such as HRV, or circulating biomarkers) to the more overt (i.e., emergency department visits, hospital admissions, and mortality). The results of these studies confirm and further support the conclusion of the 2009 PM ISA, i.e., that many $PM_{2.5}$ components and sources are associated with many health effects, and the evidence does not indicate that any one source or component is consistently more strongly related with health effects than $PM_{2.5}$ mass.

1.5.4.1 Respiratory Effects

The examination of $PM_{2.5}$ components and sources and respiratory effects was limited to epidemiologic studies (Section 5.1.11). Epidemiologic studies that examined associations between short-term $PM_{2.5}$ components and respiratory health effects and examined associations with $PM_{2.5}$ mass (n = 113), primarily focus on the components nitrate (n = 29), sulfate (n = 40), OC (n = 50), and EC/BC (n = 95). Across these studies the health effects examined range from inflammation and changes in lung function to respiratory-related emergency department visits and hospital admissions. When examining the pattern of associations for individual $PM_{2.5}$ components with those observed for $PM_{2.5}$ mass, all the components examined (i.e., evaluated in at least three studies) were positively associated with a respiratory effect in at least a few studies (Section 5.1.11.7). For EC/BC, the most extensively examined $PM_{2.5}$ component, many studies reported positive associations, but some studies also reported results indicating no association, which is consistent with the pattern of associations for $PM_{2.5}$ mass.

A more limited number of studies examined associations between long-term $PM_{2.5}$ components and respiratory effects (Section 5.2.12). Similar to short-term exposure studies, the majority of studies focus on EC/BC, and did not observe a different pattern of associations with respiratory effects than what was observed for $PM_{2.5}$ mass. Collectively, positive associations were observed in studies examining

short- and long-term $PM_{2.5}$ component exposure and respiratory effects, but there is no evidence that any one component is more strongly associated with respiratory effects than $PM_{2.5}$ mass.

Few studies examined the relationship between $PM_{2.5}$ sources and respiratory health effects. Through analyses where $PM_{2.5}$ components were apportioned into source factors, positive associations were reported for several respiratory effects, particularly asthma exacerbation, and sources representative of combustion-related activities, such as traffic and biomass burning. There were no recent studies that examined long-term exposure to $PM_{2.5}$ sources and respiratory effects.

1.5.4.2 Cardiovascular Effects

Both epidemiologic and experimental studies examined the relationship between $PM_{2.5}$ component and sources exposures and cardiovascular effects (Section 6.1.15). In short-term exposure studies, the epidemiologic evidence focuses on studies examining cardiovascular-related emergency department visits and hospital admissions with only a few studies examining other cardiovascular effects. Similar to studies examining respiratory effects and $PM_{2.5}$ components, of the studies that examined both $PM_{2.5}$ mass and components (n = 14), the most extensively examined components include EC (n = 12), OC (n = 10), sulfate (N = 9), and nitrate (n = 9). Across all components examined, most were positively associated with cardiovascular-related emergency department visits and hospital admissions in at least one study (Section 6.1.15). Although EC was positively associated with cardiovascular-related emergency department visits and hospital admissions in many of the studies evaluated, it was not possible to decipher if EC was independently associated or a marker of exposure to $PM_{2.5}$ mass.

Studies examining long-term exposure to $PM_{2.5}$ components and cardiovascular effects were few, and consistent with the long-term exposure and respiratory effects studies primarily focus on EC/BC (Section 6.2.17). These studies did not provide evidence that any one component is more strongly associated with a cardiovascular effect. Collectively, studies examining short- and long-term $PM_{2.5}$ components exposure continue to support there is not one component that is more strongly associated with a cardiovascular effect than $PM_{2.5}$ mass.

Epidemiologic and animal toxicological studies conducted source based analyses using mathematical methods to apportion $PM_{2.5}$ components into source factors (Section 6.1.15.6 and Section 6.1.15.8). Epidemiologic studies focused on cardiovascular-related emergency department visits and hospital admissions and reported positive associations with sources representative of combustion-related activities (e.g., industrial combustion, traffic), with more limited evidence for wildfires. Animal toxicological studies, which focused on markers of heart function (e.g., HR, HRV), reported associations with a variety of source categories, but the associations were dependent on the location of the study (i.e., where the $PM_{2.5}$ CAPS were collected). Additional studies focusing on long-term exposures to $PM_{2.5}$ sources were fewer in number, with epidemiologic studies only examining traffic

sources and animal toxicological studies reporting associations with a number of sources and various cardiovascular effects.

1.5.4.3 Mortality

Epidemiologic studies that examined associations with $PM_{2.5}$ components and sources and mortality have primarily focused on examining short- and long-term exposures to components (Section 11.1.11 and Section 11.2.6). Both short- and long-term exposure studies reported consistent, positive associations with $PM_{2.5}$ mass across all studies that also examined a component. While for respiratory and cardiovascular effects most studies focused on EC/BC, for studies of mortality no one component was disproportionally examined compared to the rest. Of the $PM_{2.5}$ components examined, each were found to be positively associated with mortality in at least a few studies, but overall one component was not found to be as consistently associated with mortality as $PM_{2.5}$ mass.

Compared to the 2009 PM ISA, where most epidemiologic studies of mortality conducted formal source apportionment analyses, recent studies focus more exclusively on $PM_{2.5}$ components. Of the limited number of studies that examined associations between short- and long-term source exposures and mortality, positive associations were observed for those sources representative of combustion-related activities including traffic, coal, and vegetative fires.

1.5.5 Populations and Lifestages at Potentially Increased Risk of a PM-related Health Effect

An important consideration in the evaluation of the scientific evidence for PM, and in the consideration of the extent to which the NAAQS provides public health protection with an adequate margin of safety, is whether specific populations or lifestages are at increased risk of a PM-related health effect. As detailed in the preceding sections of this chapter and subsequent chapters of this ISA, a large body of evidence demonstrates health effects related to PM exposure, particularly $PM_{2.5}$ exposure, across populations with diverse characteristics (e.g., children, older adults, people with pre-existing cardiovascular diseases, etc.). While this larger body of evidence informs the causal nature of the relationship between PM exposure and health effects, this section focuses on answering the question:

Are there specific populations and lifestages at increased risk of a PM-related health effect, compared to a reference population? That is, is the magnitude of effect or exposure greater for some populations or lifestages compared to a reference population, where applicable, or are health effects observed at lower PM concentrations for some populations or lifestages compared to others?

The evaluation of populations and lifestages potentially at increased risk builds off the approach used in the 2009 PM ISA and includes the application of a framework to characterize the evidence

informing increased risk detailed in the 2013 O_3 ISA (U.S. EPA, 2013). The focus of this evaluation is on determining the extent to which specific factors may increase the risk of a PM-related health effect in a population or lifestage relative to a reference population, where applicable. Importantly, this builds on the conclusions drawn elsewhere in the ISA, taking into consideration the relationship between exposure to PM and health effects. As detailed in the Preamble to the ISAs (U.S. EPA, 2015), the evaluation of the evidence includes (1) epidemiologic studies that conducted stratified analyses, (2) evidence from animal toxicological studies using animal models of disease and epidemiologic or controlled human exposure studies conducted in specific populations (e.g., lung function growth in children, people with mild asthma), (3) information on the dosimetry of PM within the body, and (4) consideration of information on differential exposure to PM within a population or lifestage. Overall, the framework allows for a transparent characterization of the collective body of evidence in order to draw conclusions on the degree to which the scientific evidence indicates that a specific population or lifestage is at increased risk of a PM-related health effect (Table 12-1).

Based on the causality determinations briefly summarized within this chapter, and more fully detailed in subsequent chapters, the strongest evidence indicating an effect of short- and long-term PM exposure on health is for $PM_{2.5}$ and the broad health categories of respiratory and cardiovascular effects, cancer, and mortality. As a result, the assessment of populations and lifestages potentially at increased risk of a $PM_{2.5}$-related health effect primarily focuses on studies that form the basis of these causality determinations that also conducted analyses to inform whether there is differential risk in a specific population or lifestage. It is important to note that in the evaluation of studies a number of factors can influence the ability to observe an association including, but not limited to, publication bias (i.e., not reporting null findings when examining evidence of differential risk), variability in how indicators or metrics are defined across studies (e.g., socioeconomic status, obesity, age), and variability in the population as a whole, particularly with respect to behavioral differences, biological differences (e.g., obese vs. nonobese), and adherence to treatment for pre-existing diseases.

Of the factors evaluated (see Table 12-18 for a full list), children and race were the only factors for which it was concluded that "*adequate evidence*" was available indicating that people of a specific lifestage and race are at increased risk of $PM_{2.5}$-related health effects (Section 12.5.1.1 and Section 12.5.4). For children, although stratified analyses do not indicate a difference in the risk of PM-related health effects between children and adults, there is strong evidence from studies focusing on children demonstrating health effects that are only observable in growing children, attributed to $PM_{2.5}$ exposure. Particularly recent epidemiologic studies of long-term $PM_{2.5}$ exposure have provided strong evidence of impaired lung function growth with additional evidence of decrements in lung function and asthma development. These longitudinal epidemiologic studies are consistent with and extend the evidence that was available in the 2009 PM ISA demonstrating health effects in children due to long-term $PM_{2.5}$ exposure. For race, this conclusion was based on studies that examined whether there was evidence of increased risk for $PM_{2.5}$-related health effects as well as studies focusing on whether there was evidence of differential exposure by race. Multiple studies reported that nonwhite populations across

different geographical regions are exposed to higher $PM_{2.5}$ concentrations and at increased risk for $PM_{2.5}$-related mortality, particularly due to long-term exposure. Collectively, the combination of evidence demonstrated that nonwhite populations are at increased risk for both $PM_{2.5}$-related health effects and $PM_{2.5}$ exposure compared to whites.

It was concluded that there is "*suggestive evidence"* that populations with pre-existing cardiovascular (Section 12.3.1) or respiratory (Section 12.3.5) disease, that are overweight or obese (Section 12.3.3), with particular genetic variants (Section 12.4), or that are of low SES (Section 12.5.3) are at increased risk for $PM_{2.5}$-related health effects. Epidemiologic studies that conducted analyses stratified by pre-existing cardiovascular disease tended to focus on hypertension, one of the most easily measurable cardiovascular conditions, and did not consistently indicate increased risk for several outcomes examined (e.g., mortality, stroke, blood pressure). However, the strong evidence supporting a "*causal relationship*" between short- and long-term $PM_{2.5}$ exposure cardiovascular-related mortality and ischemic heart disease (Section 6.1.16 and Section 6.2.18) indicates that individuals with underlying cardiovascular conditions related to these serious outcomes may be at increased risk of a $PM_{2.5}$-related health effect. Similarly, when evaluating pre-existing respiratory diseases, including asthma (Section 12.3.5) and COPD (Section 12.3.5), there are a limited number of studies evaluating whether there is evidence of increased risk between people with pre-existing asthma and COPD and those that do not have a pre-existing respiratory disease. However, it is important to note that epidemiologic studies, particularly those studies examining short-term $PM_{2.5}$ exposure and asthma or COPD emergency department visits and hospital admissions report generally consistent positive associations (Section 5.1.2.1 and Section 5.1.4.1), which represent exacerbations that are only possible in people with asthma or COPD. Therefore, there is limited evidence to support that people with pre-existing respiratory diseases, specifically asthma or COPD, are at increased risk for a $PM_{2.5}$-related health effect, but there is generally consistent evidence demonstrating these populations experience health effects due to a $PM_{2.5}$ exposure. Studies that examined the role of being obese or overweight on the risk of a $PM_{2.5}$-related health effect, reported evidence of increased risk for mortality associated with long-term exposures to $PM_{2.5}$, but inconsistent evidence for subclinical cardiovascular outcomes, when comparing obese or overweight individuals to normal weight individuals. However, the evaluation of studies focusing on differences in risk by weight were complicated by the different definitions of obesity used across studies. The examination of whether specific genetic characteristics dictate increased risk of a $PM_{2.5}$-related health effect is based on studies of a variety of genetic variants. Across the large number of genetic variants examined there is a consistent trend for increased risk of respiratory and cardiovascular effects associated with $PM_{2.5}$ exposure across gene variants involved in the glutathione pathway. These results are consistent with underlying mechanisms that provide biological plausibility for $PM_{2.5}$-related health effects and have shown that oxidative stress is an early response to $PM_{2.5}$ exposure. Lastly, epidemiologic studies have examined several measures of SES (e.g., income level, educational attainment, etc.) in assessing whether populations are at increased risk of a $PM_{2.5}$-related health effect. In studies examining both differential exposure as well as increased risk of health effects, there is some evidence that low SES populations are more likely to have higher $PM_{2.5}$ exposures and that low SES populations, as measured by metrics for

income, are at increased risk of $PM_{2.5}$-related mortality when compared to populations defined as higher SES.

For the remaining factors evaluated, "*inadequate evidence*" exists to determine whether having diabetes (Section 12.3.2), being in an older lifestage (i.e. older adults) (Section 12.5.1.2), residential location (including proximity to source and urban residence; Section 12.5.5), sex (Section 12.5.2), or diet (Section 12.6.2) increase the risk of $PM_{2.5}$-related health effects. Across these factors there is either limited assessment of differential risk or exposure (i.e., residential location, diet), or inconsistency in results across studies to support evidence of increased risk of a $PM_{2.5}$-related health effect (i.e., diabetes and sex). However, as stated previously this does not indicate there is no evidence of a $PM_{2.5}$-related health effect for these populations and lifestages, but limits the assessment of determining whether a specific population is at disproportionately increased risk of a health effect. For example, for older adults (Section 12.5.1.2) there is a relatively small number of studies that examined whether there is evidence of differential risk between age groups. In the evaluation of these studies there is limited evidence indicating that older adults are at increased risk of $PM_{2.5}$-related health effects when compared to other age ranges; however, epidemiologic studies focusing only on older adults demonstrate associations with respiratory-related emergency department visits and hospital admissions with additional, but more limited, evidence from epidemiologic panel studies and controlled human exposure studies that observed associations between $PM_{2.5}$ exposure and subclinical cardiovascular effects.

1.6 Welfare Effects of PM

Whereas the evaluation of the evidence for PM exposures and health effects are specific to exposure duration (i.e., short- and long-term) and PM size fraction (i.e., $PM_{2.5}$, $PM_{10-2.5}$, and UFP), the evaluation of the evidence for welfare effects focuses generally on whether there is a causal relationship between PM and visibility impairment, climate effects, and effects on materials. As detailed below, the evidence continues to support a "*causal relationship*" between PM and visibility impairment (Section 1.6.1), climate effects (Section 1.6.2), and materials effects (Section 1.6.3).

1.6.1 Visibility Impairment

It has been well characterized that light extinction from pollution is primarily due to $PM_{2.5}$, resulting in the conclusion that there is a "*causal relationship*" between PM and visibility impairment, which is consistent with the conclusions of the 2009 PM ISA (Table 1-4). This conclusion is based on additional characterization of the impact of PM size and composition on light extinction.

The relationship between PM and light extinction has been well documented (Section 13.2.2). Although reconstruction of light extinction is best achieved with detailed information on the size and

composition of PM measurements, empirical relationships between light extinction of PM components are more practical and have been successfully evaluated and widely used (Section 13.2.3). Light extinction has been found to vary depending on the available PM species monitoring data, with light extinction efficiencies varying by a factor of 10 between species. Additionally, the variation in PM species by region and season as well as urban and rural location can impact light extinction. The steep decline in $PM_{2.5}$ sulfate of −4.6% per year in rural areas and −6.2% per year in urban areas from 2002−2012 (Section 1.2.1) has impacted the apportionment of light extinction among $PM_{2.5}$ species. Although $PM_{2.5}$ sulfate is still responsible for more light extinction than any other single species, visibility in many areas has improved, and a smaller and less seasonally variable fraction of light extinction can be attributed to $PM_{2.5}$ sulfate, and an increasing share is due to nitrate and organic matter (Section 13.2.4).

1.6.2 Climate Effects

Substantial evidence indicates that PM affects the radiative forcing of the climate system, both through direct scattering and absorption of radiation, and indirectly, by altering cloud properties, resulting in the conclusion that there is a "*causal relationship*" between PM and climate effects, which is consistent with the conclusions of the 2009 PM ISA (Table 1-4). This conclusion is based on multiple recent studies that have strengthened the evidence for the effects of PM on radiative forcing and have improved the characterization of major sources of uncertainty in estimating PM climate effects, including the indirect radiative forcing effects associated with PM-cloud interactions, and the additional climate impacts and feedbacks involving atmospheric circulation and the hydrologic cycle resulting from PM effects on radiative forcing.

Due to these radiative effects, the net effect of PM has been to cool the planet over the last century, masking some of the effects of greenhouse gases on warming (Section 13.3.3). The decrease in PM concentrations in many developed countries over the last few decades has likely contributed to the recent shift toward "global brightening," which may in turn have helped drive rapid warming in North American and Europe as this greenhouse-gas warming was unmasked (Section 13.3.6). In developing countries in Asia, by contrast, there has been an increase in PM concentrations over the last several decades, but the associated radiative forcing effects are highly uncertain, due to uncertainties in emissions estimates and the lack of accurate information on the proportion of reflecting versus absorbing species. Although uncertainties in the relationship between PM and climate effects have been further elucidated since the 2009 PM ISA, there are still substantial uncertainties with respect to key processes linking PM and climate, specifically clouds and aerosols. This is because of the small scale of PM-relevant cloud microphysical processes compared to the resolution of state-of-the-art models, and because of the complex cascade of indirect impacts and feedbacks in the climate system that result from a given initial radiative perturbation caused by PM.

1.6.3 Materials Effects

Multiple recent studies further characterize soiling and corrosion processes associated with PM and add to the body of evidence of PM damage to materials. Approaches to quantify pollutant exposure corresponding to perceived soiling and damage continue to indicate that deposition can result in increased cleaning and maintenance costs and reduced usefulness of soiled material. The combination of this evidence results in the conclusion that there is a "*causal relationship*" between PM and effects on materials, which is consistent with the conclusions of the 2009 PM ISA (Table 1-4).

Assessments of the relationship between PM and effects on materials have often focused on quantitative assessments including the development of dose-response relationships and application of damage functions to stone used for historic monuments and buildings. Recent studies provide additional information on understanding soiling and corrosion process for glass and metals, and allowed for the development of new dose-response curves (Section 13.4.3), particularly for glass as well as new damage functions for materials (Section 13.4.4). Additional evidence demonstrates that atmospheric soiling can impact energy costs and climate control, energy consumption of large buildings, and efficiency of photovoltaic systems (Section 13.4.2).

Table 1-4 Key Evidence contributing to a "causal" causality determination for PM exposure and welfare effects evaluated in the current draft Integrated Science Assessment for Particulate Matter.

Key Evidence	Welfare Effect Category[a] and Causality Determination
Visibility Impairment and PM Exposure (Section 13.2): Causal Relationship	
No change in causality determination from the 2009 PM ISA; new evidence further supports the previous determination.	
Section 13.2.6	Visibility impairment by atmospheric PM with the strongest effects in the size range from 0.1 to 1.0 μm, is supported by numerous studies summarized in the 1969 PM AQCD (NAPCA, 1969), although the relationship between PM and atmospheric visibility impairment was well-established decades earlier. Additional studies supporting the relationship have been described in subsequent documents, and additional new evidence is based on extensive simultaneous network measurements of $PM_{2.5}$ and light extinction.
Climate Effects and PM Exposure (Section 13.3): Causal Relationship	
No change in causality determination from the 2009 PM ISA; new evidence further supports the previous determination.	
Section 13.3.9	Effects of PM on radiative forcing of the climate system through both absorption and scattering of radiation directly, as well as through indirect effects involving interactions between PM and cloud droplets, with corresponding impacts on temperature, precipitation, and atmospheric circulation, is supported by numerous observational and modeling studies. Research since the 2009 ISA (U.S. EPA, 2009) has improved understanding of climate-relevant aerosol properties and processes, as well as characterization of key sources of uncertainty in estimating PM climate effects, particularly with respect to PM-cloud interactions.
Materials Effects and PM Exposure (Section 13.4): Causal Relationship	
No change in causality determination from the 2009 PM ISA; new evidence further supports the previous determination.	
Section 13.4.5	Both soiling and corrosion associated with PM contribute to materials damage (U.S. EPA, 2009, 2004, 1982). Deposition of PM can physically affect materials by promoting or accelerating the corrosion of metals, by degrading paints and by deteriorating building materials such as stone, concrete and marble. Further characterization of PM effects on glass and metals along with quantitative dose-response relationships and damage functions for stone and other materials lend additional support to the causal relationship in the 2009 ISA. Recent evidence shows that deposition of PM reduces energy efficiency of photovoltaic systems.

[a]The sections referenced include a detailed discussion of the available evidence that informed the causality determinations.

1.7 Summary of Causality Determinations for All Health and Welfare Effects

The preceding sections of this chapter focused on summarizing the key evidence that formed the basis for causality determinations within this ISA. Table 1-5 and Table 1-6 detail the causality determinations for each of the exposure duration and health or welfare effects categories evaluated in this ISA and note whether these conclusions differ from those presented in the 2009 PM ISA.

There is extensive scientific evidence that demonstrates health and welfare effects from exposure to PM. In assessing the older and more recent evidence, the U.S. EPA characterizes the key strengths and remaining limitations of this evidence. In the process of assessing the evidence across studies and scientific disciplines and ultimately forming causality determinations, the U.S. EPA takes into consideration multiple aspects that build upon the Hill Criteria (Hill, 1965) and include, but are not limited to consistency in findings, coherence of findings, and evidence of biological plausibility [see U.S. EPA (2015)]. As documented by the extensive evaluation of evidence throughout the subsequent chapters of this ISA, the U.S. EPA carefully considers uncertainties in the evidence, and the extent to which recent studies have addressed or reduced uncertainties from previous assessments, as well as the strengths of the evidence. Uncertainties considered in the epidemiologic evidence, for example, include the potential for confounding by copollutants or covarying factors and exposure error. The U.S. EPA evaluates many other important considerations (not uncertainties) such as coherence of evidence from animal and human studies, evaluation of different PM components, heterogeneity of risk estimates, and the shape of concentration-response relationships. All aspects are evaluated along with the degree to which chance, confounding, and other biases affect interpretation of the scientific evidence in the process of drawing scientific conclusions and making causality determinations. Where there is clear evidence linking PM with health and welfare effects with minimal remaining uncertainties, the U.S. EPA makes a determination of a *causal* or *likely to be causal* relationship (Section P.3, Table P-2).

1.7.1 Health Effects Evidence: Key Findings

A large body of scientific evidence spanning many decades clearly demonstrates there are health effects attributed to both short- and long-term PM exposure, with the strongest evidence for a relationship between some health effects and $PM_{2.5}$. Generally, for most health effects and exposures to $PM_{10-2.5}$ and UFPs, there are more limitations and uncertainties across scientific disciplines (i.e., atmospheric chemistry, exposure science, and both epidemiology and experimental sciences), complicating the interpretation of the evidence. The collective body of evidence for each of the PM size fraction, exposure, and health outcome category combinations evaluated in this ISA was carefully considered and assessed, including the inherent strengths, limitations, and uncertainties in the overall body of evidence such as the

available methods, models and data used within and across studies, resulting in the causality determinations detailed in Table 1-5. Through identification of the strengths and limitations in the evidence this ISA may help in the prioritization of research efforts to support future PM NAAQS reviews. Examples of the key findings that support the health effects causality determinations include:

Table 1-5. Summary of causality determinations for health outcome categories for first draft PM ISA.

HUMAN HEALTH EFFECTS					
		ISA	Current PM Draft ISA		
		Indicator	$PM_{2.5}$	$PM_{10-2.5}$	UFP
Health Outcome	Mortality	Short-term exposure	Likely causal	Suggestive	
		Long-term exposure	Likely causal	*	
	Respiratory	Short-term exposure	Likely causal	Suggestive	Suggestive
		Long-term exposure	Likely causal		
	Cardiovascular	Short-term exposure	Causal	Suggestive	Suggestive
		Long-term exposure	Causal	*	
	Metabolic	Short-term exposure	*	*	*
		Long-term exposure	*	*	*
	Reproductive: Male/Female Reproduction and Fertility	Long-term exposure	Suggestive		
	Reproductive: Pregnancy and Birth Outcomes		Suggestive		
	Cancer	Long-term exposure	*	*	
	Central nervous system	Short-term exposure	*		*
		Long-term exposure	*	*	*

Causal | Likely causal | Suggestive | Inadequate

* = new determination or change in causality determination from 2009 PM ISA

Causal and Likely to be Causal Relationship

Epidemiologic evidence:

$PM_{2.5}$

- There are many epidemiologic studies conducted in diverse geographic locations, encompassing different population demographics, and using a variety of exposure assignment techniques, that continue to report consistent positive associations between short- and long-term $PM_{2.5}$ exposure and various health effects. This evidence continues to support the large body of epidemiologic studies reporting positive $PM_{2.5}$ associations with respiratory and cardiovascular effects, and mortality and in some cases strengthens and extends the evidence base.
- Recent epidemiology studies incorporate new $PM_{2.5}$ exposure assignment methods that utilize several sources of available data (i.e., satellite observations, model predictions, and ambient monitors). These methods are well validated by $PM_{2.5}$ monitors in areas with moderate-to-high population density and better allow for the inclusion of less urban areas. Although fewer monitors are available for model validation in sparsely populated rural areas compared with urban areas, $PM_{2.5}$ concentrations are typically lower and more spatially homogeneous in rural areas, resulting in the need for fewer validation sites.
- Each of the exposure assignment methods used in short- and long-term $PM_{2.5}$ exposure epidemiologic studies have inherent strengths and limitations, and vary in the degree they contribute bias and uncertainty to health effects estimates. Exposure errors most often result in the underestimation of health effects associations in short- and long-term $PM_{2.5}$ exposure studies (i.e., health effect associations are even larger than estimated). However, in long-term $PM_{2.5}$ exposure studies health effects associations can be overestimated, specifically when the exposure model has low spatial resolution and underestimates $PM_{2.5}$ exposures.

Experimental evidence:

$PM_{2.5}$ and UFP

- The large number of animal toxicological and controlled human exposure studies conducted since the 2009 PM ISA provide coherence (i.e., an indication of an effect across multiple lines of evidence) and biological plausibility for effects observed in epidemiologic studies of short- or long-term $PM_{2.5}$ exposure. Although experimental studies are conducted at PM concentrations higher than those often observed in ambient environments (e.g., concentrated ambient particle [CAP] exposures 10−15-fold higher), this practice is consistent with the design of experimental studies used in chemical and pharmacological risk assessments.
- There is strong and consistent animal toxicological evidence linking long-term UFP exposure to nervous system effects. This evidence is supported by dosimetric studies in animals showing that particles can translocate out of the respiratory tract into the brain via the olfactory nerve, however, it is unclear whether this translocation occurs in humans as well as in animals. There is also uncertainty surrounding the mechanisms and degree to which particles translocate from the respiratory tract to the brain. However, translocation of particles to the brain may not be required for UFP-related nervous system effects.
- There is uncertainty in the spatial and temporal variability in UFP concentrations and subsequently population exposures to UFPs, questioning the generalizability of the animal toxicological evidence indicating nervous system effects to the population-level.

Policy-relevant considerations:

- The expansion in the number of experimental studies, both animal toxicological and controlled human exposure, using CAP exposures provides evidence of a direct effect of PM exposure on various health effects.
- The $PM_{2.5}$ experimental evidence in combination with the increased number of epidemiologic studies that conducted copollutant analyses show that associations remain relatively unchanged when adjusting for gaseous pollutants and other particle size fractions (e.g., $PM_{10–2.5}$), addressing a key uncertainty identified in the 2009 PM ISA.
- Examination of the concentration-response (C-R) relationship has primarily been conducted for short- and long-term $PM_{2.5}$ exposure and mortality, with a more limited number of analyses examining cardiovascular morbidity effects. Across recent studies that used a variety of statistical methods to examine potential deviations in linearity, evidence continues to support a linear, no-threshold C-R relationship, but with less certainty in the shape of the curve at lower concentrations, i.e., below about 8 $\mu g/m^3$. Additionally, recent evidence from studies of long-term $PM_{2.5}$ exposure and cardiovascular mortality indicate that the C-R curve may be steeper (i.e., supralinear) at lower concentrations.
- Multicity epidemiologic studies, particularly examining short-term $PM_{2.5}$ exposure and mortality, continue to report evidence of heterogeneity in the magnitude and precision of risk estimates across cities. However, recent studies indicate that the observed heterogeneity in risk estimates is not attributed solely to differences in the composition of $PM_{2.5}$, as was hypothesized in the 2009 PM ISA, but also reflects city-specific exposure conditions (e.g., housing and commuting characteristics).
- The combination of evidence spanning atmospheric chemistry, experimental, and epidemiology show that although the composition of ambient $PM_{2.5}$ has changed over time, evidence continues to support that a multitude of $PM_{2.5}$ components and a diverse array of sources are associated with a variety of health effects, and the evidence does not indicate that any one source or component is more strongly related with health effects than $PM_{2.5}$ mass.

Suggestive of, but not Sufficient to Infer, a Causal Relationship

Epidemiologic evidence:

$PM_{2.5}$

- Recent epidemiologic studies examining short- or long-term $PM_{2.5}$ exposure and various health effects report inconsistent evidence of an association or there are relatively few studies focusing on the health effect of interest.
- Additionally, recent studies conducted a limited assessment of potential copollutant confounding for some health effects.

$PM_{10–2.5}$

- Recent epidemiologic studies continue to examine associations between short- or long-term $PM_{10–2.5}$ exposure and various health effects, and report generally positive associations (i.e., not all results are positive). However, many of these studies are conducted in locations outside of the U.S. Additionally, the overall interpretation of results across studies is complicated by the use of different methods to estimate $PM_{10–2.5}$ concentrations because the design of the $PM_{10–2.5}$ FRM was not finalized until 2006 and routine $PM_{10–2.5}$ monitoring with the FRM was not instituted until 2011.

- $PM_{10–2.5}$ concentrations are more spatially and temporally variable than $PM_{2.5}$. Although some $PM_{10–2.5}$ data are available across the nation, micro-to-neighborhood scale data are not widely available, adding uncertainty to the interpretation of results from epidemiologic studies, especially for long-term exposure studies that rely on spatial contrasts to examine associations with health effects.

UFP

- There are a limited number of epidemiologic studies examining short-term UFP exposure and health effects, with some providing initial evidence of positive associations. However, it is difficult to assess the results across studies due to the different size ranges of UFPs examined and exposure metrics used (i.e., particle number concentration, surface area concentration, mass concentration).
    - There is no national monitoring network in place to measure UFP concentrations. As a result, there is limited information on the spatial and temporal variability of UFP concentrations within the U.S., but it has been reported UFPs vary more over space and time than $PM_{2.5}$. As a result, the use of one monitor in most epidemiologic studies to estimate UFP concentrations may not adequately capture population exposure to UFPs.
    - There is a difference in the size range of UFPs examined in epidemiologic studies (0.1 um and less) and experimental studies (i.e., up to 0.3 um). This difference adds uncertainty to the examination of the coherence of effects observed in experimental and epidemiologic studies. Furthermore, the spatial and temporal variability in UFP concentrations as well as population exposures to UFPs adds uncertainty to epidemiologic findings.

Experimental evidence:

$PM_{2.5}$ and $PM_{10–2.5}$

- Animal toxicological and controlled human exposure studies provide limited, and in some instances inconsistent, evidence of effects due to short- or long-term $PM_{2.5}$ and $PM_{10–2.5}$ exposure. As a result, there is limited coherence with results from epidemiologic studies and limited evidence indicating biologically plausible pathways by which effects could occur.

UFP

- For all other health effect categories besides nervous system effects, animal toxicological and controlled human exposure studies provide limited, and in some instances inconsistent, evidence of effects due to short- or long-term UFP exposure contributing to limited coherence and biological plausibility for some health effects categories.

<u>Inadequate to Infer the Presence or Absence of a Causal Relationship</u>

$PM_{10–2.5}$ and UFPs

Epidemiologic evidence:

- Depending on the health effect, few or no epidemiologic studies examined the relationship between short- and long-term $PM_{10–2.5}$ or UFP exposures and various health effects. These studies often include single-city analyses that were conducted over short study durations. As noted previously, (1) for studies examining $PM_{10–2.5}$, the methods used to estimate $PM_{10–2.5}$

concentrations across studies varies and it is unclear how well correlated concentrations are across methods; and (2) for UFP studies, this includes inconsistency in the size ranges examined across studies and the exposure metric used, which prevents a thorough comparison of results across studies.

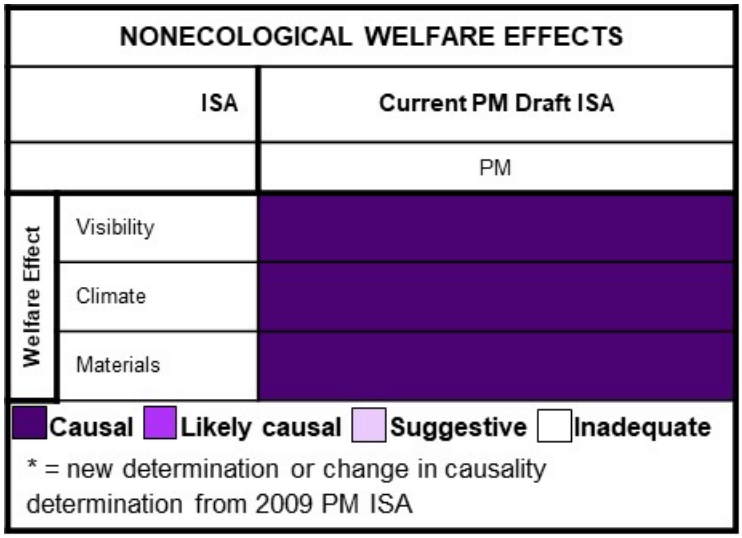
Experimental evidence:

- Depending on the health effect, few or no experimental studies examined the relationship between short- and long-term $PM_{10–2.5}$ or UFP exposures and various health effects. The few studies conducted provide inconsistent evidence of effects due to $PM_{10–2.5}$ or UFP exposures. As a result, there is limited to no evidence to support coherence of effects across multiple lines of evidence and limited to no evidence of biologically plausible pathways that could elicit an effect.

1.7.2 Welfare Effects Evidence: Key Findings

A large body of scientific evidence spanning many decades also demonstrates there are welfare effects attributed to PM. Examples of the key findings that support the welfare effects causality determinations detailed in Table 1-6 include:

Table 1-6. Summary of causality determinations for welfare effects for first draft PM ISA.



- Recent studies further confirm evidence from previous assessments supporting the strong relationship between PM and the nonecological welfare effects of visibility impairment, effects on the climate, and materials damage.

- For visibility impairment and materials damage there is extensive evidence demonstrating the relationship between PM and light extinction and PM impacts on stone, respectively.
- While there is substantial evidence indicating that PM affects the climate system, specifically through radiative forcing, there are still substantial uncertainties in key processes, such as the relationship between clouds and aerosols and the indirect impacts and feedbacks in the climate system due to the radiative effect of PM.

Table 1-7 below presents a side-by-side comparison of all causality determinations presented in this ISA and the 2009 PM ISA for each of the health and welfare effects categories evaluated in subsequent chapters.

Table 1-7 Causality determinations from the 2009 PM ISA and the current PM ISA for the health and welfare effects categories evaluated.

Summary of Causality Determinations		
CHAPTER 5. Respiratory Effects		
Short-term Exposure		
Size Fraction	2009 PM ISA	Current PM ISA
$PM_{2.5}$	Likely to be causal	Likely to be causal
$PM_{10-2.5}$	Suggestive of, but not sufficient to infer	Suggestive of, but not sufficient to infer
UFP	Suggestive of, but not sufficient to infer	Suggestive of, but not sufficient to infer
Long-term Exposure		
Size Fraction	2009 PM ISA	Current PM ISA
$PM_{2.5}$	Likely to be causal	Likely to be causal
$PM_{10-2.5}$	Inadequate	Inadequate
UFP	Inadequate	Inadequate
CHAPTER 6. Cardiovascular Effects		
Short-term Exposure		
Size Fraction	2009 PM ISA	Current PM ISA
$PM_{2.5}$	Causal	Causal
$PM_{10-2.5}$	Suggestive of, but not sufficient to infer	Suggestive of, but not sufficient to infer
UFP	Suggestive of, but not sufficient to infer	Suggestive of, but not sufficient to infer

Table 1-7 (Continued): Causality determinations from the 2009 PM ISA and the current PM ISA for the health and welfare effects categories evaluated.

Summary of Causality Determinations		
Long-term Exposure		
Size Fraction	2009 PM ISA	Current PM ISA
$PM_{2.5}$	Causal	Causal
$PM_{10-2.5}$	Inadequate	Suggestive of, but not sufficient to infer
UFP	Inadequate	Inadequate
CHAPTER 7. Metabolic Effects		
Short-term Exposure		
Size Fraction	2009 PM ISA	Current PM ISA
$PM_{2.5}$	---	Suggestive of, but not sufficient to infer
$PM_{10-2.5}$	---	Inadequate
UFP	---	Inadequate
Long-term Exposure		
Size Fraction	2009 PM ISA	Current PM ISA
$PM_{2.5}$	---	Suggestive of, but not sufficient to infer
$PM_{10-2.5}$	---	Suggestive of, but not sufficient to infer
UFP	---	Inadequate
CHAPTER 8. Nervous System Effects		
Short-term Exposure		
Size Fraction	2009 PM ISA	Current PM ISA
$PM_{2.5}$	Inadequate	Suggestive of, but not sufficient to infer
$PM_{10-2.5}$	Inadequate	Inadequate
UFP	Inadequate	Suggestive of, but not sufficient to infer
Long-term Exposure		
Size Fraction	2009 PM ISA	Current PM ISA
$PM_{2.5}$	---	Likely to be causal
$PM_{10-2.5}$	---	Suggestive of, but not sufficient to infer

Table 1-7 (Continued): Causality determinations from the 2009 PM ISA and the current PM ISA for the health and welfare effects categories evaluated.

Summary of Causality Determinations		
UFP	---	Likely to be causal
CHAPTER 9. Reproductive and Developmental Effects		
Male and Female Reproduction and Fertility		
Size Fraction	2009 PM ISA	Current PM ISA
$PM_{2.5}$	Suggestive of, but not sufficient to infer	Suggestive of, but not sufficient to infer
$PM_{10-2.5}$	Inadequate	Inadequate
UFP	Inadequate	Inadequate
Pregnancy and Birth Outcomes		
Size Fraction	2009 PM ISA	Current PM ISA
$PM_{2.5}$	Suggestive of, but not sufficient to infer	Suggestive of, but not sufficient to infer
$PM_{10-2.5}$	Inadequate	Inadequate
UFP	Inadequate	Inadequate
CHAPTER 10. Cancer		
Size Fraction	2009 PM ISA	Current PM ISA
$PM_{2.5}$	Suggestive of, but not sufficient to infer	Likely to be causal
$PM_{10-2.5}$	Inadequate	Suggestive of, but not sufficient to infer
UFP	Inadequate	Inadequate
CHAPTER 11. Mortality		
Short-term Exposure		
Size Fraction	2009 PM ISA	Current PM ISA
$PM_{2.5}$	Causal	Causal
$PM_{10-2.5}$	Suggestive of, but not sufficient to infer	Suggestive of, but not sufficient to infer
UFP	Inadequate	Inadequate
Long-term Exposure		
Size Fraction	2009 PM ISA	Current PM ISA
$PM_{2.5}$	Causal	Causal

Table 1-7 (Continued): Causality determinations from the 2009 PM ISA and the current PM ISA for the health and welfare effects categories evaluated.

Summary of Causality Determinations		
$PM_{10-2.5}$	Inadequate	Suggestive of, but not sufficient to infer
UFP	Inadequate	Inadequate
CHAPTER 13. Welfare Effects		
	2009 PM ISA	Current PM ISA
Climate	Causal	Causal
Visibility	Causal	Causal
Materials Damage	Causal	Causal

The 2009 PM ISA made causality determinations for the broad category of "Reproductive and Developmental Effects". Causality determinations for 2009 represent this broad category and not specifically for "Male and Female Reproduction and Fertility" and "Pregnancy and Birth Outcomes".

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CHAPTER 2 SOURCES, ATMOSPHERIC CHEMISTRY, AND AMBIENT CONCENTRATIONS

Summary of Sources, Atmospheric Chemistry, and Ambient Concentrations of Particulate Matter (PM)

- National 3-year average $PM_{2.5}$ concentrations decreased from 12 µg/m^3 to 8.6 µg/m^3 between the 3-year periods 2005−2007 and 2013−2015.
- SO_2 emissions decreased from 13.9 million metric tons in 2006 to 4.8 million metric tons in 2014. This decrease led to large decreases in the sulfate contribution to $PM_{2.5}$ and contributed to the decrease in $PM_{2.5}$ concentration. Emissions of NO_X and primary $PM_{2.5}$ have also decreased, but not NH_3.
- Seasonal patterns of $PM_{2.5}$ concentrations have changed from summer as the season with highest national average $PM_{2.5}$ concentration to rough equivalence in national average concentration between summer and winter. Sulfate concentrations have been historically highest in summer.
- The relative $PM_{2.5}$ contribution to PM_{10} has decreased and the relative $PM_{10-2.5}$ contribution to PM_{10} has increased since 2004.
- Extensive research has led to advances in understanding the formation of secondary organic aerosols, in particular with regard to biogenic precursor reactions, heterogeneous reactions, and production of organonitrates and organosulfates.
- For the first time, a national multipollutant monitoring network was implemented, and it includes simultaneous measurements for $PM_{2.5}$ and $PM_{10-2.5}$ using a Federal Reference Method at 78 monitoring sites.
- For the first time, a national near road $PM_{2.5}$ monitoring method was implemented, and it includes 36 monitoring sites.
- For the first time, routine monitoring of particle number count was implemented at 23 monitoring sites.

2.1 Summary Overview

This chapter presents basic concepts and new research in atmospheric sciences relevant for understanding exposure, health effects, and welfare effects discussed throughout this document. It builds on information presented in the 2009 Integrated Science Assessment for Particulate Matter (hereafter referred to as the 2009 PM ISA) (U.S. EPA, 2009) and earlier PM Air Quality Criteria Documents (AQCDs) by reviewing recent research on PM sources, chemistry, composition, measurement, monitoring, modeling, and atmospheric concentrations. Among the new results and observations are some fundamental changes in PM in the Eastern U.S. over the past decade, including a sharp decrease in the contribution of sulfate to PM, a shift in particle size distribution toward particles in 2.5 to 10 µm diameter size range, and a shift in seasonal maximum concentrations from summer to winter. These changes likely resulted from a recent sharp decline in SO_2 emissions due to stronger emission controls, as well as fuel switching and closures of coal-fired power plants. The highest $PM_{2.5}$ and PM_{10} concentrations continue to

persist in some areas in the Western U.S. Recent progress in PM measurement includes network implementation of improved methodologies for accurate measurement of particulate mass in the size range between 2.5 and 10 µm diameter, initiation of near road monitoring of $PM_{2.5}$, initiation of routine monitoring of particle number counts at a small number of near road and remote locations, and advancement of methods for retrieval and application of satellite data for estimating $PM_{2.5}$.

This chapter is organized into sections by major topic (sources, measurements, etc.) and where appropriate, content in each section is divided into subsections by size range and other subtopics such as PM composition. Section 2.2 contains a basic description of ambient PM size distributions and typical particle size characteristics to set the stage for this organization. Section 2.3 discusses sources and emissions of PM and its major precursors as well as atmospheric chemistry of PM. Section 2.4 addresses advances in measurement and modeling of PM and describes PM monitoring networks. Section 2.5 summarizes recent concentration trends, including spatial and temporal variability on national and local scales. Section 2.6 provides an overall synthesis of the chapter highlighting major new findings.

2.2 Atmospheric Size Distributions

Airborne particulate matter is a mixture of substances suspended in air as small liquid and/or solid particles. These individual particles range in size from less than 0.01 µm to more than 10 µm. Particle size is an important characteristic for health effects because different size particles penetrate into different regions of the human respiratory tract, potentially leading to distinctive health consequences for various particle size ranges (U.S. EPA, 2009). The effect of particle size on particle behavior in the respiratory system is described in Section 4.1.6. Particle size also plays an important role in welfare effects covered in CHAPTER 13, particularly for effects on radiative forcing and visibility. Properties and effects of various particle size ranges are considered separately in this document, and particle size is used as an important organizing framework for the various sections both in this chapter and in the entire document.

PM subscripts refer to the aerodynamic diameter in micrometers (µm) of 50% cut points of sampling devices. For example, U.S. EPA defines $PM_{2.5}$ as particles collected by a sampler with an upper 50% cut point of 2.5 µm aerodynamic diameter and a specific, sharp penetration curve as defined in the Code of Federal Regulations (40 CFR Part 58) (U.S. EPA, 2009). Similarly, $PM_{10-2.5}$ is the PM mass collected with an upper 50% cut point of 10 µm and a lower 50% cut point of 2.5 µm. Ultrafine particles (UFP) are often defined as particles with a diameter of <0.1 µm based on physical size, thermal diffusivity or electrical mobility (U.S. EPA, 2009). By definition, UFP encompass all particles smaller than the defined upper diameter limit. However, in practice UFP measurement methods (Section 2.4.3) have varying lower and upper size limits and measured concentration is instrument-dependent (see Preface).

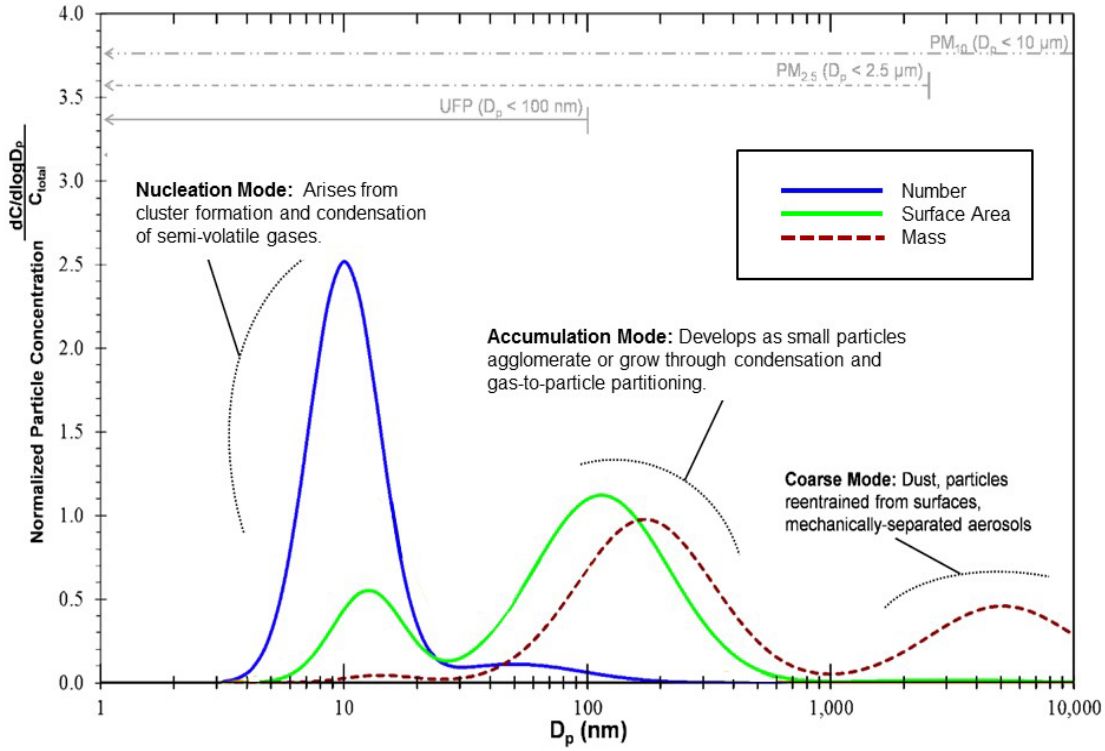
Material presented in this and following chapters will focus on particles in the fine ($PM_{2.5}$), coarse ($PM_{10–2.5}$), and ultrafine particle (UFP) size ranges as shown in Figure 2-1. There is also some limited discussion of PM_{10}. This is because longer term monitoring data exist for PM_{10} than for either $PM_{2.5}$ or $PM_{10–2.5}$, and occasionally PM_{10} data are available when $PM_{2.5}$ or $PM_{10–2.5}$ data are lacking. Each of these size ranges were described in detail in the 2009 PM ISA (U.S. EPA, 2009).

Atmospheric particle size distributions usually exhibit distinct size modes which roughly align with the above PM size ranges. An example particle size distribution, showing a nucleation mode, accumulation mode, and coarse mode, is illustrated in Figure 2-1 (Kittelson and Kraft, 2015; Kittelson, 1998). Both number of particles and particulate mass are unevenly distributed in a typical atmospheric particle size distribution, forming distinct lognormal size modes in the atmospheric particle size distribution, each with different local maxima and measurable variance (Whitby, 1978). The nucleation mode is generally made up of freshly generated particles, formed either during combustion or by atmospheric reactions of precursor gases. The nucleation mode is especially prominent near sources like heavy traffic, industrial emissions, biomass burning, or cooking (Vu et al., 2015). Particle size is not static and nucleation mode particles grow rapidly through coagulation of particles or uptake of gases by particle surfaces, giving rise to the accumulation mode. Particle size in the accumulation mode is limited by removal from the atmosphere (Friedlander, 1977) through wet and dry deposition. Coarse mode particles are formed by mechanical generation, and through processes like dust resuspension and sea spray formation (Whitby et al., 1972). Usually, the accumulation mode is the predominant contributor to PM mass and surface area, but only a minor contributor to particle number. Conversely, nucleation mode particles are only a minor contributor to PM mass and surface area, but the main contributor to particle number.

In principle, PM measurement methods are designed to correspond to one or more of the PM size modes in Figure 2-1. In practice, they are restricted to fixed particle size ranges while PM size modes are dynamic and continually changing. As a result, the subscripted PM size ranges (i.e., $PM_{2.5}$, $PM_{10–2.5}$) may not exactly match up with distinct PM size modes. However, there is a rough correspondence that can be useful for interpreting PM measurements. By number, most nucleation mode particles usually fall into the UFP range, but it is possible some fraction of the nucleation mode number distribution extends beyond above 0.1 μm in diameter. By surface area or mass, the peak of the nucleation mode corresponds to a greater diameter than for particle number, and it is more likely that a substantial fraction of particle surface area or mass is due to nucleation mode particles larger than the UFP upper limit. Most of the nucleation and accumulation mode mass is captured by $PM_{2.5}$ sampling, although a small fraction of particles that make up the accumulation mode are greater than 2.5 μm in diameter. Most coarse mode mass is captured by $PM_{10–2.5}$ sampling, but small fractions of coarse mode mass are usually smaller than 2.5 μm or greater than 10 μm in diameter.

Particles of different sizes differ in their sources, composition, chemical properties, atmospheric lifetimes, transport distances, and removal processes (U.S. EPA, 2009). Typical differences in particle

characteristics for different particle size ranges are described in Table 2-1. Although atmospheric lifetime depends on atmospheric conditions, usually UFP are transformed into the accumulation mode and $PM_{10-2.5}$ are removed from the atmosphere more rapidly than accumulation mode particles are transformed or removed, leading to shorter average atmospheric lifetimes and transport distances for particles in the UFP and $PM_{10-2.5}$ size ranges than for particles in the $PM_{2.5}$ size range (U.S. EPA, 2009). Differences in transport and atmospheric wet and dry deposition processes between different size particles were discussed in detail in the 2009 PM ISA (U.S. EPA, 2009).



Source: Adapted from Kittelson and Kraft (2015); Kittelson (1998).

Figure 2-1 Comparison of particle size distribution by particle number, surface area, and mass. The integrated area under the number, mass, and area size-distributions are proportional to the total number, surface area, and mass concentrations.

Table 2-1 Particle transport and removal by size.

	UFP	$PM_{2.5}$	$PM_{10-2.5}$
Atmospheric residence time	Hours	Days to weeks	Hours
Transport range (km, in orders of magnitude)	<1−10	10−100	<1−1,000
Removal processes	Evaporation Atmospheric reactions Growth into larger particles Diffusion to raindrops and other surfaces	Formation of cloud droplets and rain out Dry deposition Diffusion to surfaces	Dry deposition by fallout Scavenging by falling rain drops

Adapted from Kittelson and Kraft (2015); Solomon (2012); U.S. EPA (2004).

2.3 Primary Sources and Atmospheric Formation

Particulate matter is composed of both primary and secondary chemical components. Primary PM is derived from particle emissions from a specific source. Secondary PM originates from gas-phase chemical compounds present in the ambient atmosphere that have participated in new particle formation or condensed onto existing particles. Primary particles, and the gas-phase compounds that ultimately contribute to PM, are emitted by both natural and anthropogenic sources. Earlier assessments have described, in detail, the important sources of primary and secondary atmospheric particles (U.S. EPA, 2009, 2004). Table 2-2 summarizes the anthropogenic and natural sources for the major primary and secondary constituents of $PM_{2.5}$ and $PM_{10-2.5}$.

Anthropogenic sources can be divided into stationary and mobile sources. Stationary sources include fuel combustion for electricity production and other purposes, industrial processes, agricultural activities, road and building construction and demolition, and biomass combustion. Mobile sources include diesel- and gasoline-powered highway vehicles and other engine-driven sources such as locomotives, ships, aircraft, and construction and agricultural equipment. These sources directly emit combustion-derived primary PM, as well as secondary PM precursors (discussed below), and generate particles during vehicle braking, as well as fugitive dust from paved and unpaved roads.

Table 2-2 Particle formation, composition and sources.

	UFP	$PM_{2.5}$	$PM_{10-2.5}$
Formation processes	Combustion Pyrogenesis Homogeneous and/or heterogeneous nucleation Condensation and adsorption (gas-particle partitioning)	Gas-particle partitioning Particle agglomeration Reactions of gases in or on particles Cloud droplet evaporation	Mechanical degradation of solid materials (crushing, grinding, abrasion of surfaces) Evaporation of sea spray Suspension of dust
Typical chemical/material components	Sulfate Elemental carbon Metal compounds Low volatility organic compounds	Sulfate, nitrate, ammonium, and hydrogen ions Elemental carbon Low and moderate volatility organic compounds Metals: compounds of Pb, Cd, V, Ni, Cu, Zn, Mn, Fe, etc. Water	Suspended soil or street dust Fly ash from coal, oil, and wood combustion Nitrates/chlorides/sulfates from HNO^3/HCl/SO_2 reactions with coarse particles Oxides of crustal elements (Si, Al, Ti, Fe) Sea salt (Na, K, Ca, carbonate, sulfate and chloride) Pollen, mold, fungal spores Plant and animal detritus Tire, brake pad, and road wear debris
Dominant[1] primary particle sources	Combustion of fossil fuels and biomass High temperature processes (i.e., smelters, steel mills, etc.)	Combustion of fossil fuels and biomass High temperature processes	Resuspension of industrial dust and soil tracked on to roads and streets Suspension from disturbed soil (e.g., farming, mining, unpaved roads) Construction and demolition Coal and oil combustion Sea spray Biological sources
Secondary particle formation processes	Particle formation and growth due to oxidation of gas-phase anthropogenic, biogenic and geogenic precursors (NO_X, SO_2, and organic compounds)	Partitioning of gas phase products of precursor oxidation; aqueous oxidation of dissolved precursors with evaporation and growth cycling	

[1]All source-specific particles are produced in a distribution of sizes, with usually one major mode. This means that all sources will generate small quantities of particles that are both much larger and much smaller than the main size mode. For example, particles generated by construction activities generally fall into the $PM_{10-2.5}$ size fraction. However, the distribution extends into the UFP size range.

Ambient PM also forms in the atmosphere from photochemical oxidation of precursor gases. This material is referred to as secondary PM. The large, semi- and nonvolatile reaction products of these oxidation reactions may condense to form new particles or onto existing particles. Table 2-2 includes sources for several PM precursor gases. Discussion of the photochemical reactions that transform these precursor gases into secondary PM can also be found in earlier assessments (U.S. EPA, 2009, 2004). An overview of estimates of emissions of primary PM and precursors to secondary PM from major sources is given in this section.

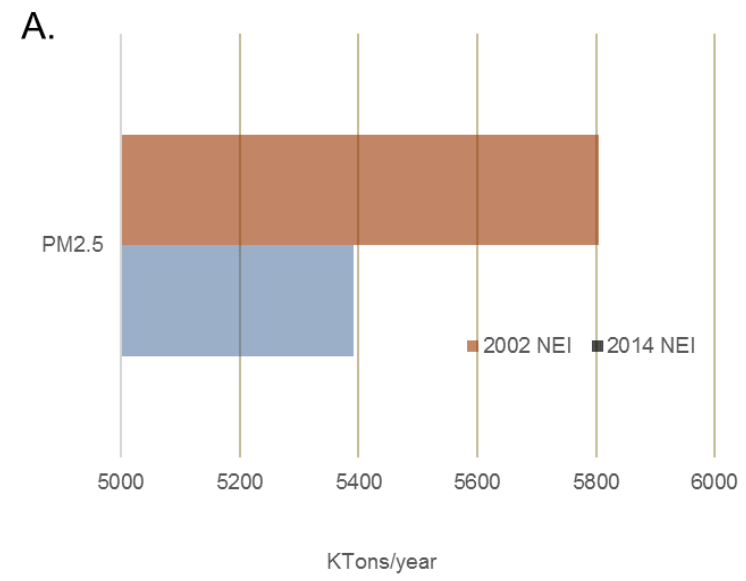
In general, the sources of $PM_{2.5}$ are very different from those of $PM_{10-2.5}$. $PM_{10-2.5}$ is almost entirely primary in origin, as described in Section 2.2, and is produced by surface abrasion or by suspension of sea spray or biological material (e.g., microorganisms, pollen, plant and insect debris).

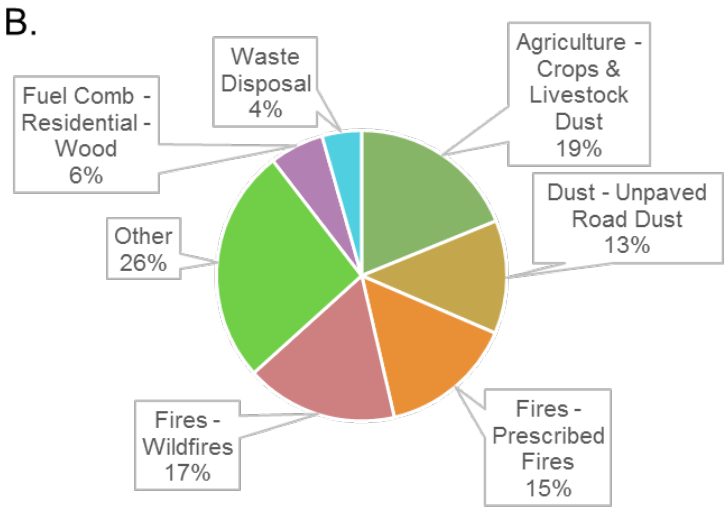
2.3.1 Primary $PM_{2.5}$ Emissions

2.3.1.1 National Scale Emissions

The relative contributions of specific sources to national emissions of primary $PM_{2.5}$ are similar to those reported in the 2009 PM ISA (U.S. EPA, 2009). Figure 2-2 shows the U.S. national average emissions of primary $PM_{2.5}$ from the 2002 National Emissions Inventory (NEI) described in the 2009 PM ISA (U.S. EPA, 2009), and the 2014 NEI, Version 2 (U.S. EPA, 2018). The NEI is a national compilation of emissions information provided by state, local, and tribal air agencies as well as source sector emission estimates developed by the U.S. Environmental Protection Agency (U.S. EPA). It focuses largely on anthropogenic sources, with information about natural sources where available. Emissions composition and mass estimates undergo continual revision as better information becomes available but are subject to varying degrees of uncertainty. For these and other reasons, ambient PM mass and composition can be quite different from what might be inferred by examining emission inventories alone (U.S. EPA, 2009).

Dust and fire each account for approximately 36% of total $PM_{2.5}$ emissions included in the 2014 NEI. Dust includes agricultural, construction, and road dust. Of these, agricultural dust and road dust make the greatest contributions to $PM_{2.5}$ mass on a national scale. Fires include wildfires, prescribed fires, and agricultural fires, with wildfires and prescribed fires accounting for most of the $PM_{2.5}$ fire emissions on a national scale.





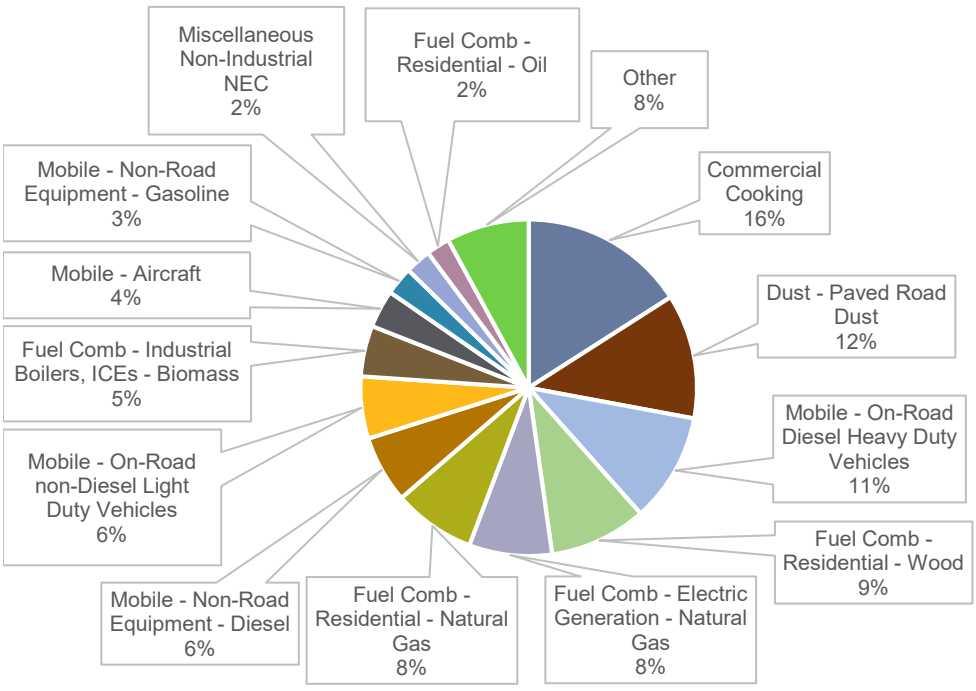
Source Permission pending: U.S. EPA (2018) and U.S. EPA (2009).

Figure 2-2 **Primary $PM_{2.5}$ emissions at the U.S. national scale. (A) $PM_{2.5}$ emissions from the 2002 U.S. EPA National Emissions Inventory versus the 2014 U.S. EPA National Emissions Inventory. (B) Largest, national-scale sources of $PM_{2.5}$. "Other" includes all remaining source sectors, all of which are emitting 2% or less of the national $PM_{2.5}$ emissions total.**

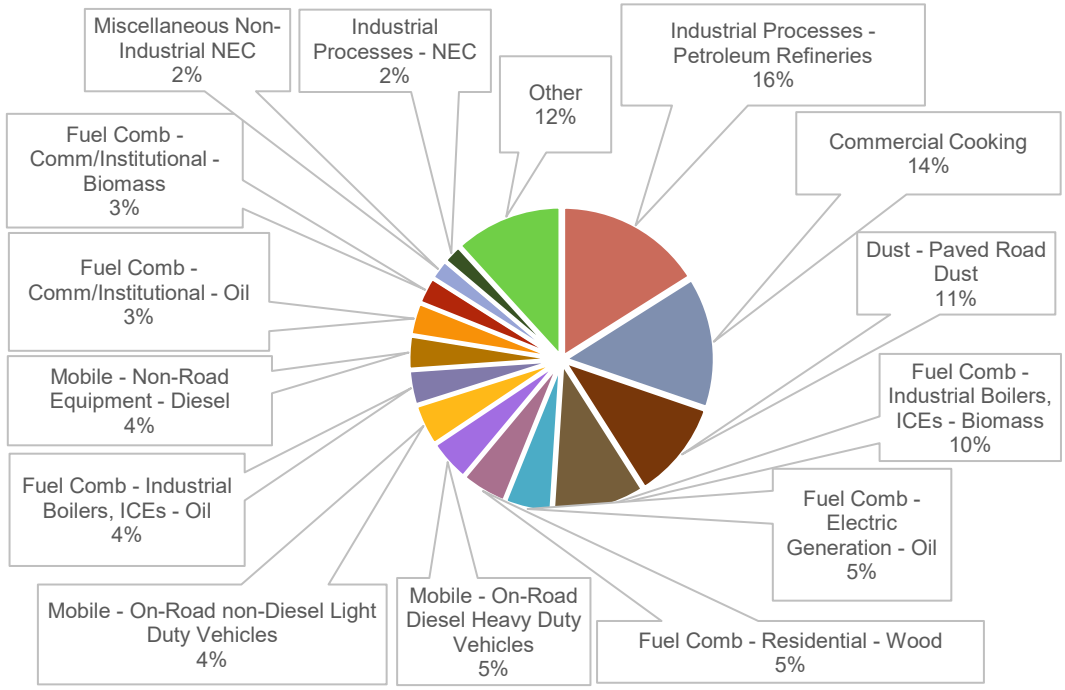
2.3.1.2 Urban Scale Emissions

The sources and relative annual average emissions of primary $PM_{2.5}$ at the urban scale can vary substantially from city to city. Figure 2-3 shows five U.S. counties containing large cities that were selected from the 2014 NEI to illustrate the variation in primary $PM_{2.5}$ source composition. In urban settings, the majority of primary $PM_{2.5}$ emissions estimated in the NEI include some combination of industrial activities, motor vehicles, cooking, and fuel combustion, and often include wood smoke. Dust accounts for a large fraction of primary $PM_{2.5}$ emissions in several of the counties, due to construction and entrainment of paved road dust, in contrast to the national scale where the largest emissions are attributed to agricultural processes and vehicular traffic on unpaved roads. While fire emissions comprise a large fraction of annual average emissions at the national scale, they represent a much smaller fraction with respect to other sources for the urban counties shown.

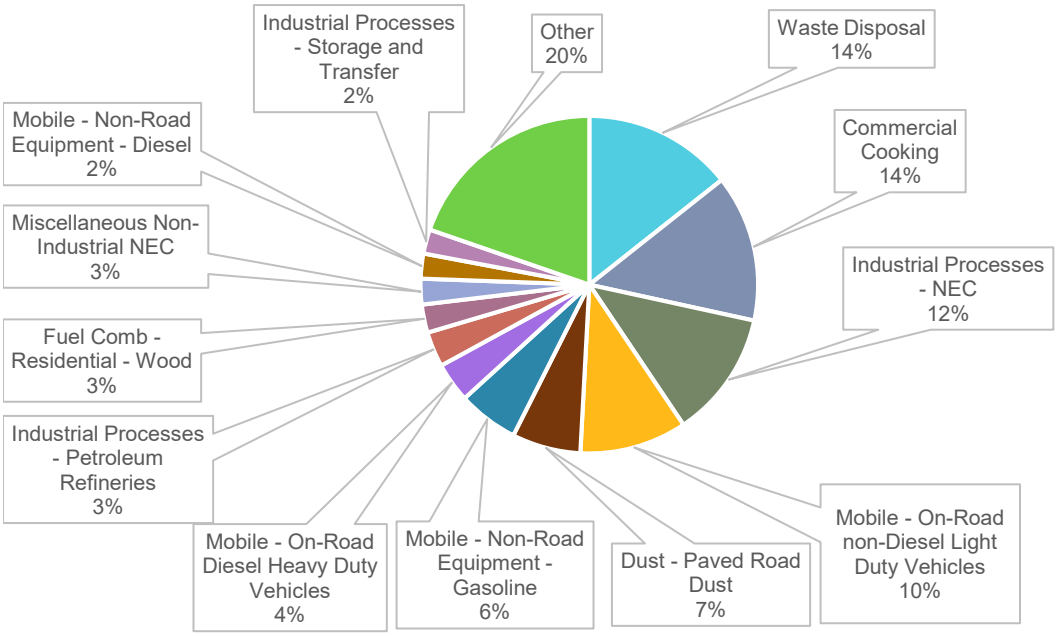
A. Queens County, NY



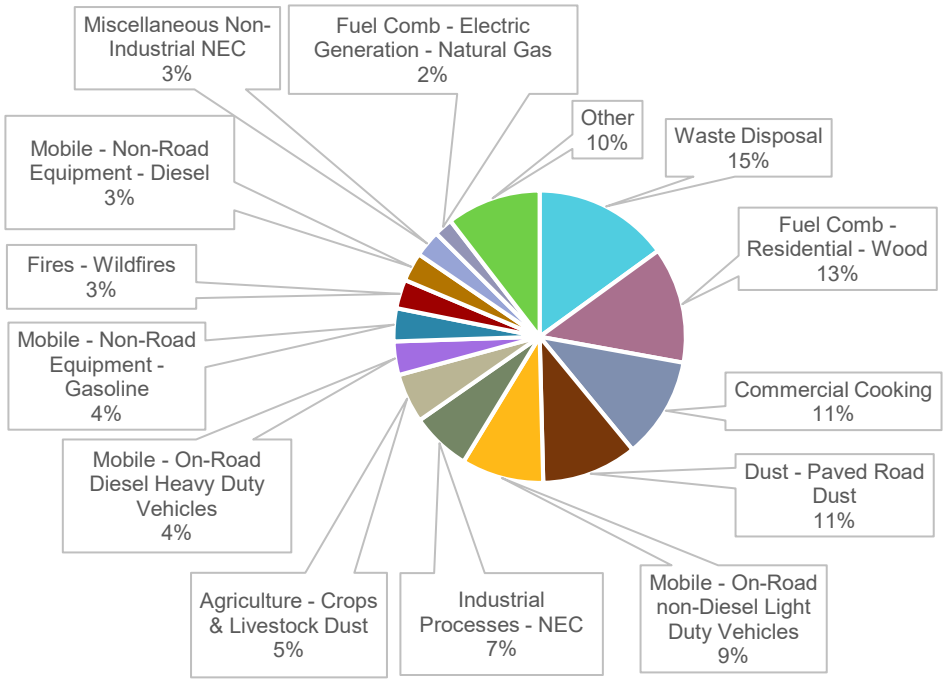
B. Philadelphia County, PA



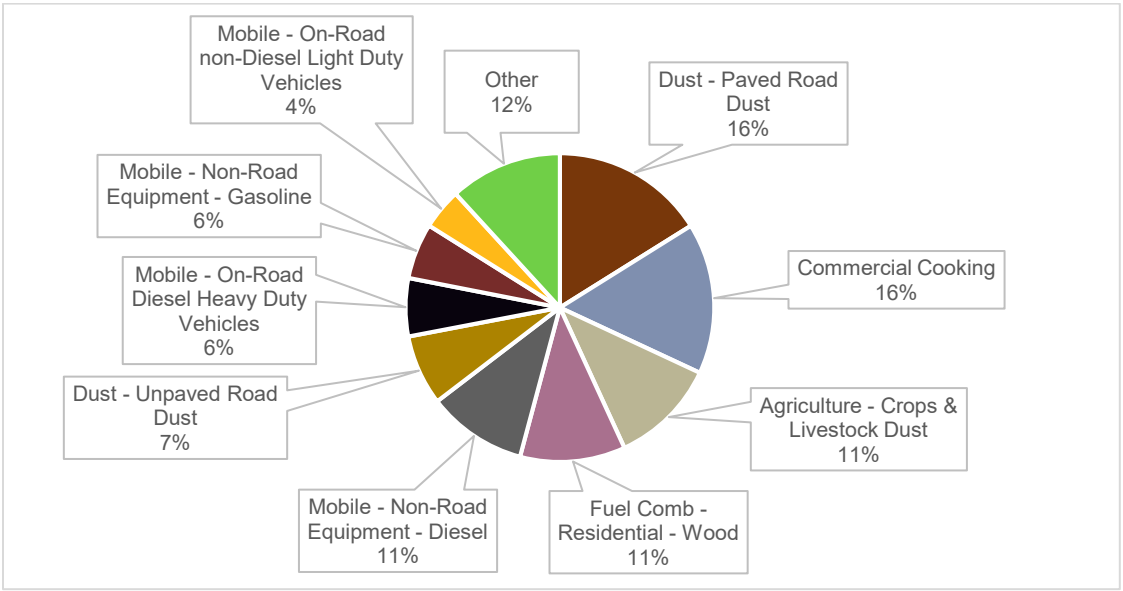
C. Los Angeles County, CA



D. Sacramento County, CA



E. Maricopa County (Phoenix), AZ



Source Permission pending: 2014 U.S. EPA National Emissions Inventory, Version 1. (U.S. EPA, 2016a).

Figure 2-3 Primary $PM_{2.5}$ emissions for (A) Queens County, NY; (B) Philadelphia County, PA; (C) Los Angeles County, CA; (D) Sacramento County, CA; (E) Maricopa County, AZ (Phoenix).

Mobile sources, as noted in the 2009 PM ISA, are a major source of primary PM at urban scales, especially light-duty gasoline and heavy duty diesel vehicles (U.S. EPA, 2009). They are discussed in further detail here because they represent a consistently large fraction of total $PM_{2.5}$ emissions in all urban areas (Section 2.3.1.2), and several important advances in engine and pollution control technology have occurred in recent years. For the example counties shown in Figure 2-3, mobile sources account for an estimated 13−23% of the NEI's total primary $PM_{2.5}$ emissions. Primary $PM_{2.5}$ emitted by mobile sources is due to direct tailpipe emissions, brake, clutch and tire wear. Significant changes in both gasoline and diesel emissions controls have led to reductions in primary $PM_{2.5}$ emitted from newer vehicles. Light-duty vehicles in the U.S. (i.e., passenger cars and light-trucks under 8,500 lbs. gross vehicle weight rating) are rapidly transitioning from port fuel injection (PFI) with fuel injected upstream of the exhaust valve to direct, in-cylinder fuel injection systems, also known as gasoline direct injection (GDI). In 2007, a new U.S. EPA PM emissions standard required reduction of diesel PM emissions by 90% to 0.01 g/bhp-hour (U.S. EPA, 2009). Their impact on UFP are discussed in Section 2.3.4. Mobile sources are also responsible for $PM_{2.5}$ dust suspension on and off-road. (Note: dust is also present in the coarse mode and is discussed further in Section 2.3.3 as it pertains to primary $PM_{10-2.5}$ emissions).

2.3.2 Secondary $PM_{2.5}$ Formation

After emission, primary particles transform in size and chemical composition due to coagulation with other particles, gas-to-particle condensation of semivolatile gases, and photochemical aging processes that oxidize particle components or generate oligomers. Particle dynamics, gas-particle partitioning, aging and other heterogeneous chemical processes have been discussed in earlier PM assessments (U.S. EPA, 2009, 2004). Much is understood about the physical processes that lead to the growth of particles in the atmosphere, but the reaction mechanisms that contribute to these processes as well as to the formation and chemical transformation of particles with time remains an area of active research.

Secondary $PM_{2.5}$ accounts for a substantial fraction of the $PM_{2.5}$ mass with both natural and anthropogenic sources (U.S. EPA, 2009). It forms by way of atmospheric photochemical oxidation reactions of both inorganic and organic gas-phase precursors. Reactions leading to sulfate production from SO_2, nitrate production from NO_X (i.e., NO + NO_2) and the gas-to-particle equilibrium between NH_3 and NH_4^+ are relatively well understood. As noted, above, formation of secondary PM, often referred to as secondary organic aerosol (SOA) in the atmospheric chemistry literature, is less well resolved. Considerable recent research on mechanisms, kinetic details, and secondary organic component identification has been reported in the literature since the 2009 PM ISA. The following sections will briefly summarize the important developments in new secondary organic PM formation, including the identification of previously unknown precursors, interactions among biogenic and anthropogenic reactants, and the role of aqueous-phase chemistry.

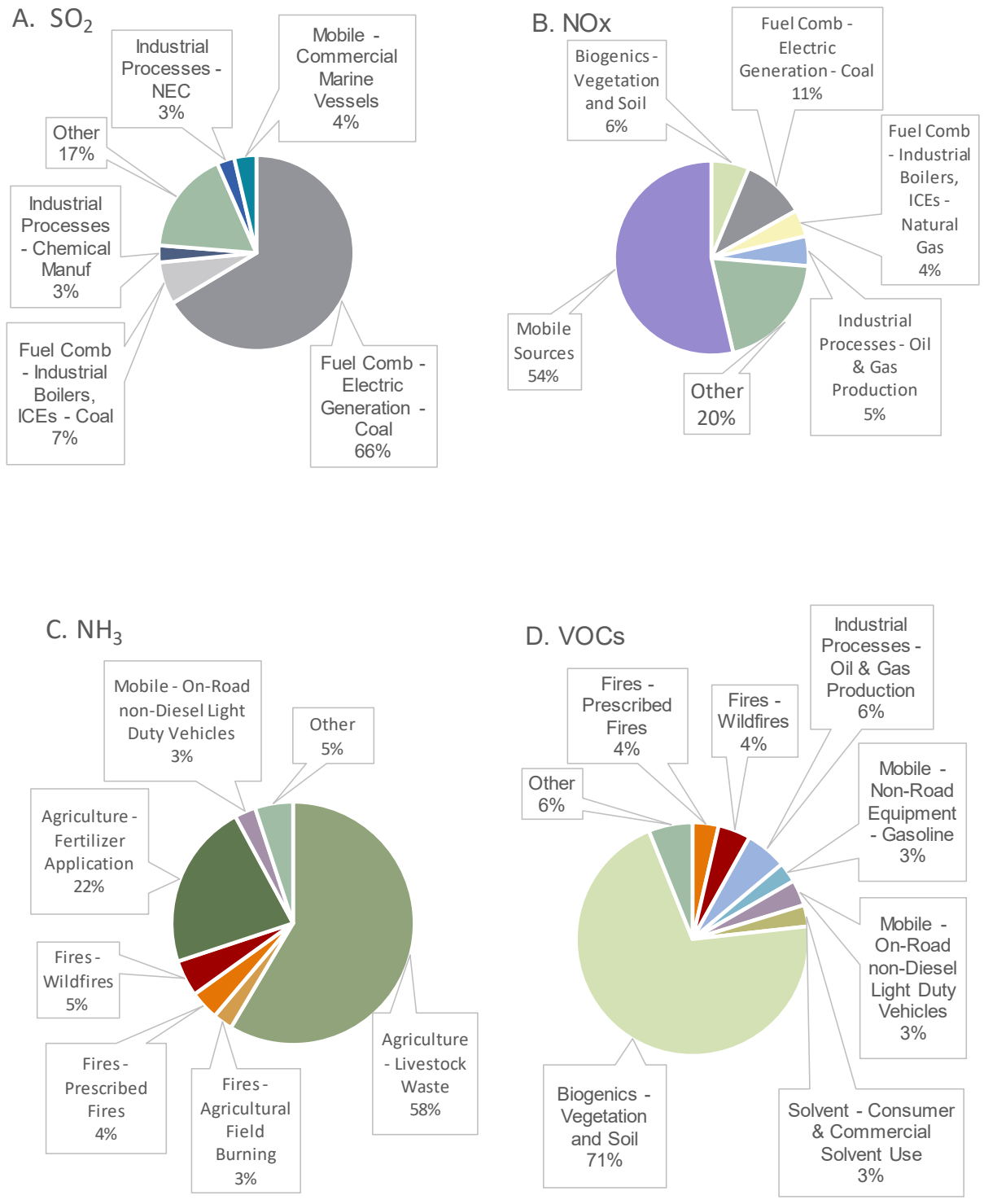
2.3.2.1 Precursor Emissions

Secondary PM is derived from the oxidation of a range of organic and inorganic gases of anthropogenic and natural origin. Figure 2-4 shows relative source contributions to emissions of major $PM_{2.5}$ precursors from the 2014 NEI. Anthropogenic SO_2 and NO_X are the predominant precursor gases in the formation of secondary $PM_{2.5}$. Ammonia plays an important role in the formation of sulfate and nitrate PM by neutralizing sulfuric and nitric acid, leading to more stable PM with lower volatility (i.e., ammonium nitrate). The oxidation of volatile organic compounds (VOCs) may also yield semi- and nonvolatile compounds that contribute to PM and the formation of new particles.

The relative proportions of the various anthropogenic source categories (i.e., as fractions of the total emissions inventory) are very similar to those presented in the 2009 PM ISA (U.S. EPA, 2009). Sulfur dioxide emissions are mainly from electricity generating units (fuel combustion used in electricity generation (66%). NO_X is emitted by a range of combustion sources, including various mobile sources (54%). Ammonia emissions are primarily emitted by livestock waste from animal husbandry operations (55%) and fertilizer application (22%). Estimates of biogenic emissions were provided in the 2014 NEI and appear as the predominant organic precursor on the national scale (71%).

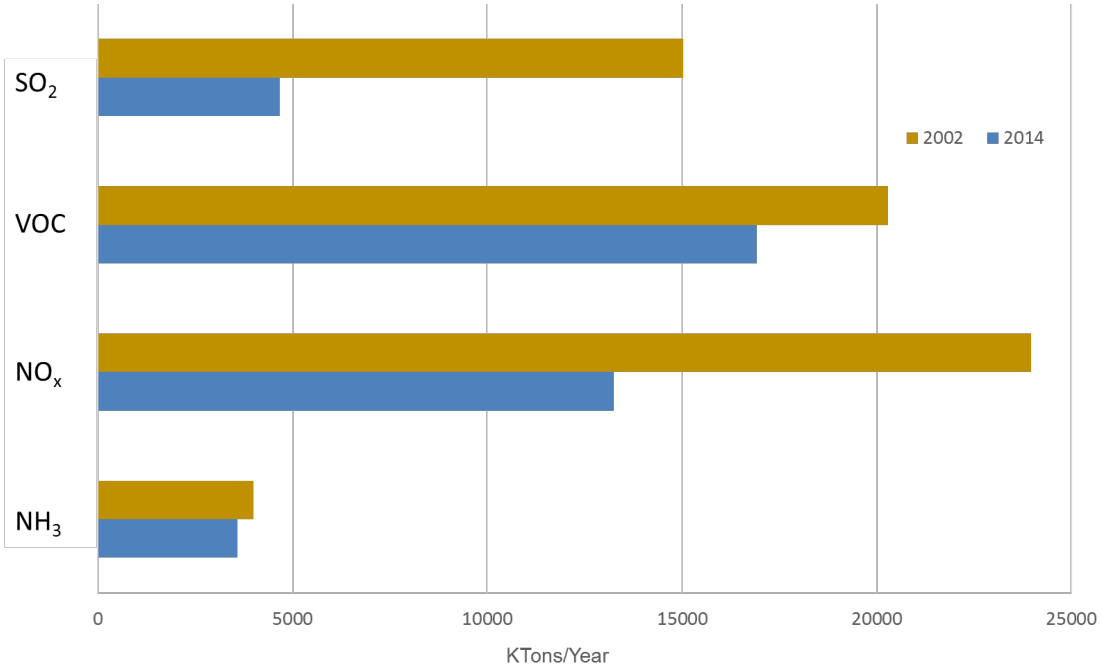
The greatest change in precursor emissions since the publication of the 2009 PM ISA (U.S. EPA, 2009) is the reduction in SO_2 emissions. Figure 2-5 shows the difference in NEI national emission estimates for SO_2, NO_X, and NH_3 between the 2006 NEI and the 2014 NEI, showing SO_2 decreasing from 13.9 million metric tons (MMT) in 2006 to 4.8 MMT in 2014, a 65% decrease. NO_X also exhibited a substantial decrease over this period while NH_3 emissions are similar. VOC's cannot be compared because biogenics were not included in the 2006 NEI.

Anthropogenic emissions of SO_2 in the U.S. have shown dramatic declines since the implementation of the 1990 amendments to the Clean Air Act (USC Title 42 Chapter 85). Annual SO_2 emissions from electric utilities declined by 79% in the 2004−2016 time frame (U.S. EPA, 2017). In the same period, SO_2 emissions by highway and nonhighway vehicles declined by 84% and 90%, respectively. Hand et al. (2012b) studied reductions in EGU-related annual SO_2 emissions during the 2001−2010 period. They found that emissions decreased throughout the U.S. by 6.2% per year, with the largest reductions in the western U.S. at 20.1% per year. The smallest reduction (1.3% per year) occurred in the Great Plains states. These trends, and emissions of sulfide gases that serve as precursors to ambient SO_2, are discussed in detail in the 2017 Integrated Science Assessment for the Sulfur Oxides (U.S. EPA, 2017).



Source Permission pending: 2014 U.S. EPA National Emissions Inventory, Version 2 (U.S. EPA, 2018).

Figure 2-4 Relative $PM_{2.5}$ precursor emissions by U.S. sector: (A) sulfur dioxide (SO_2), (B) nitrogen oxide; (NO_X), (C) ammonia (NH_3), (D) volatile organic compounds (VOCs).



SO_2 = sulfur dioxide; VOC = volatile organic compounds; NO_x = nitrogen oxides; NH_3 = ammonia; KTons = kilotons.
Source Permission pending: U.S. EPA (2018) and U.S. EPA (2009).

Figure 2-5 Difference in select $PM_{2.5}$ precursor emissions from the 2002 and 2014 National Emission Inventories.

2.3.2.2 Secondary Inorganic Aerosols

Particulate sulfate, nitrate, and ammonium formation processes were summarized in the 2009 PM ISA (U.S. EPA, 2009) and presented in more detail in the 2004 PM AQCD (U.S. EPA, 2004) and ISAs for oxides of sulfur and nitrogen (U.S. EPA, 2008b). Together, these $PM_{2.5}$ components produced by secondary formation often account for the majority of $PM_{2.5}$ mass (see Section 2.5.2.1.4).

SO_2 reacts in both the gas phase and in aqueous solution in clouds and particles to form sulfate. Dissolved SO_2 rapidly partitions into four forms with the same oxidation state, with their relative concentrations dependent on pH:

$$S(IV) = SO_2(aq) + H_2SO_3(aq) + HSO_3^-(aq) + SO_3^{2-}(aq)$$

Equation 2-1

S(IV) is then oxidized to sulfuric acid in cloud water by H_2O_2, O_3, or O_2 in the presence of Fe(III). Reaction with H_2O_2 dominates at pH values below 5.3. Reaction with either dissolved O_3 or O_2 catalyzed by Fe(III) becomes most important at pH values greater than about 5.3 (U.S. EPA, 2008a). SO_2

is also oxidized to H_2SO_4 in the gas phase by hydroxyl radical or organic radicals formed in atmospheric photochemical processes (Berndt et al., 2012; Mauldin et al., 2012; Welz et al., 2012) with a characteristic time scale of about 10 days (Sander et al., 2011).

NO_2 can be converted to gaseous HNO_3 by reaction with OH radicals during the day. At night, NO_2 is also oxidized to HNO_3 by a sequence of reactions initiated by O_3 that produce nitrate radicals and dinitrogen pentoxide as intermediates. Both processes are important in the atmosphere.

Both H_2SO_4 and HNO_3 react with atmospheric ammonia (NH_3). Atmospheric particulate NH_4NO_3 is in equilibrium with gas-phase NH_3 and HNO_3. Lower temperature and higher relative humidity shifts the equilibrium towards particulate NH_4NO_3 because of the large sensitivity of the equilibrium constant to temperature. This results in a strong seasonal dependence in particulate nitrate concentrations, with much higher winter than summer concentrations in many locations (see Section 2.5.2.2.4). In aqueous aerosols, sulfuric acid can be partly or totally neutralized by NH_3. At low atmospheric NH_3 concentrations, equilibrium formation of ammonium sulfate is favored over ammonium nitrate; any nitrate remains in the gas phase as nitric acid. When NH_3 concentration exceeds SO_4^{2-} concentration, excess NH_3 can react with HNO_3 to form NH_4NO_3. (U.S. EPA, 2008a).

Ambient particle acidity is a difficult property to measure and is usually estimated by models. Recent measurement attempts in the U.S. Southeast have led to questions concerning the predictability of particle acidity on the basis of relative atmospheric NH_3, H_2SO_4 and HNO_3 concentrations—species which would otherwise be expected to quickly react and achieve thermodynamic equilibrium. For example, Weber et al. (2016), after evaluating the observational record, suggested that pH buffering by partitioning of ammonia between the gas and particle phases produced a relatively constant particle pH of 0−2 throughout the 15 years of decreasing atmospheric sulfate concentrations. They saw little change in particle ammonium nitrate concentrations that would have been expected, had particle pH values increased with decreasing sulfuric acid concentrations. They concluded that fairly constant emissions of semivolatile NH_3 related to agriculture ensures that the acid/base gas-particle system in the southeastern U.S. remains insensitive to changing SO_2 concentrations. Other observations indicated that the extent of neutralization of sulfuric acid and bisulfate by ammonium can be incomplete even in the presence of excess atmospheric NH_3 and proposed that uptake of NH_3 is inhibited by organic compounds coating particle surfaces (Kim et al., 2015), in accord with laboratory studies (Liggio et al., 2011). Pye et al. (2018), in their combined modeling study and evaluation of available measurements, suggest that the inconsistencies among the different measurements of particle composition, especially concerning to the fraction of condensed-phase organosulfate, must be resolved before conclusions can be drawn concerning the validity of current approaches to modeling particle acidity.

2.3.2.3 Secondary Organic Aerosols

As discussed in the 2004 PM AQCD (U.S. EPA, 2004) the study of the chemical mechanisms responsible for the formation of secondary PM related to VOC precursor oxidation has been the subject of active research. Oxygenated organic compounds appeared, based on observations, to be the dominant form of organic PM in Northern Hemisphere midlatitudes (Zhang et al., 2007). However, the mechanism(s) responsible for their formation were not well resolved, as evidenced by the persistent underprediction of observed OC concentrations by chemical transport models. This underprediction was significant for summertime PM (Wyat Appel et al., 2008; Morris et al., 2006), when biogenic precursor concentrations and photochemical reaction conditions are most favorable for SOA formation.

Substantial research on isoprene, aromatic hydrocarbons and further reaction of gas phase secondary products has been reported. Studies of isoprene as a major precursor led to identification of a number of previously unknown products as well as advances in understanding yields and mechanisms (Carlton et al., 2009). Modeling studies that included oxidation of aromatic precursors indicated that a large fraction of SOA could be derived from aromatic precursors. SOA production not only from simple aromatic compounds, but also from less volatile polycyclic aromatic compounds like naphthalene and substituted naphthalenes were reported (Kleindienst et al., 2012; Chan et al., 2009), and polycyclic aromatic hydrocarbons could account for up to 54% of total SOA from oxidation of diesel emissions (Zhao et al., 2014). Additional precursors remain possible, and the products of aromatic and biogenic compound oxidation that appear in particles may have not been fully identified.

As reported in the 2009 PM ISA (U.S. EPA, 2009), in the presence of high NO_X concentrations, the oxidation of biogenic hydrocarbons is observed to produce larger quantities of SOA. High ambient NO_X concentrations in the atmosphere are typically due to anthropogenic emissions. Mixtures, as a rule, of both biogenic and anthropogenic precursors produce greater SOA yields than mixtures dominated by just one class of precursors (Shilling et al., 2013). The presence of anthropogenic particles also enhances the formation of SOA, by providing additional volume and surface area to which semivolatile VOC oxidation products can partition or adsorb (Hoyle et al., 2011). Carlton et al. (2010) predicted that more than 50% of biogenic SOA in the Eastern U.S. could be controlled by reducing anthropogenic NO_X emissions. These findings are consistent with the satellite observations of (Goldstein et al., 2009) of a cooling haze of secondary particles over the Southeastern U.S. associated with a mixture of biogenic VOCs with anthropogenic NO_X.

Recent insight into the role of anthropogenic NO_X and SO_X in enhancing the production secondary PM include the identification of organosulfates and organonitrates among particle-phase organic compounds. The 2009 PM ISA discussed the early indications that SOA chemistry with anthropogenic SO_X yielded compounds with oxidized sulfur functional groups (U.S. EPA, 2009). Organosulfates had been observed as products of isoprene (Surratt et al., 2007), and monoterpenes (Surratt et al., 2008). Subsequently, oxidation of sesquiterpenes (Chan et al., 2011), and glyoxal (Lim et al., 2016) were also found to yield organosulfates under similar conditions. These products have been

estimated to account for 40% of PM sulfate (Vogel et al., 2016), 30% of PM organic matter (Surratt et al., 2008), 6−14% of total atmospheric sulfur concentration (Lukacs et al., 2009), and 5−10% of $PM_{2.5}$ organic mass (Tolocka and Turpin, 2012). The chemical mechanism that may explain the formation of organosulfate compounds is described in the ISA for Sulfur Oxides (U.S. EPA, 2017).

Substantial SOA mass from highly functionalized nitrate products of isoprene and monoterpenes were observed in several studies (Fisher et al., 2016; Lee et al., 2016; Kourtchev et al., 2014; Nguyen et al., 2011), accounting for as much as 10−20% of carbonaceous aerosol mass in urban locations (Day et al., 2010; Holzinger et al., 2010). In flow reactor experiments, organic nitrates accounted for up to 40% of SOA mass (Berkemeier et al., 2016). O'Brien et al. (2013), in their study of SOA collected during the CalNex 2010 field study, found that the identities of nitrogen-containing organics and total proportion of OC varied as a function of time-of-day. These differences could be explained by multiple reaction mechanisms, including one that relies upon the nitrate radical as a reactant. In the presence of both NO_X, SO_X and O_3, Lim et al. (2016) identified organonitrates, organosulfates, and organic compounds containing both nitrogen and sulfur, in their smog chamber study of the photochemistry of glyoxal in the presence of sulfate or sulfuric acid particles at high and low relative humidities.

Aqueous particle reactions and cloud processing as well as repeated cycles of volatilization and condensation of semivolatile reaction products have been shown to be important processes for SOA evolution. Production of OH in cloud water was described by Hallquist et al. (2009) and estimates of the magnitude of in-cloud formation of SOA comparable to that of gas phase formation were reported (Liu et al., 2012). High molecular weight organic compounds appear to increase with decreasing cloud water pH (Cook et al., 2017). Cloud water has been shown to provide a medium for oligomer formation involving methylglyoxal (Cook et al., 2017; Yasmeen et al., 2010), syringol and guaiacol (Cook et al., 2017; Yu et al., 2016; Yu et al., 2014a) when influenced by wildfire emissions (Cook et al., 2017; Yasmeen et al., 2010).

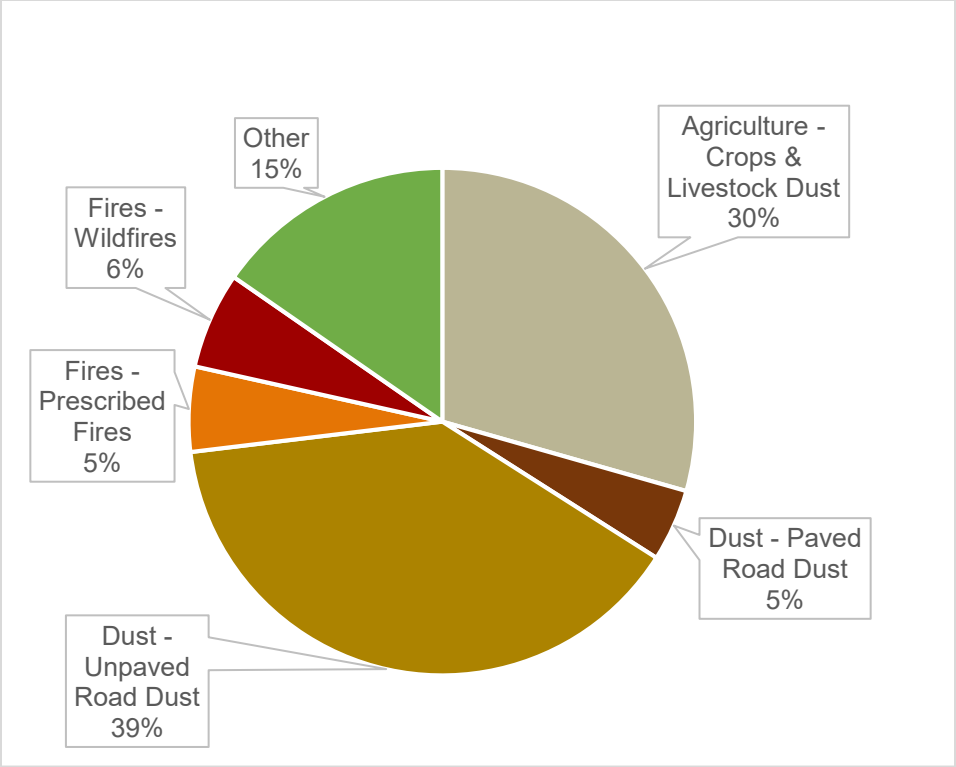
In summary, consistently higher-than-predicted measured OC concentrations, along with the observations of unexpectedly large fractions of secondary-to-total organic $PM_{2.5}$, motivated an intensive research effort to identify additional chemical processes that could explain these differences. This effort has yielded new observations of high SOA yields from isoprene and intermediate volatility organic compounds; identification of new sulfur and nitrogen containing products that account for a substantial fraction of SOA mass; identification of cloud water and aqueous aerosols as reaction media potentially as productive as the gas phase; and enhancement of SOA yields from biogenic precursors when anthropogenic reactants are also present. Given the rapid discovery of new precursors, products, and even reaction media, a high degree of uncertainty remains regarding the contribution of SOA to organic aerosol.

2.3.3 Primary $PM_{10-2.5}$ Emissions

As described in the 2004 PM AQCD (U.S. EPA, 2004), crustal materials dominate the $PM_{10-2.5}$ fraction throughout the U.S. and fugitive dust has been identified as the largest source of measured PM_{10} in many locations in the western U.S. Mineral dust, organic debris, and sea spray have also been identified as mainly in the coarse fraction (U.S. EPA, 2004). Road and construction dust represent a mechanism for suspension of crustal material on paved and unpaved roads. Wildfire plumes are now known to entrain soil representing another potential source of ambient $PM_{10-2.5}$ (Kavouras et al., 2012). Estimates of $PM_{10-2.5}$ sources from the 2014 NEI are summarized in Figure 2-6, and are very similar to those reported in the 2009 PM ISA (U.S. EPA, 2009).

Quantification of dust emissions is highly uncertain. Dust storms, like wildfires, are common but intermittent emissions sources. The suspension and resuspension of dust by any mechanism is difficult to quantify. Current NEI estimates of dust emissions across the U.S. are based on limited emissions profile and activity information. Dust injected into the upper troposphere is also transported from other continents into the U.S. by strong atmospheric currents, notably from the African and Asian deserts. Some of these particles fall into the $PM_{10-2.5}$ size range. These particles are considered to be part of the "background" component of PM, discussed in Section 2.5.4.

As discussed in the 2004 PM AQCD (U.S. EPA, 2004) and the 2009 PM ISA (U.S. EPA, 2009), primary biological aerosol particles (PBAP) contribute to coarse PM. However, estimating emissions is highly problematic. No emission rates have yet been reported, though Despres et al. (2012) described the occurrence, sources and measurement methods for different categories of PBAP. Barberán et al. (2015) characterized the distribution of airborne microbes in settled dust from ~1,200 locations in the continental U.S. They found substantial variability in the composition of microbial communities that could be related largely to climatic factors (mean annual temperature and precipitation) and soil composition (soil pH and net primary productivity). No estimates were given of the rates at which these particles are emitted into the atmosphere.



Source Permission pending: 2014 U.S. EPA National Emissions Inventory, Version 2 (U.S. EPA, 2018).

Figure 2-6 National emissions of PM_{10}.

2.3.4 Ultrafine Particles

UFP primary sources were not treated separately in the 2009 PM ISA because there is almost complete overlap between UFP and $PM_{2.5}$ sources. Particles in the $PM_{2.5}$ size range typically begin as primary UFP, or are formed through secondary particle formation, and grow through coagulation or gas-to-particle condensation (see Section 2.2). However, UFP sources are addressed independently in this ISA with a focus on sources for which near-source human exposure is substantial, such as roads and airports, as well as on new particle formation, for which a substantial amount of new research has recently been conducted.

Ambient UFPs originate from two distinct processes: primary emissions and new particle formation (NPF). Primary UFP originate from a large variety of sources, such as transportation (road traffic, ships and aircraft), power plants, municipal waste incineration, construction and demolition, vegetation fires, domestic biomass burning, cooking and cigarette smoke (Kumar et al., 2013; Janhaell et al., 2010; Langmann et al., 2009; Morawska et al., 2008). Primary sources of UFP are largely the same as $PM_{2.5}$, and much of $PM_{2.5}$ mass is initially emitted as UFP before atmospheric coagulation and growth (see Section 2.2). Atmospheric NPF involves the production of very small, molecular clusters and

subsequent growth of these clusters to larger sizes, typically a few tens of nm in particle diameter (Kulmala et al., 2014; Zhang et al., 2012b). As described in Section 2.2, UFP consists mainly of nucleation mode particles, but nucleation mode aerosols often have short atmospheric lifetimes as particles coagulate into the accumulation mode.

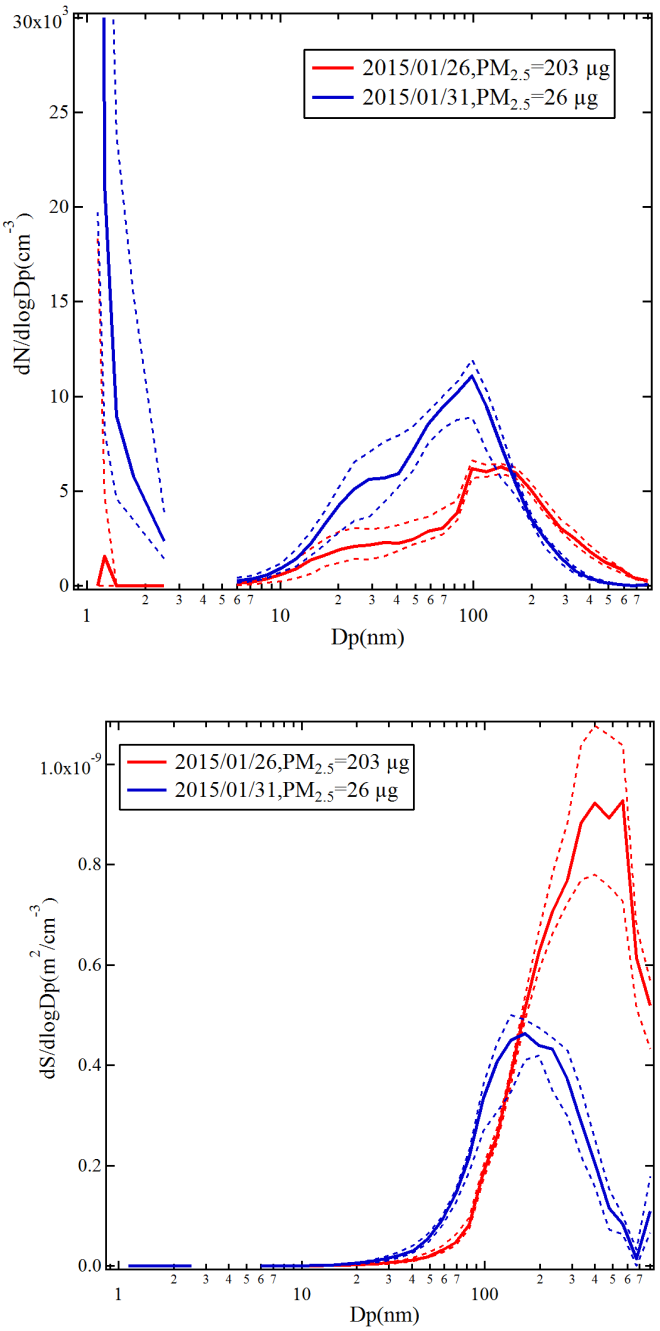
As Table 2-3 shows, UFP can be subdivided into a cluster mode, nucleation mode, Aitken mode, and a portion of the accumulation mode in order of increasing size, although a naming convention for primary ultrafine particles has not been established (Giechaskiel et al., 2014; Kumar et al., 2010). The size ranges refer to the particle diameter, encompassing the disparate definitions found in the scientific literature.

Table 2-3 Modes of atmospheric particle populations.

Mode	Size Range	Sources[a]	Main Components
Cluster mode	<3 nm	NPF	Secondary compounds capable of forming extremely low volatility complexes
Nucleation mode	<30 nm	NPF, COM	Secondary compounds of very low volatility, nonvolatile additives in fuels, lubricants
Aitken mode	10−100 nm	NPF, COM	Soot, secondary compounds of very low volatility, semivolatile compounds
Accumulation mode	30−1,000 nm	NPF, COM, OTH	Soot, secondary semi- and low-volatility organic and inorganic compounds

[a]NPF = atmospheric new particle formation and growth, COM = combustion, OTH = other primary sources.

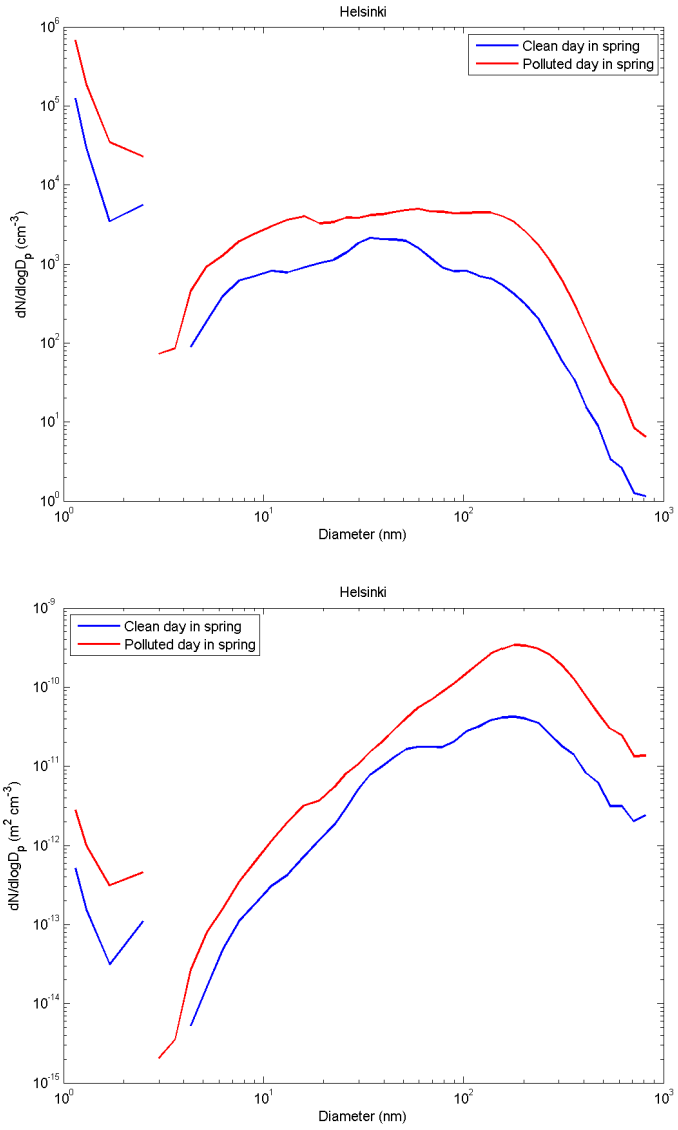
In the atmosphere, the cluster mode is usually well separated from the other modes and has a relatively high number concentration (Figure 2-7 and Figure 2-8), even though only few atmospheric measurements on the character of this mode currently exist. The relative magnitudes and mean diameters of the nucleation, Aitken and accumulation modes vary with the time of day and location depending on the dominant particle sources and aging processes. As a result, these three modes are often not distinguishable in individual particle number distributions. Even when cluster mode or sub-0.01 µm size particles are not considered, ultrafine particles tend to dominate the total particle number concentration. Contrary to this, accumulation mode particles dominate the submicron particulate mass concentration, as explained in Section 2.2.



[a]The cluster mode, along with overlapping nucleation, Aitken and accumulation modes can be seen in the particle number distribution.

Source Permission pending: Kulmala et al. (2014).

Figure 2-7 Examples of the particle number distribution (top) and surface-area distribution (bottom) during clean (blue) and polluted (red) conditions in Nanjing, China, during winter.[a]



[a]The cluster mode, along with the overlapping nucleation, Aitken and accumulation modes can be seen in both the number and size distributions.

[b]Units on the bottom panel should be dS/dlogDp but are mislabeled in the original figure.

Source Permission pending: Kulmala et al. (2014).

Figure 2-8 Examples of the particle number distribution (top) and surface-area distribution (bottom) during clean (blue) and polluted (red) conditions in Helsinki, Finland, during spring.[a,b]

2.3.4.1 Primary Sources

Motor vehicles are a major, if not the most important, source of UFP in urban environments (Morawska et al., 2008). Their role as a major source of $PM_{2.5}$ mass and impacts of new engines and control technologies were discussed in Section 2.3.1.2. Here, these new engine and control technology advances are discussed with a focus on their impact on UFP emissions.

The number concentration, size distribution, morphology and chemical composition of mobile source-derived primary UFP are determined by the composition of the fuel used and lubricating oil, driving conditions, engine after-treatment system, as well as environmental conditions (Karjalainen et al., 2014; Rönkkö et al., 2014; Fushimi et al., 2011; Gidney et al., 2010; Heikkilä et al., 2009; Johnson, 2009). As discussed in Section 2.3.2.1, recent changes in engine and emissions control technology have influenced PM emissions from both gasoline and diesel vehicles, with light duty vehicles rapidly transitioning from port fuel injection (PFI) to gasoline direct injection (GDI), and heavy-duty diesel vehicles complying with a new U.S. EPA PM emission standard requiring reduction of diesel PM emissions by 90% to 0.01 g/bhp-hour (U.S. EPA, 2009).

The number of particles emitted by GDI vehicles can be one to two orders of magnitude higher than for PFI vehicles (Fushimi et al., 2016; Mamakos et al., 2012). For both GDI and PFI vehicles, the largest number of particles are sub-200 nm, with a more distinctly bimodal distribution characterized by a larger contribution to particle number from a sub-30 nm nucleation-mode particles for PFI (Karavalakis et al., 2013; Kittelson et al., 2006), and somewhat larger particles generally observed for GDI (Fushimi et al., 2016; Myung et al., 2015; Choi et al., 2014; Myung et al., 2014).

The new heavy-duty diesel PM emissions requirements as well as additional required reductions in NO_X emissions phased in by 2010 led to UFP emissions reduction of more than 90% compared to earlier diesels. However, CDPF regeneration resulted in approximately one order of magnitude increase in particle number. As a result, in spite of much lower average UFP emissions, there can still be discrete periods of extremely high UFP formation that do not reflect the overall reduction in UFP emissions. These UFP releases may have been due to thermal desorption of adsorbed sulfates stored within the exhaust catalyst system (Khalek et al., 2015; Ruehl et al., 2015).

Most of the particles emitted by marine and aircraft engines are in the ultrafine size range (Moldanova et al., 2013; Jonsson et al., 2011; Lack et al., 2009; Whitefield et al., 2008). Emissions of UFPs appears to be a strong function of fuel sulfur content, with reduced emissions for lower sulfur fuels (Lack et al., 2009). The size distribution of UFP produced by marine ships is usually bimodal with a nucleation mode below 30 nm and another mode between about 30 and 100 nm (Pirjola et al., 2014; Hallquist et al., 2013; Petzold et al., 2010).

Biomass burning is also a major source of UFP. The mean particle number diameter produced by burning fresh vegetation varies usually from a few tens of nm up to about 150−200 nm (Maruf Hossain et al., 2012; Zhang et al., 2011a; Janhaell et al., 2010).

2.3.4.2 New Particle Formation

New particle formation (NPF) was described in the 2009 PM ISA (U.S. EPA, 2009) as an important atmospheric process responsible for the formation of UFP, especially in remote continental areas but also in urban environments under certain conditions. Particle nucleation rates are observed to be higher in summer than in winter, and during daytime as compared to nighttime, consistent with photochemical processes. While sulfuric acid and water vapor had been identified as the major nucleating species, research was proceeding on nucleation mechanisms involving other chemical species. Numerous subsequent advances in our understanding of these mechanisms have occurred since the 2009 PM ISA (U.S. EPA, 2009).

Atmospheric NPF starts with the formation of molecular clusters. Subsequent growth via the uptake (condensation) of low volatility gas molecules occurs for some of these clusters, while others dissociate (Vehkamaki and Riipinen, 2012; Zhang et al., 2012b). If growing clusters reach the size threshold of 1.5−2 nm in diameter, they are more likely to grow further by additional vapor uptake (Kulmala et al., 2014). The processes involved in the initial steps of atmospheric NPF are collectively referred to as nucleation (Kulmala et al., 2013).

Key constituents in the initial steps of atmospheric NPF are (1) gaseous compounds of very low volatility, mainly sulfuric acid and highly oxidized organic compounds, (2) compounds which can facilitate the formation of low volatility complexes, such as gaseous ammonia or amines that form acid-base complexes with inorganic or organic acids, (3) water molecules which cluster through hydrogen-bonding, and (4) possibly ions that can form clusters through electrostatic interactions. Low-volatility compounds capable of initiating NPF primarily originate from photochemical oxidation reactions in the gas phase. As noted, above, the most important compound in this respect is sulfuric acid (Kulmala et al., 2014; Kerminen et al., 2010; Sipila et al., 2010). Other low-volatility compounds that play important roles in the early steps of NPF, at least in continental boundary layers, are extremely low volatility organic compounds (ELVOC) (Krechmer et al., 2015; Ehn et al., 2014; Riccobono et al., 2014; Donahue et al., 2013; Kulmala et al., 2013). Gas-phase ammonia and amines form acid-base complexes with inorganic or organic acids, facilitating cluster formation and subsequent NPF (Kürten et al., 2014; Almeida et al., 2013). Ions originating from radon decay and external radiation (cosmic rays and gamma radiation from soils) participate actively in the formation of clusters in the atmosphere, having the potential to affect nucleation rates (Kirkby et al., 2011) and ion-induced, or ion-mediated, particle formation mechanisms are expected to be important in locations with low temperatures and pre-existing aerosol surface areas, and high ion and sulfuric acid concentrations (Yu, 2010). Measurements conducted at a few continental locations suggest that ion-mediated pathways typically contribute a few percent to the total new particle formation rate, with slightly higher contributions estimated for some elevated sites and in Antarctica (Hirsikko et al., 2011; Manninen et al., 2010).

Averaged over a large-scale (~100 mile^2) NPF event, observed particle formation rates varied mostly in the range 0.01−10 cm^{-3} s^{-1} (Kulmala and Kerminen, 2008). Higher formation rates, up to about

100 cm^{-3} s^{-1} have been reported in some urban areas, and especially in heavily-polluted environments (Salma et al., 2011; Shen et al., 2011; Yue et al., 2009; Iida et al., 2008). The vast majority of particle growth rates associated with large-scale NPF events lie in the range 1−10 nm/hour (Kulmala and Kerminen, 2008) and increase with particle size (Hakkinen et al., 2013; Kuang et al., 2012b; Yli-Juuti et al., 2011). These findings indicate that it typically takes a few hours for newly-formed particles to grow into the 25−100 nm size range and between about half a day and 3 days before newly-formed particles grow larger than 100 nm in diameter. The main sink for molecular clusters and new particles is their coagulation with larger pre-existing particles and, in cases where their number concentration is very large, also by their coagulation with each other (Westervelt et al., 2014).

Direct observations show that secondary particles (i.e., those originating from NPF) are usually composed primarily of organic compounds, especially in forests (Han et al., 2014; Pennington et al., 2013; Pierce et al., 2012; Pierce et al., 2011), but also in many rural or urban environments (Bzdek et al., 2014; Setyan et al., 2014; Bzdek et al., 2013; Ahlm et al., 2012; Smith et al., 2008). Exceptions for this pattern are areas near large sulfur emissions sources, in which sulfate may comprise up to about half of the ultrafine particle (Crilley et al., 2014; Bzdek et al., 2012; Zhang et al., 2011b; Wiedensohler et al., 2009).

Pre-existing particles serve as an important sink for low-volatility vapors, clusters, and growing UFPs. Therefore, primary ultrafine particles tend to decrease both new particle formation and growth rates (Kulmala et al., 2014). It is because of this competition that particle number concentrations are expected to be governed by primary particle emissions in highly polluted settings and by nucleation in remote continental sites, although nucleation still occurs in urban environments and can still be the major source (U.S. EPA, 2009).

2.4 Measurement, Monitoring and Modeling

2.4.1 $PM_{2.5}$ and PM_{10}

PM Federal Reference Method (FRM) samplers and Federal Equivalence Method (FEM) monitors are designed to measure the mass concentrations of ambient particulate matter. An FRM is a method that has been approved (40 CFR Part53) for use by states and other monitoring organizations to assess NAAQS compliance and implementation. The FRMs for $PM_{2.5}$, $PM_{10-2.5}$, and PM_{10} measurement are specified in CFR 40 Part 50, Appendices L, O, and J, respectively. A FEM is based on different sampling or analytical technology from the FRM but provides the same decision-making quality for making NAAQS attainment determinations. In practice, a large fraction of the FEM monitors in operation for PM are automated and designed to provide hourly data, while the FRMs for $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$ require sampling for 24-hours and provide a daily average $PM_{2.5}$ concentration, including pre- and

post-sampling gravimetric laboratory analysis. $PM_{2.5}$ FEMs, their performance criteria, and evaluation of their performance were described in detail in the 2009 PM ISA (U.S. EPA, 2009).

Operating principles and performance of FRMs and FEMs for PM were discussed in detail in the 2004 PM AQCD (U.S. EPA, 2004) and 2009 PM ISA (U.S. EPA, 2009). The FRMs for PM are based on gravimetric measurement of mass concentration after collection on filters. There are two broad categories of FEMs for PM measurement, those that are filter-based and designed for collection of 24-hour samples, of which very few are in use, and automated monitors designed for quantification of PM on hourly or shorter time scales, of which there are several hundred in operation. Filter-based FEMs include virtual impactor/dichotomous sampler techniques, in which a sampler is designed to separate particles by their inertia into separate flow streams, in this case $PM_{2.5}$ and $PM_{10-2.5}$. There are three widely used short time resolution automated FEMs: (1) beta attenuation monitors which measures absorption of beta radiation by PM, which is proportional to PM mass; (2) Tapered Element Oscillating Microbalance (TEOM), monitors, which continuously records the mass of particles collected on a filter substrate and are typically configured with the Filter Dynamics Measurement System (FDMS), which is designed to ensure the sample is appropriately conditioned and that volatile aerosols are measured; and (3) optical methods that utilize a spectrometer, which allow calculation of aerosol mass concentrations over a wide range of cut points.

At the time of completion of both the 2004 AQCD (U.S. EPA, 2004) and 2009 PM ISA (U.S. EPA, 2009), considerable effort was still focused on improvement of measurement methods for PM mass. Examples are the development of the $PM_{10-2.5}$ FRM and the Filter Dynamics Measurement System-TEOM (FDMS-TEOM) (Grover et al., 2006), both of which are described in detail in the 2009 PM ISA (U.S. EPA, 2009). More recently, there has been little new emphasis on method development research for PM mass measurement.

2.4.2 $PM_{10-2.5}$

Although the $PM_{10-2.5}$ FRM and FEMs were already discussed in the 2009 PM ISA (U.S. EPA, 2009), the state of technology for $PM_{10-2.5}$ measurement is reviewed here because the large data set of nationwide $PM_{10-2.5}$ network measurements is reported for the first time in Section 2.5. $PM_{10-2.5}$ FRM and FEMs now used for routine network monitoring are considerably improved compared to methods used in the previous key analyses of $PM_{10-2.5}$ sampling issues (U.S. EPA, 2004; Vanderpool et al., 2004). New results reveal changing trends in $PM_{2.5}/PM_{10}$ ratios (see Section 2.5.1.1.4).

There are three categories of methods widely used for ambient sampling of $PM_{10-2.5}$. The first is the $PM_{10-2.5}$ FRM (40 CFR Part 50, Appendix O), which determines $PM_{10-2.5}$ mass as the arithmetic difference between separate, collocated, concurrent 24-hour PM_{10} and $PM_{2.5}$ measurements at local conditions of temperature and pressure. This is sometimes referred to as the difference method for $PM_{10-2.5}$ sampling. The difference method was selected as the FRM to preserve the particle size limits for

$PM_{2.5}$ and PM_{10}, which are defined by fractionation curves with characteristic shapes and cut-off sharpnesses established for the $PM_{2.5}$ and PM_{10} FRMs as well as to preserve integrated sample filter collection and gravimetric measurement technology used for all previous FRMs for PM indicators to maximize comparability between $PM_{2.5}$, PM_{10}, and $PM_{10–2.5}$ measurements. $PM_{10–2.5}$ FRMs are largely deployed as part of a multipollutant monitoring network (see Section 2.4.6).

A second category of $PM_{10–2.5}$ methods are the automated FEM monitors that utilize either a difference method or dichotomous separator in the design of the method. Automated difference method FEMs use two measurement devices similar to the FRM difference method. Automated dichotomous FEMs also rely on two measurement devices, but instead of having separate inlets, use one flow stream, that splits the particles into larger and smaller PM mass fractions to be analyzed separately. Automated $PM_{10–2.5}$ FEMs are also largely deployed at NCore stations.

The third category of $PM_{10–2.5}$ methods deployed are for the IMPROVE program. In the IMPROVE sampling methods, two of the four sampling modules operated provide data that are used to calculate a $PM_{10–2.5}$ concentration similar to how the FRM difference method is calculated. Although not an FRM or FEM, the IMPROVE program $PM_{10–2.5}$ data are included as they represent a consistent national network at over 150 locations. IMPROVE program sites are typically located in class one areas and national parks to support the Regional haze program.

There were early observations of poor precision for $PM_{10–2.5}$ mass measurements for both the difference method (Allen et al., 1999; Wilson and Suh, 1997), and dichotomous samplers (Camp, 1980), as well as discussion of the inherently lower precision of both the old difference method and dichotomous sampling compared to $PM_{2.5}$ and PM_{10} FRMs (Allen et al., 1999). The early observations of poor precision were not based on the performance of $PM_{10–2.5}$ samplers in current use in the NCore and other sampling networks, as a number of improvements have facilitated greater precision of the difference method (Allen et al., 1999) and the development of a FRM for $PM_{10–2.5}$ (40 CFR Part 50 Appendix O). Precision better than 5% was demonstrated by using identical instrumentation for both $PM_{2.5}$ and PM_{10} except for the sampler cut-point; using the same filter type, filter material, filter face velocity, and ambient-to-filter temperature difference, lowering blank variability, and increasing gravimetric analytical precision (Allen et al., 1999). These are provisions that are now specified in the FRM and used for measurements of $PM_{10–2.5}$ in national sampling networks that use the $PM_{10–2.5}$ FRM or FEM to obtain differences in PM_{10} and $PM_{2.5}$ mass. Because of these improvements, high uncertainties reported for previous measurements described in U.S. EPA (2004) no longer apply to the difference methods in use as FRMs and FEMs on which current $PM_{10–2.5}$ network measurements are based.

2.4.3 Ultrafine Particles: Number, Surface Area, Mass

In this section measurement methods for UFP are reviewed. In Section 2.4.3.1 methods for counting particle number and measuring particle number distribution are described. Because UFP mass is

usually so small, the number rather than the mass of UFP are usually reported. As this can be instrument-dependent, differences in particle number measurement methods in common use are discussed. Section 2.4.3.2 reviews surface area measurements and Section 2.4.3.3 reviews mass measurements. There are a number of reasons why measurements in the UFP size range are more challenging than mass measurements of $PM_{2.5}$ or $PM_{10–2.5}$, and these can result in differences in the upper size limit for sampling UFP mass and number. These challenges and differences are explained in Section 2.4.3.3.

2.4.3.1 Particle Number and Number Distribution

Particle number measurement is a rapidly advancing area of research, and large uncertainties and biases are likely associated with UFP measurement. The U.S. EPA has not yet established reference methods for ambient or source UFP number measurement. However, use of particle number measurements for regulatory and certification purposes has driven technological development of particle number measurements in the European Union (EU), where a network of UFP monitoring stations that uses PM electrical properties for both counting and sizing particles to measure particle number distributions are classified into six size classes every 10 minutes has been developed (Wiedensohler et al., 2012).

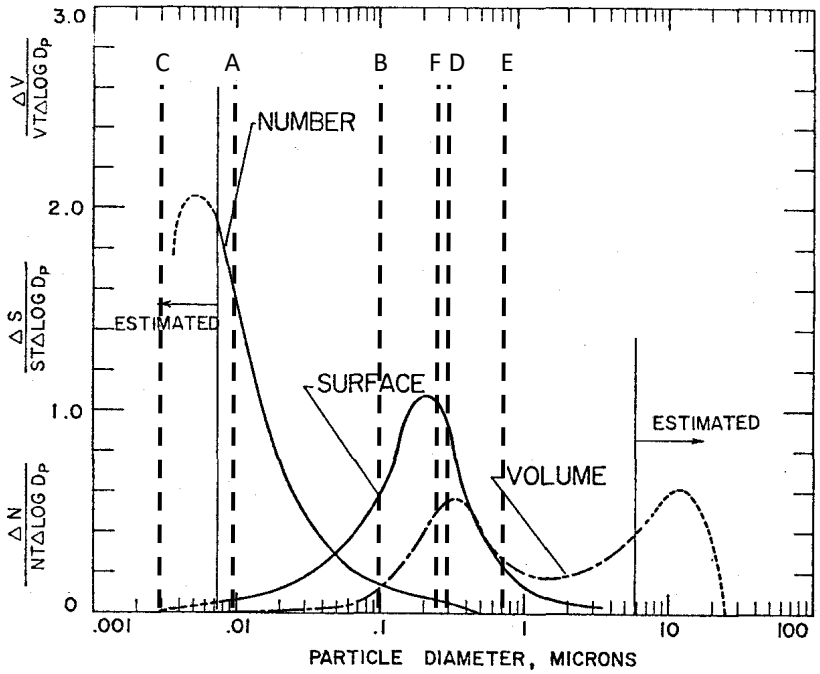
Condensation particle counters (CPC) are one of the most common means of determining total number concentration (the majority which is usually in the UFP range) for both ambient and source particle measurements. Particles enter a water or alcohol saturated vapor chamber and grow by condensation to a size that allows measurement using an optical particle counter (OPC). In some cases CPC instrumentation is used to measure UFP number without size classification under the assumption that particles with Dp > 0.1 µm do not significantly contribute to particle number measurements. The 2009 PM ISA (U.S. EPA, 2009) reported the development of a water-based CPC more suitable for long-term field studies. Before the development of this technology particle number measurements were mainly restricted to short-term, intensive field studies. Water-based CPC instruments have since found limited use in network monitoring applications (see Section 2.4.5 and Section 2.5.1.1.5).

The 2009 PM ISA also reported a reduction in detection size down to <0.002 µm in diameter with mobility particle sizers (U.S. EPA, 2009). More recently, substantial progress has been made in measuring sub-0.003 µm particles and clusters, as well as gaseous compounds involved in the initial steps of atmospheric NPF. Advances include development of particle counters (CPCs) capable of measuring particle number counts and number distributions down to about 0.001 µm in particle mobility diameter (Kangasluoma et al., 2015; Lehtipalo et al., 2014; Kuang et al., 2012a; Jiang et al., 2011; Vanhanen et al., 2011; Iida et al., 2008). These advances are especially useful for investigating atmospheric nucleation of particles (see Section 2.3.4).

Other recent advances include current efforts to develop a miniaturized CPC for use in personal monitoring applications (He et al., 2013). CPCs can be used as stand-alone instruments to measure total particle number but are often used downstream of other particle classifiers to determine UFP number or particle-number size distributions. Classification of UFP size may be via the inertial, diffusional, or electric mobility properties of the aerosol and sometimes more than one means of classification may be used. Faraday cup electrometers (FCE) can also be used downstream of other particle classifiers to determine UFP number or particle-number size distributions (Dhaniyala et al., 2011; McMurry et al., 2011; Fletcher et al., 2009). Size classification of UFP was reviewed in the 2009 PM ISA (U.S. EPA, 2009) and methods based on inertial, gravitational, centrifugal, and thermal techniques were reviewed (Marple and Olson, 2011). Advances in the development of size classification methods have mainly concerned classification by electrical mobility. A unique particle mobility within an electric field can be established relative to particle size (Hinds, 1999) and aerosols can be charged with radioactive sources such as Kr-85, Am-241, or Po-210 or using a soft-X-ray source (Jiang et al., 2014). Other instruments that classify by size using electrical mobility were described in the 2009 PM ISA (U.S. EPA, 2009).

The size ranges measured by instruments widely used in field research are superimposed on a typical particle number size distribution (Whitby et al., 1972) illustrated in Figure 2-9. The vertical lines in Figure 2-9 show the lower and upper size limits of various UFP sampling methods. In earlier literature, CPCs used for particle number measurement variable lower limit particle size detection levels were reported, but they were often near 0.01 μm (Liu and Kim, 1977), shown as Line A. In several field studies described in this ISA, particles are sized by diffusive or electrical methods before counting to limit measurements to particle number count to below 0.1 μm (Evans et al., 2014; Liu et al., 2013; Rosenthal et al., 2013), shown as Line B. In these cases, resulting particle number measurements are the number of particles between Line A and Line B in Figure 2-9. Since the number distribution continues below 0.01 μm (Line A), it is possible that some fraction of the total number of particles smaller than 0.01 μm are too small to be detected, except without specialized research methods for counting clusters, as described above.

Moreover, the peak of the number distribution can change considerably over time or over short distances. At less than 50 meters from a major highway there were more particles in the 0.006 to 0.025 μm size range than in the 0.025 to 0.05 μm size range, but at 100 meters from the highway there were more particles in the 0.025 to 0.05 μm size range than in the 0.006 to 0.025 μm size range (Zhu and Hinds, 2002). It is possible that actual particle number could decrease with distance from a busy road at the same time that the fraction of the particles is large enough to be detected may increasing, making interpretation of particle number data difficult.



Vertical lines are: (A) lower size limit from a widely used condensation particle counter (CPC) from 1977; (B) upper size limit definition of UFP; (C) lower size limit of a newer CPC; (D) and (E) upper size limits for particle number measurements from different epidemiologic studies. (Line F is not used.)

Source Permission pending: Original figure showing example particle size distribution from Whitby et al. (1972), vertical lines correspond to lower and upper size ranges for sampling procedures reported by Viana et al. (2015); Evans et al. (2014); Meier et al. (2014); Olsen et al. (2014); Liu et al. (2013); Rosenthal et al. (2013); Hampel et al. (2012); Iskandar et al. (2012); Verma et al. (2009); Liu and Kim (1977).

Figure 2-9 Size ranges collected by various UFP sampling procedures.

The development of CPCs that can detect particles as small as 0.003 µm could complicate comparison of particle number concentrations measured with different particle counters. As Figure 2-9 shows there is a difference in number of particles counted between older particle counters with size limits down to 0.010 µm (between Lines A and B) and newer particle counters with size limits down to 0.003 µm (between Lines B and C). In one study where two different particle counters were used, one with a lower size limit of 0.003 µm gave 14−16% higher number counts than one with a lower size limit of 0.007 µm (Hampel et al., 2012). In the Pittsburgh Air Quality Study, the average particle number count in the size range 0.003 to 0.010 µm was 5,600 cm^{-3} (Stanier et al., 2004), while the average particle number count for the entire 0.003 to 2.5 µm size range was 22,100 cm^{-3}. This corresponds to 25% of total particle number count accounted for by particles in the range of 0.003 to 0.010 µm.

In other studies, particle number has been counted without size classifying before counting over size ranges up to 0.3 µm (Meier et al., 2014; Olsen et al., 2014) or 0.7 µm (Iskandar et al., 2012), as shown in Lines D and E of Figure 2-9 as an indicator UFP number. Although 0.3 µm is well above the nominal UFP upper limit of 0.1 µm, the use of a larger upper size limit was more convenient and was

justified by observations that most particles are smaller than 0.1 µm. Figure 2-9 shows that the greatest number of particles are smaller than 0.1 µm, but that a part of the particle number distribution extends beyond it. Recent studies verified that 75% of particles smaller than 0.7 µm (Iskandar et al., 2012) and roughly 5/6 of particles smaller than 0.5 µm by number were smaller than 0.1 µm (Evans et al., 2014).

An additional complication for electrometer based measurements (but not for CPCs) is that the number of particles that can be detected varies with particle size. For example, an electrometer can have a size detection limit of 0.02 µm, this does not indicate that a single particle with a diameter of 0.02 µm can be detected. Instead, lower count detection varies with particle size because the amount of charge required for detection by an electrometer increases with decreasing particle size. For example, a UFP 3031 electrometer has an estimated lower detection limit of 408 cm^{-3} for 0.02−0.03 µm particles but falls off to 120 cm^{-3} for 0.07 to 0.1 µm particles (Vedantham et al., 2015). Detection of particle number using an electrometer is thus limited by a size below which no particles are counted, as well as by a minimum detectable particle number count that varies with size.

To summarize, the variety of instruments and approaches used for measuring particle number present potentially large uncertainties for use in field studies to estimate exposure and health impacts, and complicate comparison of particle number concentrations between field studies using different measurement methods. Not removing particles larger than 0.1 µm before measurement introduces a bias of greater than 10−20%. Differences in the lower size limit of detection between different particle counters could produce an even greater uncertainty that has not been fully characterized. Underlying these uncertainties is the knowledge that because there is a lower size limit for particle detection, there is inherently some unknown fraction of particle number concentration that is accounted for by particles that are too small to be detected. This is an especially important consideration for comparing recent data to older data. As particle number counting technology rapidly advances, the lower size limit of detection is decreasing and the number of particles capable of being detected is correspondingly increasing. In essence, different widely used UFP measurement methods do not measure the same particle size range, and serious biases in particle number measurements are both likely and difficult to assess.

2.4.3.2 Surface Area

Particle surface area is usually measured by radioactive or electrical labeling of particles using an electrical aerosol detector or radiation detector (U.S. EPA, 2009). There have been new advances in measurement of UFP surface area. The epiphaniometer directly measures surface area via surface deposition of Pb-211 onto sampled particles and subsequent measurement of the α-activity of particles deposited on a filter using an annular surface barrier detector (Gini et al., 2013; Gaggeler et al., 1989). Surface area may also be approximately determined via unipolar diffusion charging of particles with active surface area related to the electrical charge transferred to particles under controlled charging conditions (Jung and Kittelson, 2005). Excess ions are removed using an ion trap charge is measured via

electrometer (Geiss et al., 2016). The diffusion charge surface area relationship is only valid within a particle size range of approximately 0.02 to 0.4 µm (Geiss et al., 2016; Kaminski et al., 2012; Asbach et al., 2009). Diffusion charge surface area shows good agreement with TEM projected surface area for particle sizes of primary interest for UFP characterization (i.e., DP < 0.1 µm) but appears to underestimate surface area for larger particles (Ku and Maynard, 2005). Instrumentation and methods used to estimate "lung-deposited surface area" are described in Section 4.1.7.

2.4.3.3 Mass

Inertial classification to the most common UFP size definition (i.e., an inertial 50% cutpoint Dp less than 0.1 µm) can be accomplished for UFP mass sampling by using a low-pressure impactor as an initial scalper stage and using sample filter media in the flow exiting the impactor. In such cases, UFP mass can be designated as $PM_{0.1}$, which makes reference to the 0.1 µm 50% cutpoint in a manner analogous to nomenclature used for other size-classified particle mass measurements (e.g., $PM_{2.5}$).

Measurement of UFP mass gravimetrically can be problematic due to the small amount of collected mass, long sampling periods involved, and the potential loss of semivolatile particles. While inertial classifiers can be used to classify or determine the size distribution of UFP, the pressure drop across the sub-0.1 µm stage required for sampling UFP may present challenges with respect to evaporative loss of particulate matter (Hata et al., 2012; Furuuchi et al., 2010; Singh et al., 2003).

To address this, particles with a larger aerodynamic diameter cutpoint have been sampled using a high volume slit impactor with 50% cutpoints of 0.18 or 0.25 µm to increase the sample collected for mass determination and/or compositional analyses and to reduce the pressure drop across the inertial classification stage to reduce evaporative losses. For example, Misra et al. (2002) designed a sampler with a 0.25 µm inertial 50% cutpoint D_p to quantify $PM_{0.25}$ (Saffari et al., 2015; Misra et al., 2002), and a design by Demokritou et al. (2002) later evolved into a commercial sampler with a 0.18 µm cutpoint for sampling near the UFP range.[38] Sampling of $PM_{0.25}$ or $PM_{0.18}$ increases sampled mass over a time interval and reduces the pressure differential necessary for inertial classification relative to $PM_{0.1}$. In the available studies, the estimated upper limit of the measured PM mass that has been referred to as the ultrafine particle size range usually varies between about 0.1 and 0.3 µm of the particle aerodynamic diameter, depending on the PM sampling device used (Cheung et al., 2016; Borgie et al., 2015; Viana et al., 2015; Daher et al., 2013; Kudo et al., 2012; Mueller et al., 2012; Chen et al., 2010; Bruggemann et al., 2009).

Concentrated ambient particles (CAPs) are frequently used in controlled human exposure and animal toxicology studies. The technology that allows for CAPs is the virtual impactor with a high volume slit design (Sioutas et al., 1994c; Sioutas et al., 1994a, b). Briefly, ambient air is accelerated

[38] BGI 900 High Volume Cascade Impactor Guidance Manual, https://bgi.mesalabs.com/wp-content/uploads/sites/35/2014/10/BGI900_MANUAL_1.0.0.pdf.

through a high-volume nozzle that lets smaller particles pass through in a small fraction of the flow stream, but removes larger particles by impaction in a larger fraction of the flow stream. Classification by size has been achieved by placing two or three virtual impactors in sequence in a Versatile Aerosol Concentration Enrichment System (VACES) (Maciejczyk et al., 2005; Ghio et al., 2000; Sioutas et al., 1995b; Sioutas et al., 1995a). The Ultrafine Particle Concentrator (UPC) was developed by Sioutas et al. (1999) as a laboratory aerosol concentration device and was incorporated into a variation of the VACES by Kim et al. (2001). Ambient air is introduced in the system through three inlets: 0.18 µm impactor, 2.5 µm impactor, and ambient air with no upstream cutpoint (Kim et al., 2001). The VACES was briefly described in the 2004 PM AQCD (U.S. EPA, 2009). Because virtual impaction works best for particles much larger than 0.1 µm, UFP concentration requires supersaturation for particle growth to an optimal size for virtual impactor operation, and a subsequent drying step after separation to return particles to their original size.

The original description of the Harvard Ultrafine Concentrated Ambient Particle System (HUCAPS) includes an outlet impactor with a 0.2 µm cut point (Gupta et al., 2004). A 0.3 µm cut point using the HUCAPS has also been described (Liu et al., 2017) and the VACES, uses 0.18 µm cut point inlet impactor for its nominally ultrafine size range (Kim et al., 2001).

Other approaches to PM delivery in controlled exposure studies can result in particle size ranges up to 0.3 µm. Previously described high volume ambient samplers designed to collect a UFP fraction have also been used in controlled exposure studies with UFP, by collecting PM on a filter substrate, extracting the PM from the filter, and nebulizing and drying the extract to reconstitute the aerosol (Cheng et al., 2016; Morgan et al., 2011), (Zhang et al., 2012a), (Cacciottolo et al., 2017; Woodward et al., 2017). In other controlled clinical exposure studies PM with MMD <0.1 µm was generated by spark discharge (Schaumann et al., 2014) or sampled directly from automobile exhaust (Tyler et al., 2016).

UFP CAPS and other delivery systems for controlled exposure studies are generally not limited to the nominal UFP size limit of less than 0.1 µm. Instead, they usually involve a particle size ranging up to 0.18 to 0.3 µm without exclusion by impaction or other means of removal. Under these circumstances, a large fraction of the mass range targeted for investigation of UFP effects in controlled exposure studies can come from particles larger than the nominal size of 0.1 µm. Consequently, a difference in mass between practical mass sampling methods targeting UFP and what would be measured below 0.1 µm is likely. However, as described in Section 2.4.3.1, the difference in particle number measurements is likely to be much less.

2.4.4 Chemical Components

Measurement of PM components is potentially useful for providing insight into what sources contribute to PM mass as well as for discerning differential toxicity. Sulfate, nitrate, ammonium, organic carbon and elemental carbon as well as a suite of elements are measured in national speciation monitoring

networks (see Section 2.4.5) and intensive field studies mainly by collection on filters, using methods described in detail in the 2004 PM AQCD (U.S. EPA, 2004) and 2009 PM ISA (U.S. EPA, 2009). New advances in PM speciation analysis has included new network applications for OC analysis and better characterization of sampling errors of major PM components. Fourier Transform Infrared Spectroscopy has been applied to OC and organic functional group determination in national networks (see Section 2.4.6) for monitoring $PM_{2.5}$ species (Weakley et al., 2016). Characterization of sampling errors due to loss of ammonium nitrate and semivolatile organic material during sampling, adsorption of organic vapors during sampling, and generation of elemental carbon during analysis of organic carbon have emerged as the main sources of measurement error and considerable effort has been devoted to their minimization or correction (U.S. EPA, 2009, 2004).

New research has focused on seasonal differences in the impacts of these errors, indicating 40−50% loss of $PM_{2.5}$ nitrate from Teflon filters in summer and less than 10% in winter, with summer losses largely balanced out by an increase in retained water (Malm et al., 2011; Nie et al., 2010; Vecchi et al., 2009). The volatilized nitrate is minimized in network nitrate sampling methods (Solomon et al., 2014), but not with most $PM_{2.5}$ mass methods, making a negative bias in the $PM_{2.5}$ FRM possible if the nitrate contribution to $PM_{2.5}$ mass is large enough. Further research has also continued on quantification of positive OC artifacts due to vapor adsorption on filters (Vecchi et al., 2009; Watson et al., 2009), including observation of more vapor adsorption in summer than winter (Cheng et al., 2010; Vecchi et al., 2009). Minimization of sampling error has been investigated by adjusting filter deposit area, flow rate, and passive exposure time (Chow et al., 2010a); using denuders upstream of filters (Chow et al., 2010b); and characterizing backup filter correction and its influence on the split between OC and EC (Cheng et al., 2009) to reduce the positive adsorption artifact. Considerable research has also focused on measurement of particulate organic species, elemental analysis, and single particle mass spectrometric analysis, and some novel sampling and analytical approaches for measurement of PM components, but these are beyond the scope of this review because they have not been used for interpreting health and welfare impacts.

2.4.5 Satellite Remote Sensing

Instruments sensing back-scattered solar radiation on satellites have made it possible to characterize tropospheric aerosol properties on the global scale. Satellite-based measurements used for estimating $PM_{2.5}$ are becoming more widely used and have recently been combined with modeled data and ground-level measurements to extend the spatial coverage over which $PM_{2.5}$ concentrations can be estimated and to improve the spatial resolution of $PM_{2.5}$ estimates used to assign exposure in health studies. The satellite borne instruments vary in their complexity and in the aerosol properties they can measure. Satellite instruments measure radiance (electromagnetic energy flux), that can then be used to provide information on the aerosol column amount, or the aerosol optical depth (AOD). Because $PM_{2.5}$ is not directly measured, computational algorithms involving a range of assumptions must be applied to

obtain estimates of $PM_{2.5}$ concentrations from AOD. These inferred measurements involve potential errors that are not encountered with the FRM or other ground-based $PM_{2.5}$ measurements. This section focuses on the estimation of $PM_{2.5}$ concentration from AOD and its strengths and limitations. Studies involving fusion of AOD with spatiotemporal modeling for prediction of exposure concentration are discussed in Section 3.3.3.

Depending on the wavelengths sampled and the spectral resolution of the instruments, information about the composition of particles of diameter <2 μm and particles of diameter >2 μm can be obtained (Engel-Cox et al., 2004). Satellite AOD observations have extensive spatial coverage, making these data attractive for estimating surface PM concentrations. AOD is a measure of the extinction of light in the atmosphere and is directly related to the presence of particulate matter as the individual particles scatter light. A higher AOD reflects greater scattering, indicating higher PM loadings. However, this relationship is not linear due to multiple factors including atmospheric (e.g., thickness of the boundary layer, cloud presence, humidity) and particle (chemical speciation, size distribution) characteristics, and can be impacted by surface characteristics as well (Martin, 2008). Data cannot be collected when clouds and snow are present, limiting the completeness of satellite datasets (Hoff and Christopher, 2009) or from excessive amounts of smoke being mistaken for clouds when AOD > 4 (van Donkelaar et al., 2011).

Spatial and temporal resolution with which concentration can be estimated by satellite images varies with the satellite data source. Satellite/instrument retrievals, and further analyses, provide AOD at varying spatial resolutions down to 500 meters [e.g., Reid et al. (2015); Hoff and Christopher (2009)]. The Moderate Resolution Imaging Spectroradiometer (MODIS) passes the U.S. twice daily with 10 km or 1 km resolution, while the Geostationary Operational Environmental Satellite (GOES) Aerosol/Smoke Product (GASP) produces data in 30-minute intervals with 1 km resolution, and the Multiangle Imaging Spectroradiometer (MISR) produces nearly continuous AOD data but with 17.6 km resolution. Additionally, AOD can be estimated at the earth's surface by the Aerosol Robotic Network (AERONET), which measures AOD from the ground surface and has sites distributed globally. AERONET AOD measurements may provide some validation of satellite AOD measurements.

The many factors that impact the relationship between AOD and $PM_{2.5}$ concentrations lead to widely varying and sometimes relatively low, correlations when linear relationships are developed. In the Hoff and Christopher (2009) review, the correlation (R) (not specified as Spearman or Pearson) ranged from 0.4 to 0.98 across cited studies. Errors in satellite data may occur because the retrievals are sensitive to the aerosol vertical distribution and the optical properties of the particles, which in turn are determined by their morphology and composition, whether they are internally or externally mixed, and the surface contribution to satellite measured reflectance. Hu (2009) observed a Pearson $R = 0.67$ for the eastern U.S. and $R = 0.22$ for the western U.S. The authors attributed poor retrieval in the western U.S. to variation in topography and meteorology. Moreover, satellite data are obtained during brief overpass, and can't be integrated over the longer averaging times used in ground-based measurements. Satellite observations have been compared with AERONET to determine how remote sensing influences measurements of

AOD. Kim et al. (2015) compared AOD for the southeastern U.S. from AERONET with that from MODIS and MISR and found correlations of 0.83 and 0.74, respectively. Normalized mean biases were −18% for MODIS and 1.5% for MISR compared with AERONET. The amplitudes of seasonal peaks were larger in satellite observations compared with the surface data. Kim et al. (2015) suggested that two main factors contribute to this finding: in summer, the mixed layer is deeper, which allows for vertical mixing to greater heights where the sensitivity of the satellite measurements is greater, and there is biogenic SOA production from isoprene oxidation; conversely in winter, the shallower mixed layer depth restricts the extent of vertical mixing, and SOA formation is greatly reduced compared to summer.

The influence of surface reflectance on the relationship between estimated $PM_{2.5}$ and AOD depends on the wavelength range of the retrieval system. The most commonly used algorithm for retrieving AOD from MODIS uses reflected sunlight in the 470 to 2,110 nm wavelength range and is more reliable over dark surfaces than over bright surfaces, because bright surfaces typically show high reflectivity in the red and near-infrared frequencies, resulting in low signal to noise ratios over bright surfaces. However, retrievals of AOD over bright surfaces are possible by making use of reflected sunlight measured in the 412−470 nm channels (Sorek-Hamer et al., 2015). R^2 was determined between retrievals of AOD over the San Joaquin Valley using a mixed effects model. In this model fixed effects represent average relationship between AOD and $PM_{2.5}$ over all monitors in the study area for the study period (2005−2008) and random effects reflect daily variability in the relationship between $PM_{2.5}$ and AOD. R^2 was 0.69, root mean square predicted error (RMSPE) was 9.1 ± 1.2 μg/m^3 and normalized RMPSE was 0.44 ± 0.05.

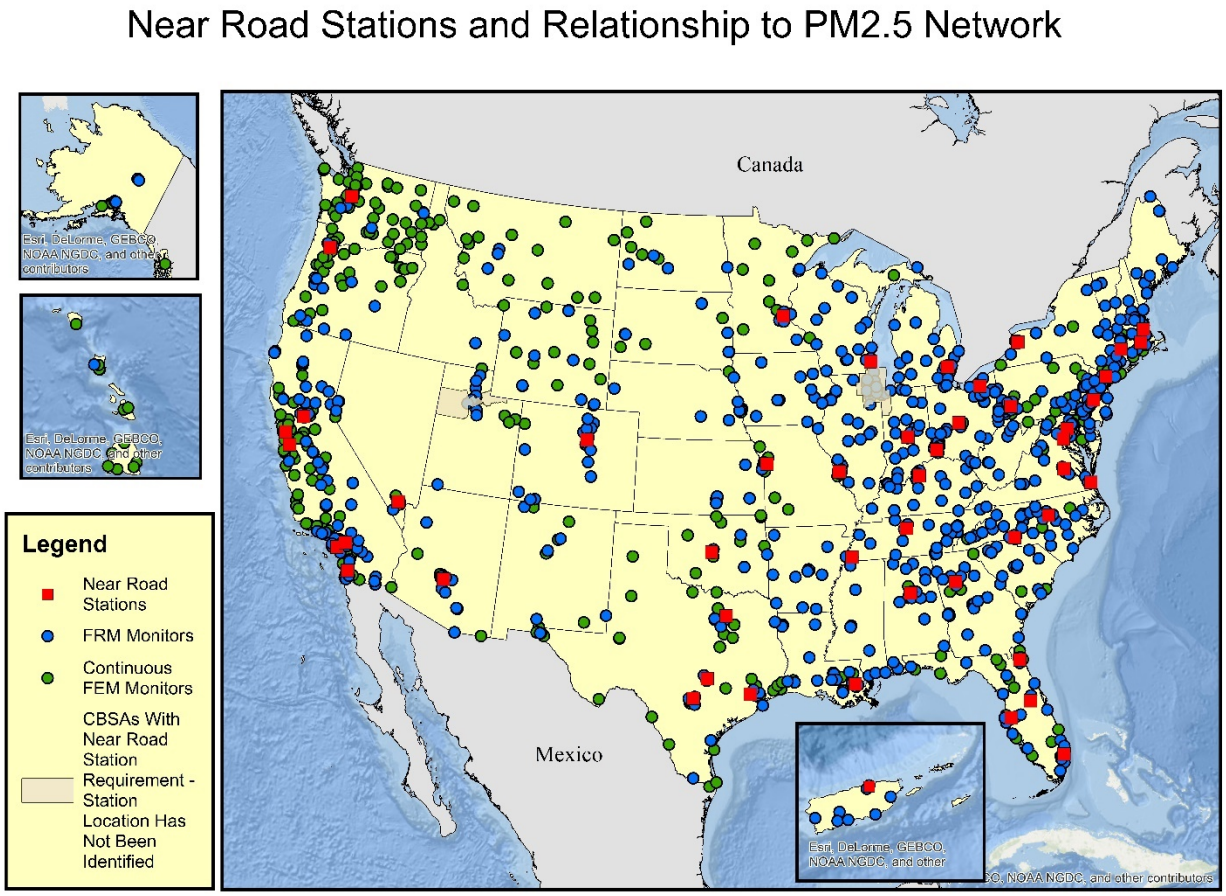
Spatial resolution of the satellite image influences the relationship between estimated $PM_{2.5}$ and AOD. More recently, Chudnovsky et al. (2013b) used the Multiangle Implementation of Atmospheric Correction (MAIAC) AOD, derived from MODIS radiances with a 1 km resolution over New England from 2002 to 2008 to assess how AOD resolution impacted the coefficient of determination with $PM_{2.5}$ using a simple linear fit. The 1 km resolution retrievals displayed greater spatial variability over New England than did the 10 km resolution with an increase in the sample of cloud free cells. They found that, in their application, the R^2 decreased as the resolution was decreased (from a median of about 0.5 at 1 km resolution to about 0.2 at 10 km), suggesting that higher resolution AOD products can provide increased spatial detail and higher accuracy. Using the same data from New England from 2002 to 2008, Chudnovsky et al. (2013a) also compared the correlation between AOD and fixed-site $PM_{2.5}$ concentration derived from 10 km resolution MODIS data and 1 km resolution MAIAC data with concentration from 84 fixed-site $PM_{2.5}$ monitors. Correlations (not stated whether Pearson or Spearman) were similar (R = 0.62 for MODIS and 0.65 for MAIAC) across all data and when broken down by region and season. The 1 km resolution MAIAC data were found to have valid AOD measures for a larger fraction of the monitoring sites compared with 10 km MODIS data. Chudnovsky et al. (2013a) noted that comparisons between AOD and fixed-site monitor $PM_{2.5}$ concentration data can sometimes produce inverse relationships. The AOD averaged over an area can be lower or higher than the $PM_{2.5}$

concentration measured at a fixed-site monitor depending on the spatial distribution of primary $PM_{2.5}$ sources.

To summarize, satellite-based measurements are becoming more widely used for estimating $PM_{2.5}$ to provide more extensive spatial coverage than can be obtained with $PM_{2.5}$ monitoring network data. The satellite based instruments measure radiance to provide information on AOD, and computational algorithms are then used to estimate $PM_{2.5}$ from AOD. These algorithms can be complex, and there is considerable uncertainty in the $PM_{2.5}$ estimated from AOD. This is because of the many factors that influence the relationship between $PM_{2.5}$ and AOD, including boundary layer thickness, cloud presence, humidity, PM composition and size distribution, and ground reflectivity. Satellite based $PM_{2.5}$ estimates are more accurate over dark surfaces on days without clouds than over bright surfaces or with clouds present, but they can also be used effectively in hybrid models that may incorporate other data sources, including CMAQ model output, surface measurements, and land use variables (Section 3.3.3).

2.4.6 Monitoring Networks

Objectives for PM monitoring include: (1) supporting air quality analyses used to conduct assessments of exposure, health risks, and welfare effects, (2) characterizing air quality status, including providing the public with timely reports and forecasts of the air quality index (AQI), (3) determining compliance with the NAAQS, (4) developing and evaluating air pollution control strategies, and (5) measuring trends and overall progress for air pollution control programs. Federal rules that regulate monitoring programs and details of the various sampling networks relevant for PM measurement are described in the 2009 PM ISA (U.S. EPA, 2009) and updated in the 2016 PM IRP (U.S. EPA, 2016b). Data from U.S. EPA's ambient air monitoring network are available from two national databases. The AirNow database provides data used in public reporting and forecasting of the AQI and the Air Quality System (AQS) database is the U.S. EPA's long-term repository of ambient air monitoring data. The current $PM_{2.5}$ network as of May 2018 is shown in Figure 2-10. As of May 2018, there are 738 FRM monitors and 839 continuous mass FEM monitors.



Source Permission pending: U.S. Environmental Protection Agency 2016 analysis of data from monitoring networks.

Figure 2-10 $PM_{2.5}$ Network Including Near Road Monitors.

There are a number of other major national monitoring networks for PM that have been in place for multiple decades. PM_{10} is also monitored in a national network for comparison of PM_{10} data to the NAAQS. As of May 2018, there are 420 FRM monitors and 351 continuous FEM monitors in the PM_{10} network. $PM_{2.5}$ components are measured in two monitoring networks, the Chemical Speciation Network (CSN), and the Interagency Monitoring of Protected Visual Environments (IMPROVE) network, which was implemented to better understand the relationship between PM composition and properties with atmospheric visibility (U.S. EPA, 2016b). As of May 2018, there are 153 CSN stations and 152 IMPROVE stations. The field and laboratory approaches used in the CSN and IMPROVE network as well as their historical evolution, measurement errors and uncertainties, and differences between them have been thoroughly reviewed (Solomon et al., 2014). Monitor locations and number of monitors required for the $PM_{2.5}$, PM_{10}, CSN, and IMPROVE networks are discussed in the 2016 PM IRP (U.S. EPA, 2016b) and monitor siting criteria are described in CFR 40 Part 58 Appendix D and the

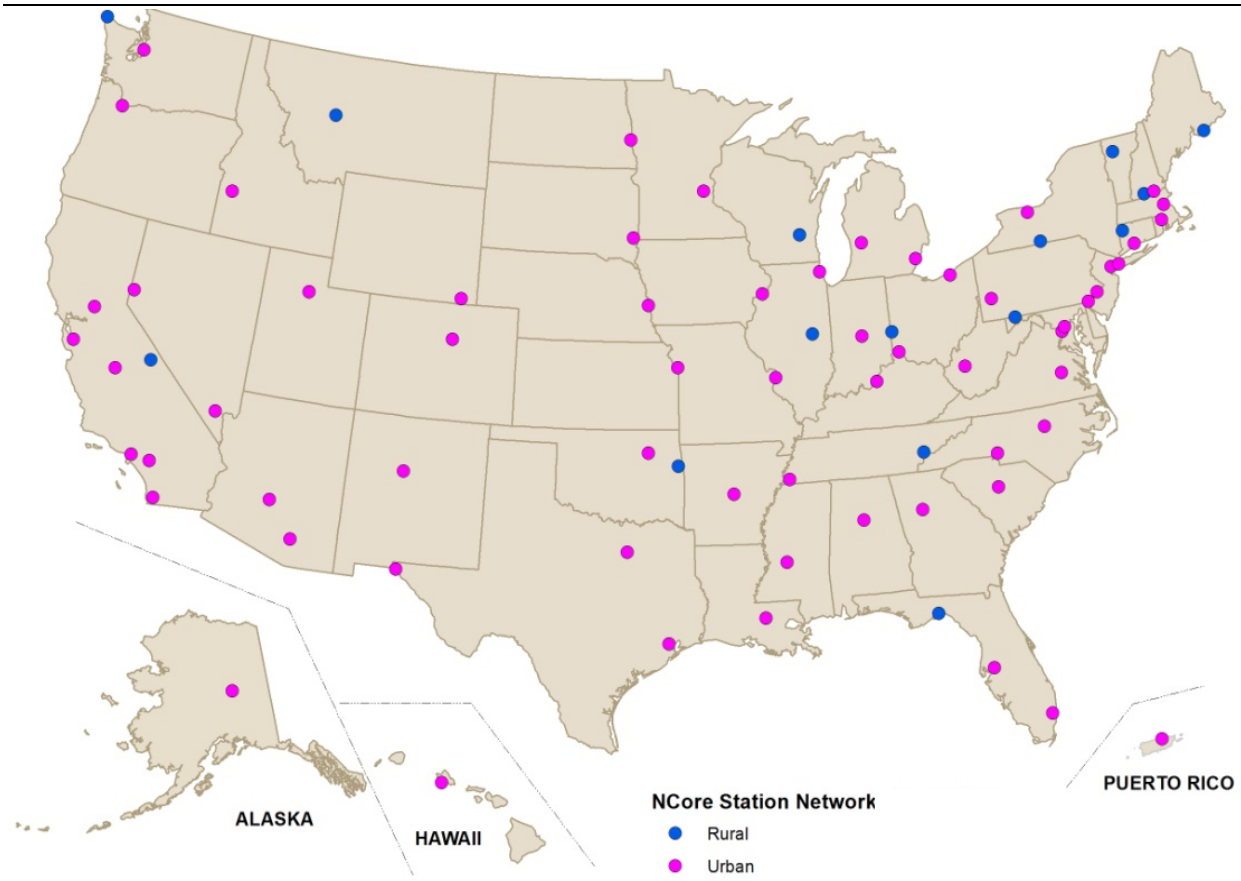
SLAMS/NAMS/PAMS Network Review Guidance (U.S. EPA, 1998). Maps of these other national monitoring networks are not included in this ISA, but have been presented along with extensive discussion of PM monitoring networks in the 2009 PM ISA (U.S. EPA, 2009).

Extensive new PM monitoring efforts now complement these long-standing networks by providing additional data supporting multiple objectives, including for PM research. These new monitoring efforts include near road monitoring for $PM_{2.5}$, and the National Core (NCore) network for multipollutant measurement, as well as monitoring of additional PM measurements that are associated with special projects or are complementary to other networks, including particle number, black carbon, and continuous component monitoring (U.S. EPA, 2016b).

$PM_{2.5}$ near road monitors located within 50 meters of roads with heavy traffic are identified in Figure 2-10. By January 1, 2015 22 core based statistical areas (CBSAs) with a population of 2.5 million or more were to have a $PM_{2.5}$ monitor operating at a near road location and by January 1, 2017 30 CBSAs with a population between 1 million and 2.5 million were to have a $PM_{2.5}$ monitor at a near road location.

The NCore network in Figure 2-11 is a relatively new national air quality monitoring network that has been operating since January 1, 2011 and has 78 monitoring sites designed for measurement of multiple pollutants, including $PM_{10–2.5}$ (Weinstock, 2012). The purpose of the NCore network is to support long-term science and policy objectives by contributing data from the latest monitoring technology over a wide range of representative urban and rural locations (Weinstock, 2012). $PM_{10–2.5}$ is measured nationwide in both the NCore and IMPROVE networks. The number of monitoring locations for $PM_{10–2.5}$ is considerably smaller than the number of $PM_{2.5}$ or PM_{10} monitors. As of May 2018, $PM_{10–2.5}$ was being monitored at 140 IMPROVE stations in addition to the 78 NCore monitoring sites.

Another new development is the routine monitoring of particle number at several sites in the U.S. Hourly particle number monitoring data over a period of several years has been reported to AQS from an urban and a rural site in New York state, and additional monitors reported data for shorter periods. At least three near road network monitoring sites will also include particle number measurements (U.S. EPA, 2016b).



Source Permission pending: U.S. Environmental Protection Agency 2016 analysis of data from monitoring networks.

Figure 2-11 National Core (NCore) Multipollutant Monitoring Network.

2.4.7 Chemistry-Transport Models

This section briefly reviews scientific advances in chemistry-transport models (CTMs)—numerical models of atmospheric transport, chemistry, and deposition of PM. The 2009 PM ISA (U.S. EPA, 2009) provided a description of the relevant processes and numerical methods. Key observations were that the largest errors in photochemical modeling were still thought to arise from the meteorological and emissions inputs to the model (Russell and Dennis, 2000) and that additional uncertainty was introduced by the parameterization of meteorological and chemical processes (U.S. EPA, 2009). Alternative approaches to modeling these processes were discussed and compared (U.S. EPA, 2009). Most major regional-scale air-related modeling efforts at U.S. EPA use the Community Multiscale Air Quality modeling system (CMAQ) (Byun and Schere, 2006; Byun and Ching, 1999). Recent updates to CTM model design, and in particular to CMAQ, are described below. Use of CTMs for exposure assessment studies, including combination of CTMs with other models or data to increase spatial resolution of the concentration field, are described in Section 3.3.2.4.

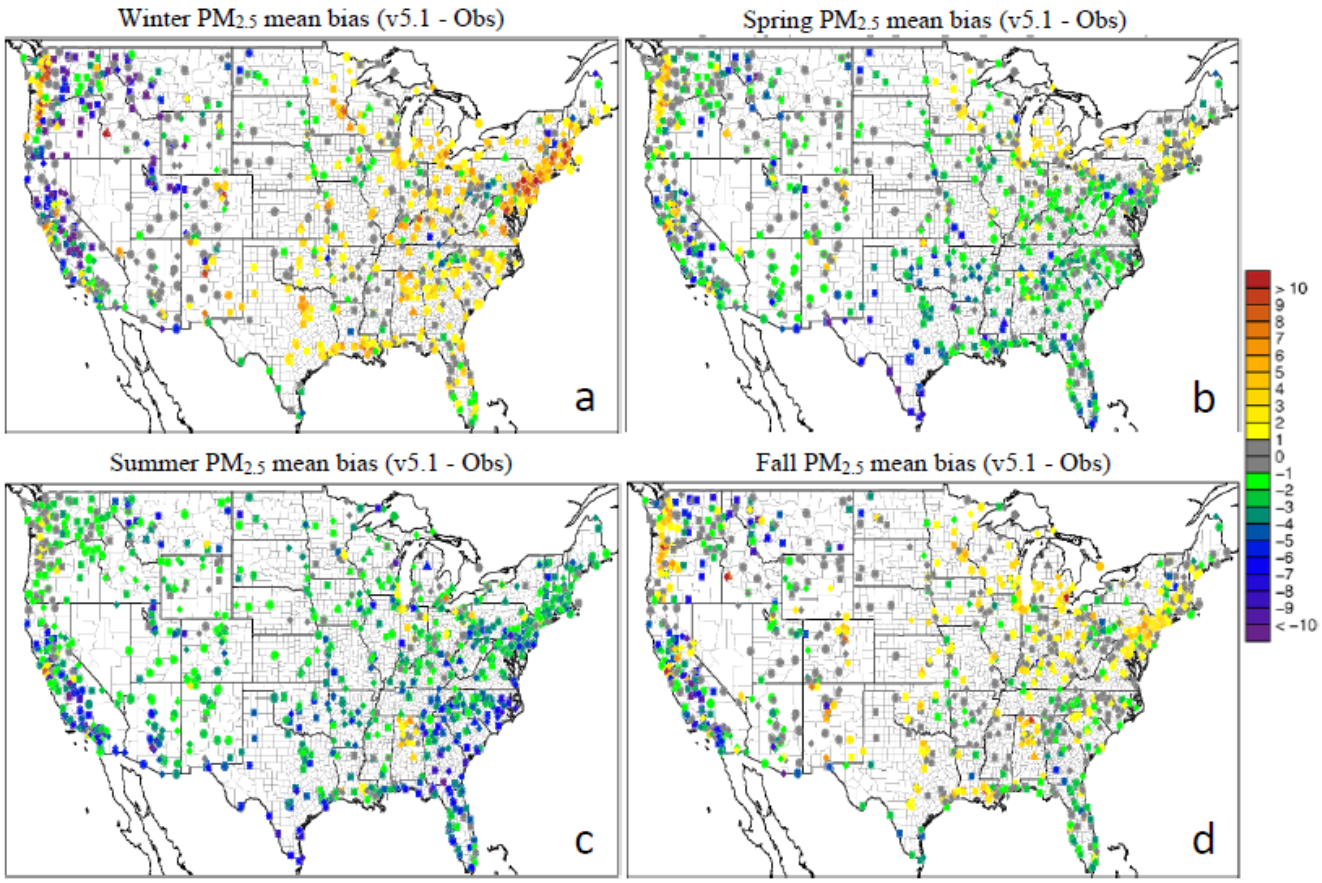
Numerous advances in atmospheric science have been codified in CTMs, including improved algorithms that better simulate long-chain alkanes important for urban aerosol (Woody et al., 2016), biogenic secondary organic aerosol from isoprene and terpenes (Pye et al., 2017), aging of organic aerosols from combustion (Ciarelli et al., 2017), chemistry within cloud droplets and aerosol water (Fahey et al., 2017), gas-phase oxidant chemistry relevant for the formation of aerosol precursors, and dry deposition by gravitational settling (Nolte et al., 2015). Many processes that influence $PM_{2.5}$ are strongly affected by the weather, and accordingly considerable scientific effort has focused on improving the representation of meteorological processes in CTMs and interactions with aerosols (Tuccella et al., 2015). Improved algorithms for understanding the influence of weather on emissions of $PM_{2.5}$ from sources such as sea spray (Grythe et al., 2014), wind-blown dust (Foroutan et al., 2017), and emissions of precursors such as VOCs from plants (Bash et al., 2016) and ammonia from agricultural lands (Bash et al., 2013; Flechard et al., 2013; Pleim et al., 2013), have also advanced the capabilities of CTMs.

All of these improvements in specific processes work in concert to improve the CTM's performance at quantifying the spatial and temporal distribution of $PM_{2.5}$. CTMs are rigorously evaluated using $PM_{2.5}$ observations from extensive monitoring networks. Figure 2-12 shows the pattern of seasonal mean bias in $PM_{2.5}$ in CMAQ Version 5.1, which is the most recently published in the peer-reviewed literature (Appel et al., 2017). Compared to the prior version of CMAQ (v. 5.02), seasonal variability is generally improved as simulated concentrations decrease during winter and increase during summer, especially for organic carbon. Other CTMs that have reported comparisons between $PM_{2.5}$ simulated over North America and measurements of ambient $PM_{2.5}$, updated since the previous review, include the Comprehensive Air-quality Model with Extensions (Koo et al., 2014) and the Weather Research and Forecasting model coupled with Chemistry (Crippa et al., 2016).

A number of chemical transport models have been configured to conduct their simulations online with the meteorological model. This may include feedbacks between the physical and optical properties of aerosols, solar radiation, and clouds (Forkel et al., 2015; Gan et al., 2015; Yu et al., 2014b; Wong et al., 2012). The modeling community has sought to evaluate these models as part of the Air Quality Model Evaluation International Initiative (AQMEII-2)—an effort "to promote policy-relevant research on regional air quality model evaluation across the atmospheric modeling communities" (Im et al., 2015b). Five modeling groups submitted results for North America which were compared against observations of $PM_{2.5}$ at 659 stations (Im et al., 2015a). The study reported the root mean squared error for WRF-CMAQ v5.0.1 simulations of 24-hour averaged $PM_{2.5}$ as 3.08 $\mu g/m^3$ at urban monitoring sites, although another study reported larger errors for individual seasons (Hogrefe et al., 2015).

Since CTMs are often used to estimate the impact of a change in emissions, it is also important to evaluate the ability of the modeling system to respond correctly to emission perturbations. While it is challenging to isolate the impact of a single emission change in ambient observations, a few studies have conducted decade-long simulations to examine the modeling system's (both the model and the inputs) ability to capture long-term trends. Over the U.S. and Europe, substantial reductions in sulfur dioxide and

nitrogen oxides have created an opportunity to compare the model results with the trends in ambient observations (Banzhaf et al., 2015; Xing et al., 2015; Cohan and Chen, 2014; Civerolo et al., 2010). Studies have shown that CMAQ is skilled at capturing the seasonal and long-term trends in sulfate $PM_{2.5}$, in part because the emission changes are large and well quantified. CMAQ also captures the long-term trend in nitrate $PM_{2.5}$; however, the model has less skill for seasonal variability in nitrate $PM_{2.5}$, owing to uncertainties in ammonia emission trends (Banzhaf et al., 2015; Xing et al., 2015).



[a]DJF = December + January + February, MAM = March + April + May, JJA = June + July + August, SON = September + October + November.

Source Permission pending: Appel et al. (2017).

Figure 2-12 Seasonal average $PM_{2.5}$ mean bias (µg m^{-3}) in Community Multiscale Air Quality (CMAQ) simulations for 2011 at Interagency Monitoring of Protected Visual Environments (IMPROVE) (circles), Chemical Speciation Network (CSN) (triangles), air quality system (AQS) hourly (squares) and AQS daily (diamonds) sites for (a) winter (DJF)[a], (b) spring (MAM)[a], summer (JJA)[a] and fall (SON)[a].

2.5 Ambient Concentrations

2.5.1 Spatial Distribution

This section focuses on two spatial scales, the regional scale and urban/neighborhood scale. The regional scale is useful for understanding geographic differences between regions, especially with respect to PM concentrations, composition, and size. The urban and neighborhood scales are useful for understanding primary $PM_{2.5}$, $PM_{10-2.5}$, and UFP, because there are usually numerous sources, and PM concentrations can decrease steeply with distance from sources, resulting in considerable variation in PM concentrations over relatively short distances. The urban scale refers to citywide conditions with dimensions on the order of 4 to 50 km. The neighborhood scale refers to an extended area of a city with dimensions on the order of 0.5 to 4 km (CFR 40 Part 58 Appendix E, 2018).

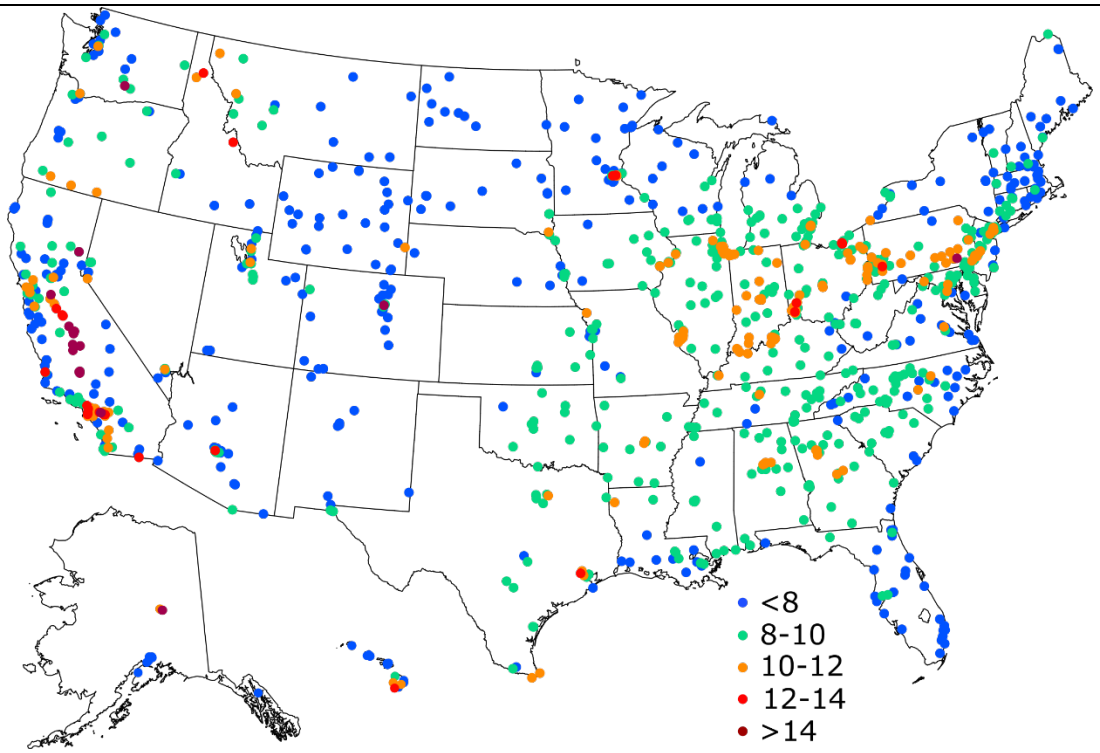
Much of our understanding of spatial and temporal variation in PM concentrations is based on observations from PM monitoring networks. Spatial and temporal differences in $PM_{2.5}$ concentrations have also been predicted from models based on covariate data for both fine and large spatial scales (Yanosky et al., 2014; Paciorek and Liu, 2009; Yanosky et al., 2009). In general, stronger cross-validation agreement and greater precision for $PM_{2.5}$ than for PM_{10} or $PM_{10-2.5}$ have been observed for predictive models of PM concentration, probably because $PM_{10-2.5}$ concentrations exhibited greater spatial variability (Yanosky et al., 2014; Yanosky et al., 2009). Regionally predictive capability in one study was best for the Northeast and Midwest and poorest in the Northwest and Central Plains, with intermediate performance in the Southeast, South Central and Southwest (Yanosky et al., 2014). Pang et al. (2010) compared two computational estimation methods, Bayesian maximum entropy and ordinary kriging, and concluded that lower $PM_{2.5}$ estimation errors and error variances were obtained with a Bayesian maximum entropy approach.

2.5.1.1 Variability Across the U.S.

2.5.1.1.1 $PM_{2.5}$

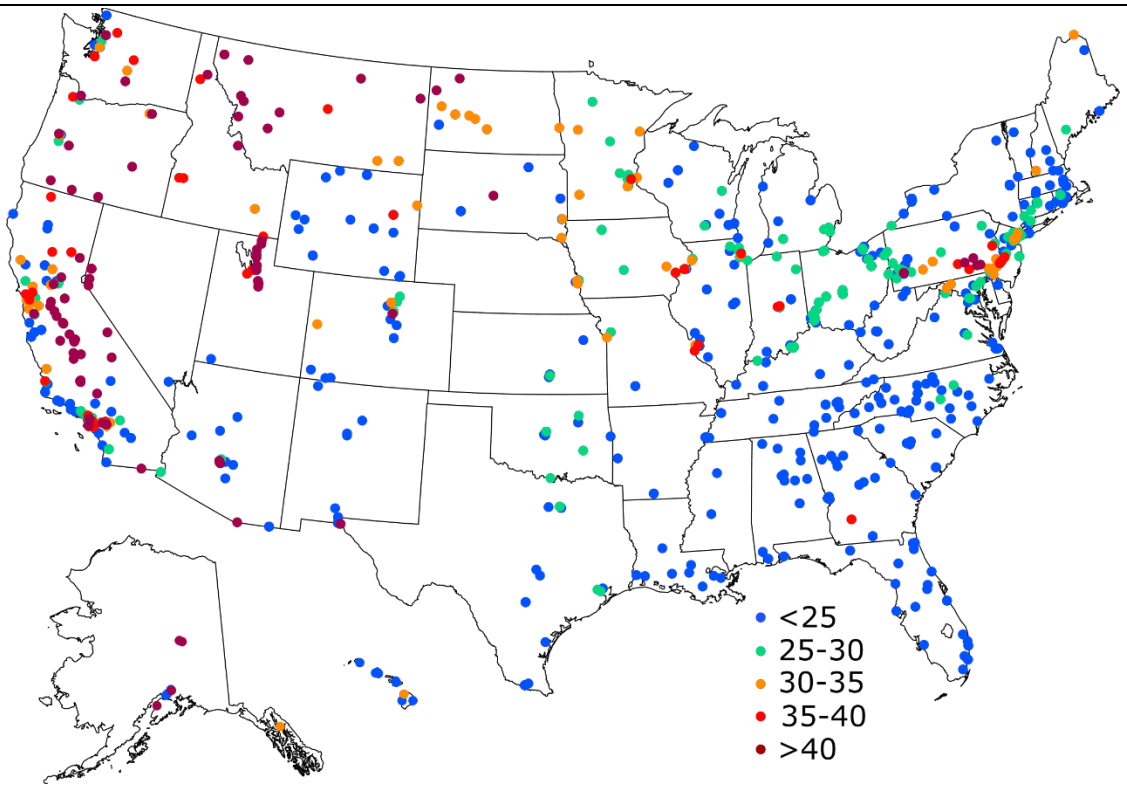
$PM_{2.5}$ concentrations have decreased considerably compared to those reported in the 2009 PM ISA (U.S. EPA, 2009). Figure 2-13 shows the 3-year mean of the 24-hour $PM_{2.5}$ concentrations for network monitoring sites across the U.S. from 2013−2015. Figure 2-14 shows the 98th percentile $PM_{2.5}$ concentrations over the 3-year period from 2013−2015 at monitors across the U.S. Although concentrations have decreased, the geographic distribution of average concentrations is similar to the period 2005−2007 reported in the 2009 PM ISA (U.S. EPA, 2009). Some of the highest 3-year average 24-hour $PM_{2.5}$ concentrations are in the San Joaquin Valley and the Los Angeles-South Coast Air Basin of California. Many sites in the Northwest, including Oregon, Idaho, Western Montana, and Utah

experienced 98th percentile $PM_{2.5}$ concentrations greater than 40 µg/m^3. Numerous sites in the Central Valley of California also reported 98th percentile $PM_{2.5}$ concentrations above 40 µg/m^3. In the Eastern U.S. there is a zone of elevated $PM_{2.5}$ with annual average concentrations greater than 10 µg/m^3 and 98th percentile concentrations greater than 25 µg/m^3 in the Ohio Valley, and stretching into to Eastern Pennsylvania. Both annual average and 98th percentile concentrations are generally lower than what was observed in the 2005−2007 period as reported in the 2009 PM ISA, continuing the downward trend reported there (U.S. EPA, 2009).



Source Permission pending: U.S. EPA 2016 analysis of Air Quality System network data 2013−2015.

Figure 2-13 Three-year average $PM_{2.5}$ concentrations 2013−2015.



Source Permission pending: U.S. EPA 2016 analysis of Air Quality System network data 2013−2015.

Figure 2-14 98th percentile 24-hour $PM_{2.5}$ concentrations 2013−2015.

Specific regional concentration patterns are also evident from $PM_{2.5}$ data derived from satellites (see Section 2.4.5), including the higher average abundance in the eastern half than in the western half of the U.S., with especially high concentrations in the Ohio Valley; the Sonoran desert region, which extends from Mexico into Arizona and inland areas of Southern California and is subject to frequent dust storms; the Los Angeles urban area; the San Joaquin Valley; and the Big Bend area of Texas, which is also subject to dust storms (Lary et al., 2014).

Table 2-4 contains summary statistics for $PM_{2.5}$ reported to AQS for the period 2013−2015. The table provides a distributional comparison between annual, 24-hour and 1-hour averaging times, as well as between quarters. The mean of annual average concentrations based on 24-hour samples across all sites during the 3-year period was 8.6 µg/m^3. This compares to a mean of annual average concentrations of 12 µg/m^3 for 2005 to 2007 (U.S. EPA, 2009), a substantial decrease.

Table 2-4 Summary statistics for $PM_{2.5}$ 2013−2015 (concentrations in µg/m^3).

	N	Mean	1	5	10	25	50	75	90	95	98	99	2nd Highest	Max
Annual (FRM[a] + 24h FEM[b])	1,533	8.6	2.1	4.6	5.5	7.1	8.7	9.9	11.3	12.1	14.1	15.4	26.3	28.8
Daily (FRM[a])	328,881	8.9	1.5	2.7	3.5	5.1	7.6	11.2	15.4	18.7	23.9	28.9	161.0	167.3
Daily (24-h FEM[b])	350,293	8.5	0.0	1.6	2.5	4.4	7.1	10.9	15.6	19.3	25.1	30.8	231.7	270.1
Hourly (1-h FEM[c])	8,424,430	8.5	−2.1	0.0	1.1	3.7	6.9	11.0	17.1	22.0	30.0	37.4	985	1,167
Daily (FRM[a] + 24-h FEM[b])	679,104	8.7	0.4	2.1	3.0	4.8	7.4	11.0	15.5	19.0	24.5	29.9	231.7	270.1
1st quarter[d]	158,434	9.7	0.5	2.2	3.2	5.1	8.0	12.3	18.0	22.6	29.8	36.2	155.8	170.7
2nd quarter[d]	161,586	7.7	0.5	2.1	3.0	4.6	6.9	10.0	13.3	15.7	18.8	21.5	133.3	167.3
3rd quarter[d]	162,366	8.9	0.4	2.3	3.2	5.1	7.8	11.4	15.4	18.2	22.2	26.4	231.7	270.1
4th quarter[d]	160,851	8.4	0.3	1.9	2.7	4.4	6.9	10.7	15.5	19.5	26.0	32.2	150.1	161.0

[a]FRM refers to Federal Reference Method.

[b]24-h FEM refers to Federal Equivalence Method with a 24-h sampling period.

[c]1-h FEM refers to Federal Equivalence Method with a 1-h sampling period.

[d]1st Quarter = January + February + March, 2nd Quarter = April + May + June, 3rd Quarter = July + August + September, 4th Quarter = October + November + December. Quarterly data includes FRM, 24-h FEM, and 1-h FEM data.

Source: U.S. EPA 2016 analysis of Air Quality System network data 2013−2015.

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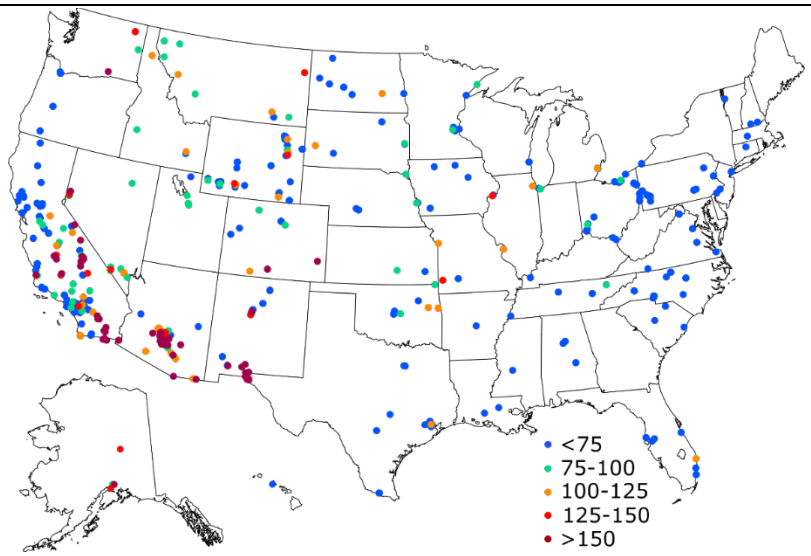
Average $PM_{2.5}$ concentrations were somewhat higher in winter (January−March) than in other seasons. The higher winter average contrasts with results from the 2009 PM ISA, in which slightly higher concentrations in summer were reported (U.S. EPA, 2009). This replacement of summer with winter as the season with the highest national average concentration is analyzed in more detail in Section 2.5.2.2. Table 2-4 still shows higher average $PM_{2.5}$ concentrations in summer than in fall or spring. This pattern of elevated summer and winter average $PM_{2.5}$ concentrations with lower concentrations in fall and spring has been observed since the initiation of the $PM_{2.5}$ monitoring network, and is also explored in detail in Section 2.5.2.2. The 99th percentile $PM_{2.5}$ concentration was considerably higher in winter than other seasons. This observation was consistent with trends reported in the 2009 PM ISA, which were attributed to wintertime stagnation events (U.S. EPA, 2009). The impact of meteorology on seasonal $PM_{2.5}$ concentrations is discussed in Section 2.5.2.2.

The distribution of 24-hour and 1-hour average FEM data are comparable up to the 90th percentile. At the 95th percentile, the 1-hour average is about 3 $\mu g/m^3$ higher than the 24-hour average, and at the 98th percentile it is 6 $\mu g/m^3$ higher. These concentration differences are consistent with those observed in 2005−2007 data reported in the 2009 PM ISA, although actual concentrations are 4−5 $\mu g/m^3$ lower in 2013−2015 than for 2005−2007. The deviation between 1-hour and 24-hour averaging times results from short duration spikes in $PM_{2.5}$ that have more influence on the 1-hour distribution, than the 24-hour average distribution (U.S. EPA, 2009).

2.5.1.1.2 PM_{10}

PM_{10} mass includes all of the other PM mass size fractions considered in this chapter, i.e., $PM_{2.5}$, $PM_{10-2.5}$, and UFP. Like $PM_{2.5}$, geographic trends are very similar to those reported in the 2009 PM ISA (U.S. EPA, 2009). Figure 2-15 shows the 98th percentile of PM_{10} concentration at monitors across the U.S. The highest concentrations were observed in the Western U.S., including the San Joaquin Valley, Imperial Valley, and other areas of California, as well as the Southwest, including Arizona, New Mexico, Colorado, and El Paso, TX. In contrast, throughout the Northeast and Southern U.S. 98th percentile PM_{10} concentrations are generally below 100 $\mu g/m^3$. In the Midwest, Oklahoma, Texas, and Florida, concentrations between these extremes were generally observed for 98th percentile PM_{10}.



Source Permission pending: U.S. EPA 2016 analysis of Air Quality System network data 2013−2015.

Figure 2-15 98th percentile PM_{10} concentrations (2013−2015).

Table 2-5 gives summary statistics for PM_{10} for the period 2013−2015. The national average concentration based on FRM was 21.1 µg/m^3, which is 15% lower than the average for 2005−2007 reported in the 2009 PM ISA (U.S. EPA, 2009). However, at the 99th percentile, PM_{10} concentrations were almost identical to 2005−2007 data, with a FRM 99th percentile concentration of 91 µg/m^3 in 2005−2007 and 92 µg/m^3 in 2013−2015. Table 2-5 does not exclude any data for exceptional events and many of the areas with increasing trends are in California (fires) and Arizona (dust). These sporadic natural events could have a more important impact on the trends of the upper percentiles than the average.

While some concentrations exceeded 150 µg/m^3, 99th percentile concentration was well below this concentration for all monitor types and averaging periods, and 98th percentile concentrations were below 100 µg/m^3. Summer concentrations appear to be typically higher than other seasons, with the highest average concentration as well as the highest concentration at all percentiles up to the 95th percentile for summer. However, the most extreme events appear to be more likely in the spring, as indicated by the highest 98th and 99th percentile concentrations. Winter concentrations are the lowest at all percentiles, with average concentrations 6 µg/m^3 lower in winter than in summer.

Table 2-5 Summary statistics for PM_{10} 2013−2015 (concentrations in µg/m^3).

	N	Mean	1	5	10	25	50	75	90	95	98	99	2nd Highest	Max
Daily (FRM[a])	186,552	21.1	2	5	6	10	17	25	37	49	69	92	3,916	3,972
Daily (24-h FEM[b])	311,632	23.8	3	5	7	11	18	29	43	57	80	106	1,739	1,739
Daily (1-h FEM[c])	7,341,950	23.8	1	2	5	9	17	28	45	62	93	127	12,445	13,304
Daily (FRM[a] + 24-h FEM[b])	498,184	22.8	2	5	7	11	18	27	41	54	76	101	3,916	3,972
1st quarter[d]	123,249	19.3	2	4	5	9	14	23	37	49	69	89	1,482	1,488
2nd quarter[d]	125,605	24.0	2	5	7	11	18	28	42	55	83	122	3,284	3,916
3rd quarter[d]	124,999	25.3	4	8	10	14	20	30	44	56	78	102	1,006	1,265
4th quarter[d])	124,331	22.4	2	5	7	11	17	27	42	55	76	96	2,187	3,972

[a]FRM refers to Federal Reference Method.

[b]24-h FEM refers to Federal Equivalence Method with a 24-hour sampling period.

[c]1-h FEM refers to Federal Equivalence Method with a 1-hour sampling period.

[d]1st quarter = January + February + March, 2nd quarter = April + May + June, 3rd quarter = July + August + September, 4th quarter = October + November + December. Quarterly data includes FRM, 24-h FEM, and 1-h FEM data.

Source: U.S. EPA 2016 analysis of Air Quality System network data 2013−2015.

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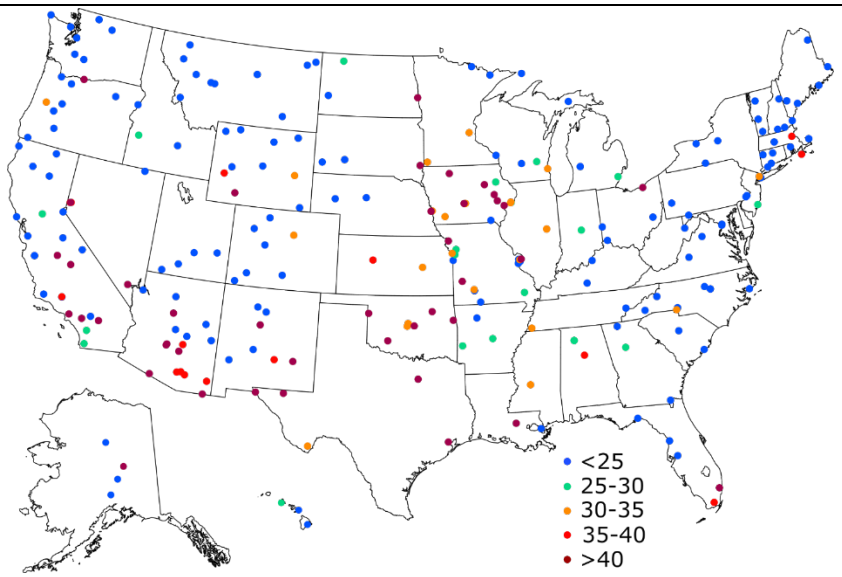
2.5.1.1.3 $PM_{10-2.5}$

As described in Section 2.4.2 and Section 2.4.6, $PM_{10-2.5}$ measurement capabilities and availability of $PM_{10-2.5}$ ambient concentration data have greatly increased since the 2009 PM ISA. At that time $PM_{10-2.5}$ concentrations were not routinely monitored, other than in the IMPROVE program, and $PM_{2.5}$ and PM_{10} measurements could only be compared between different types of samplers with different designs and flow rates (U.S. EPA, 2009).

Figure 2-16 shows the 98th percentile concentrations for $PM_{10-2.5}$ between 2013−2015. 98th percentile concentrations greater than 40 µg/m^3 were observed in multiple locations, not only in California and the Southwestern states of Nevada, Arizona, and New Mexico, but also in Texas, Oklahoma, Missouri, Iowa, and Alaska. St. Louis, Cleveland, south Florida also stand out as urban areas with some of the highest $PM_{10-2.5}$ concentrations.



Source Permission pending: U.S. EPA 2016 analysis of Air Quality System network data 2013−2015.

Figure 2-16 98th percentile concentrations for $PM_{10-2.5}$ between 2013−2015.

Table 2-6 shows summary statistics on national $PM_{10-2.5}$ concentrations from 2013−2015. Data for FRMs and IMPROVE national mean and percentile concentrations are quite different than FEM, typically a factor of 2 or more higher for FEM data than the filter-based FRM and IMPROVE data, probably because of differences in site locations such as the urban-rural mix. Concentrations of several hundred micrograms per cubic meter were occasionally observed, but 98th percentile concentrations were

under 50 µg/m^3 regardless of method or averaging period. Concentrations were typically higher in summer than in other seasons on average, and at all percentiles up to the 95th percentile. However, 98th and 99th percentile concentrations for $PM_{10–2.5}$ are highest in the fall rather than the spring, although the very highest concentration was observed in the spring.

These observations are supported by additional studies showing that the highest concentrations of $PM_{10–2.5}$ were generally observed in the Southwestern U.S. (Li et al., 2013). They are also consistent with urban data from the 2009 PM ISA (U.S. EPA, 2009)showing $PM_{10–2.5}$ comprised most of PM_{10} in Denver and Phoenix, but not in other major cities (U.S. EPA, 2009). At two urban sites in Denver and two comparatively rural sites in Greeley, CO, average $PM_{10–2.5}$ concentrations over the course of a year averaged 9.0 to 15.5 µg/m^3, with the highest values in Northeast Denver (Clements et al., 2012). $PM_{10–2.5}$ concentrations up to 5 times higher than $PM_{2.5}$ concentrations were reported (Clements et al., 2014b). $PM_{10–2.5}$ concentrations in Denver were highest when winds were coming from the urban core, and highest in Greeley when winds were coming from Denver and other large communities (Clements et al., 2012).

Table 2-6 Summary statistics for $PM_{10-2.5}$ 2013−2015 (concentrations in $\mu g/m^3$).

	N	Mean	1	5	10	25	50	75	90	95	98	99	2nd Highest	Max
Daily (FRM[a] + IMPROVE[b])	74,095	5.7	0	0.3	0.6	1.6	3.8	7.4	12.7	17.3	24.8	31.5	178.7	178.7
Daily (24-h FEM[c])	34,619	12.4	−0.6	1.2	2.3	4.7	9.0	15.9	25.5	33.6	45.2	56.4	695.5	858.6
Daily (FRM[a] + 24-h FEM[c] + IMPROVE[b])	108,714	7.8	0	0.4	0.8	2.2	5.0	10.0	17.6	24.3	34.6	43.2	695.5	858.6
1st quarter[d]	26,760	5.7	−0.4	0.1	0.3	1.0	2.9	7.0	14.0	20.0	30.0	38.8	301.5	341.8
2nd quarter[d]	27,737	8.2	−0.1	0.5	0.9	2.3	5.3	10.4	18.1	24.3	35.4	45.5	695.5	858.6
3rd quarter[d]	27,238	9.2	0.5	1.4	2.1	3.7	6.7	11.5	19.0	25.3	33.9	40.3	227.4	295.0
4th quarter[d]	26,979	8.2	0	0.5	0.9	2.3	5.1	10.5	18.9	26.3	38.2	47.7	180.0	185.1

[a]FRM refers to Federal Reference Method.

[b]IMPROVE refers to IMPROVE sampler used for PM measurement in the IMPROVE network (see Section 2.4.6).

[c]24-h FEM refers to Federal Equivalence Method with a 24-hour sampling period.

[d]1st quarter = January + February + March, 2nd quarter = April + May + June, 3rd quarter = July + August + September, 4th quarter = October + November + December. Quarterly data includes FRM, 24-h FEM, and 1-h FEM data.

Source: U.S. EPA 2016 analysis of Air Quality System network data 2013−2015.

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2.5.1.1.4 $PM_{2.5}/PM_{10}$

In numerous earlier studies summarized in the 2009 PM ISA (U.S. EPA, 2009) as well as in an extensive analysis of data reported in the 1996 PM AQCD (U.S. EPA, 1996), the ratio of $PM_{2.5}$ to PM_{10} was higher in the East than in the West in general. Crude estimates of the fraction of PM_{10} accounted for by $PM_{2.5}$ were obtained by dividing the 3-year average $PM_{2.5}$ concentration by the 3-year average PM_{10} concentration for 15 cities in the 2009 PM ISA (U.S. EPA, 2009, 179916}. PM_{10} was estimated to contain less $PM_{2.5}$ than $PM_{10-2.5}$ in Phoenix and Denver (3-year mean $PM_{2.5}/PM_{10}$ ratios of 0.19 and 0.32, respectively), but more $PM_{2.5}$ than $PM_{10-2.5}$ in Philadelphia ($PM_{2.5}/PM_{10}$ = 0.74), New York ($PM_{2.5}/PM_{10}$ = 0.68) and Pittsburgh ($PM_{2.5}/PM_{10}$ = 0.67) (U.S. EPA, 2009). By comparison, in Europe $PM_{2.5}$ usually accounts for 50 to 90% of PM_{10} and ratios are fairly constant for individual sites, but vary between sites (Putaud et al., 2010).

A more current and comprehensive comparison of the relative contributions of $PM_{2.5}$ and $PM_{10-2.5}$ to PM_{10} by region and season using data from the NCore Network is now possible. Figure 2-11 (Section 2.4.6) shows a map of NCore monitors in operation on a routine basis. Table 2-7 provides average $PM_{2.5}/PM_{10}$ ratios from the NCore network based on a FRM designed specifically for $PM_{10-2.5}$ (see Section 3.4.3) averaged over the entire period of monitoring site operation at 28 locations distributed throughout the U.S. The data indicate roughly equivalent amounts of $PM_{2.5}$ and $PM_{10-2.5}$ at most urban sites, with $PM_{2.5}/PM_{10}$ ratios ranging from 41 to 61% for all urban sites except Dayton, OH and Columbia, SC, and from 61 to 66% for rural sites in the Northeast. Although the Dayton, OH monitor is located within a defined CBSA, it is on the property of a rural county high school. In general, the $PM_{2.5}/PM_{10}$ ratios observed from the new NCore data are considerably lower than the $PM_{2.5}/PM_{10}$ ratios for Eastern U.S. sites reported in the 2009 PM ISA (U.S. EPA, 2009) and other earlier studies.

Table 2-7 $PM_{2.5}/PM_{10}$ ratios from National Core network (NCore).

Location	Landscape	Years	Avg $PM_{2.5}$	Avg $PM_{10-2.5}$	$PM_{2.5}/PM_{10}$
Dayton, OH	Rural	2011−2015	9.5	4.7	0.66
Litchfield, CT	Rural	2012−2015	5.3	2.8	0.66
Peterborough, NH	Rural	2011−2015	4.4	2.2	0.66
Columbia, SC	Urban	2011−2015	9.2	5.0	0.65
Beltsville, MD	Rural	2011−2015	8.1	4.3	0.64
McFarland Hill, ME	Rural	2015	4.2	2.1	0.64
Londonderry, NH	Rural	2011−2015	6.1	4.0	0.61
Raleigh, NC	Urban	2011−2015	8.7	5.7	0.61
Charlotte, NC	Urban	2011−2015	9.3	6.2	0.60
Providence, RI	Urban	2011−2015	7.2	4.6	0.59
Cincinnati, OH	Urban	2011−2015	10.6	7.7	0.58
Little Rock, AR	Urban	2011−2015	10.5	8.2	0.58
Louisville, KY	Urban	2014−2015	9.6	7.0	0.58
Philadelphia, PA	Urban	2014−2015	10.2	7.2	0.58
Wilmington, DE	Urban	2011−2015	10.0	7.4	0.57
Portland, OR	Urban	2011−2015	7.6	5.3	0.56
Seattle, WA	Urban	2005−2015	6.5	5.3	0.56
Grand Rapids, MI	Urban	2011−2015	9.2	7.4	0.55
Birmingham, AL	Urban	2012−2015	11.3	11.1	0.53
Davenport, IA	Urban	2013−2015	8.3	7.7	0.53
Jackson, MS	Urban	2015	9.4	9.7	0.53
New Haven, CT	Urban	2012−2015	8.3	7.2	0.53
Newark, NJ	Urban	2015	9.1	8.0	0.53
Boston, MA	Urban	2011−2015	7.2	7.2	0.52
Fairbanks, AK	Urban	2012−2015	12.2	10.1	0.52

Table 2 7 (Continued): $PM_{2.5}/PM_{10}$ ratios from National Core network (NCore).

Location	Landscape	Years	Avg $PM_{2.5}$	Avg $PM_{10-2.5}$	$PM_{2.5}/PM_{10}$
Memphis, TN	Urban	2013−2015	8.4	9.4	0.51
St. Louis, MO	Urban	2011−2015	10.9	11.3	0.50
Detroit, MI	Urban	2011−2015	10.0	11.0	0.48
San Jose, CA	Urban	2011−2015	9.9	10.7	0.47
Tulsa, OK	Urban	2011−2015	9.2	11.4	0.46
Albuquerque, NM	Urban	2011	7.1	9.4	0.45
Cleveland, OH	Urban	2013−2015	11.9	18.8	0.42
Denver, CO	Urban	2015	7.1	11.1	0.41

Source: U.S. EPA 2016 analysis of Air Quality System network data 2011−2015.

The lower $PM_{2.5}/PM_{10}$ ratios indicate a generally higher fraction of $PM_{10-2.5}$ in the Eastern U.S. than was reported in the 2009 PM ISA. The trend of a greater $PM_{2.5}$ fraction in the East and greater $PM_{10-2.5}$ fraction in the West (U.S. EPA, 2009) is generally preserved, but the data in Table 2-7 show $PM_{2.5}$ contributing only slightly more to PM_{10} mass than $PM_{10-2.5}$ in urban sites of the Northeast. $PM_{10-2.5}$ made a greater contribution to PM_{10} not only at most western sites, but also in the Midwest (Cleveland, Detroit). Important exceptions to lower $PM_{2.5}/PM_{10}$ ratios in the Western U.S. were the major cities of the Pacific Northwest (Seattle, Portland), where $PM_{2.5}$ accounted for most of PM_{10} and $PM_{2.5}/PM_{10}$ ratios were similar to Eastern locations. $PM_{2.5}$ was 60% or more of PM_{10} at only 9 of 33 NCore stations. All of these were either rural Northeastern (Litchfield, CT, Peterborough, NH, Beltsville, MD, McFarland Hill, ME, Londonderry, NH) or urban Southeastern (Charlotte, NC, Raleigh, NC, Columbia, SC) sites. It appears that PM_{10} in the U.S. has become considerably coarser than observed in the 2009 PM ISA (U.S. EPA, 2009), and that in many urban areas $PM_{10-2.5}$ mass makes a similar or greater contribution to PM_{10} mass than does $PM_{2.5}$ mass.

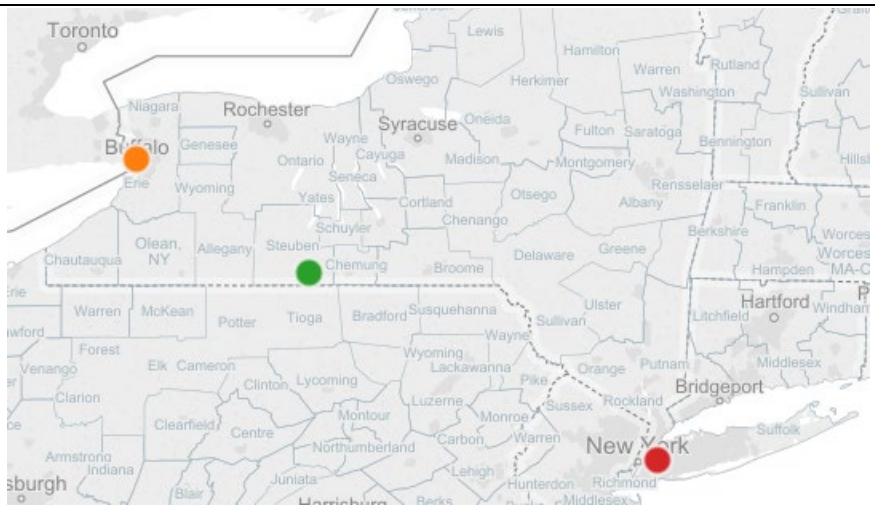
2.5.1.1.5 Ultrafine Particles

Key atmospheric science related uncertainties identified in the 2009 PM ISA for linking measurable particle number concentration with adverse UFP effects were the lack of data on UFP concentrations, lack of data on UFP composition, lack of data on spatial and temporal evolution of UFP size distribution and chemical composition, the lack of a UFP network in the U.S., and the lack of information on spatial and temporal variability in UFP concentration. There are few long-term average data on particle number concentrations in the U.S. Annual average particle number concentrations reaching 22,000 cm^{-3} for particles from 0.003 to 0.5 µm in Pittsburgh (Stanier et al., 2004) and monthly

average concentrations exceeding 30,000 cm^{-3} for particles from 0.017 to 0.1 μm (Hughes et al., 1998) and from 0.014 to 0.7 μm (Singh et al., 2006) in Los Angeles have been reported. The 2009 PM ISA (U.S. EPA, 2009) described several ambient UFP characteristics. Number concentrations dropped off quickly with distance from a road, and greater spatial variability occurred for UFP than $PM_{2.5}$ on an urban scale. Traffic was described as a major source, but high number concentrations during new particle formation events were also described. OC was identified as the major UFP component in several studies, along with substantial contributions from EC and sulfate. Higher winter than summer concentrations were reported in several northern locations. UFP concentration peaks during rush hour in urban areas were described, and broad midday peaks in summer were also noted in some instances, possibly due to NPF after photochemical reactions (U.S. EPA, 2009).

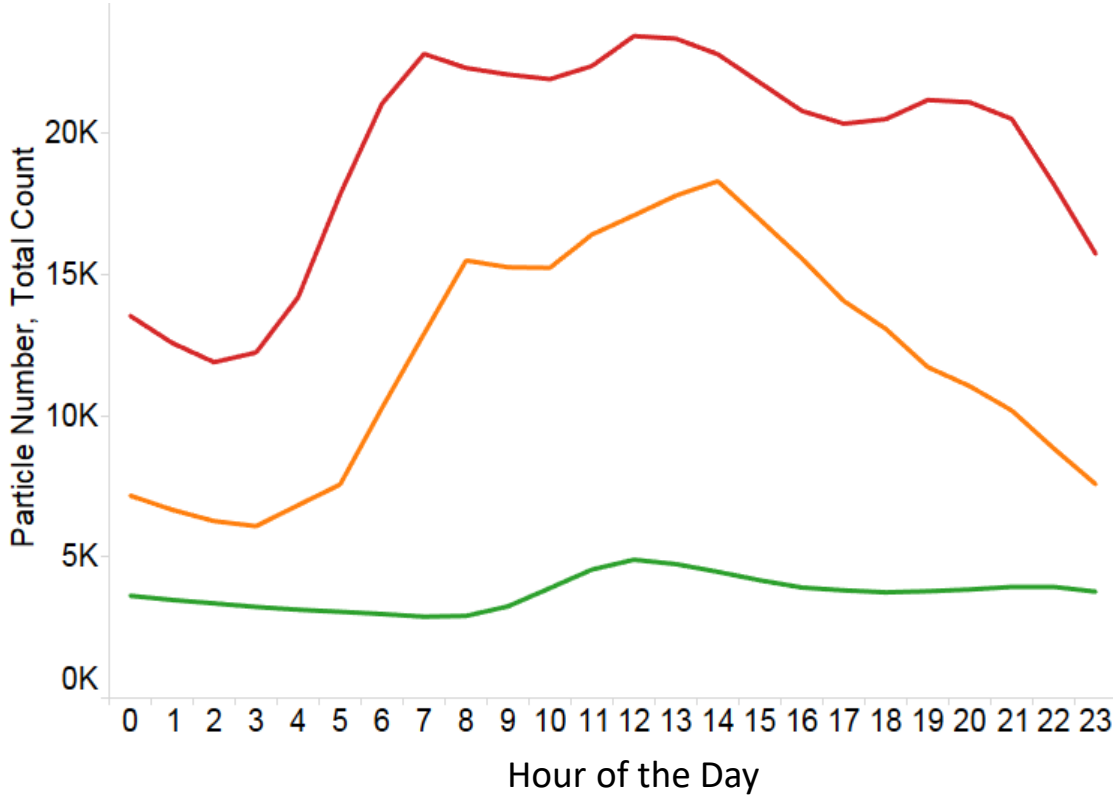
Results from a number of field studies reported in the 2009 PM ISA (U.S. EPA, 2009) described spatial and temporal variations in total particle number concentrations used as an estimate of UFP number concentration. In general, spatial variability of total particle number concentration increased with increasing distance between measurements, increasing source variation in the area studied, and increasing particle size within the UFP size range. Figure 2-17 shows three sites in the state of New York where UFP measurements have been initiated. Hourly results over several years from these sites are presented in Figure 2-18 and provide a much larger data set for comparing spatial and temporal variability than has been previously available (NYDEC, 2016). Figure 2-18 shows the average particle count of each location at each hour of the day, beginning and ending at midnight. The Buffalo data are averaged over three sites. There is a pronounced difference in particle number concentration between locations, with urban particle number counts several times higher than the background site. Not shown in Figure 2-18, the highest particle number counts at three sites in Buffalo were observed at a near road site.

The particle numbers remain fairly constant throughout the day at the Steuben County background site, although particle number counts are slightly elevated on average during the midday hours. In contrast, particle numbers display daily trends, peaking around 8:00 a.m. in Buffalo and New York City (NYC), and remain high into the evening hours, with distinct rush hour and early afternoon peaks. These results are consistent with spatial and temporal results reported in the 2009 PM ISA, but are based on a much larger data set. The state of New York is continuing to analyze the data for seasonal differences in the frequency of high particle number counts and nucleation events, and neighborhood scale differences in a near road environment (NYDEC, 2016).



Source Permission pending: U.S. EPA 2016 analysis of Air Quality System network data.

Figure 2-17 Sites in New York state which reported particle number counts to air quality system (AQS).



Line colors in the graph correspond to the colors of the sites on the map, i.e., orange data was collected in Buffalo, green data was collected in Steuben County, and red data was collected in NYC.

Source Permission pending: U.S. EPA 2016 analysis of Air Quality System network data 2012−2015.

Figure 2-18 Average hourly particle number concentrations from three locations in New York state for 2014−2015.[39]

Routine monitoring to obtain long-term average particle number distributions is a relatively recent development (Wiedensohler et al., 2012) using electromobility and electrometer based methods developed for the European UFP monitoring network (Section 2.3.4.1). Average particle concentrations classified by size from 24 European monitoring sites over a period of 2 years were recently described (Asmi et al., 2011). As one example, at the Ispra, Italy site number concentrations averaged 1,341 cm^{-3} for 0.03 to 0.05 µm, 4,448 cm^{-3} for 0.05 to 0.1 µm, and 2,129 cm^{-3} for 0.1 to 0.5 µm, corresponding to an average of 73% of airborne particles smaller than 0.1 µm (Asmi et al., 2011). This is an upper limit value because a substantial number of particles can be smaller than the 0.03 µm lower size limit for these data

[39] NYC and Steuben County also include 6 months in 2012. Buffalo data are from three different sites, with the sampler moved between sites over the 2-year period. Data for the orange line depicting Buffalo are all from Buffalo, but not all from the same site within Buffalo.

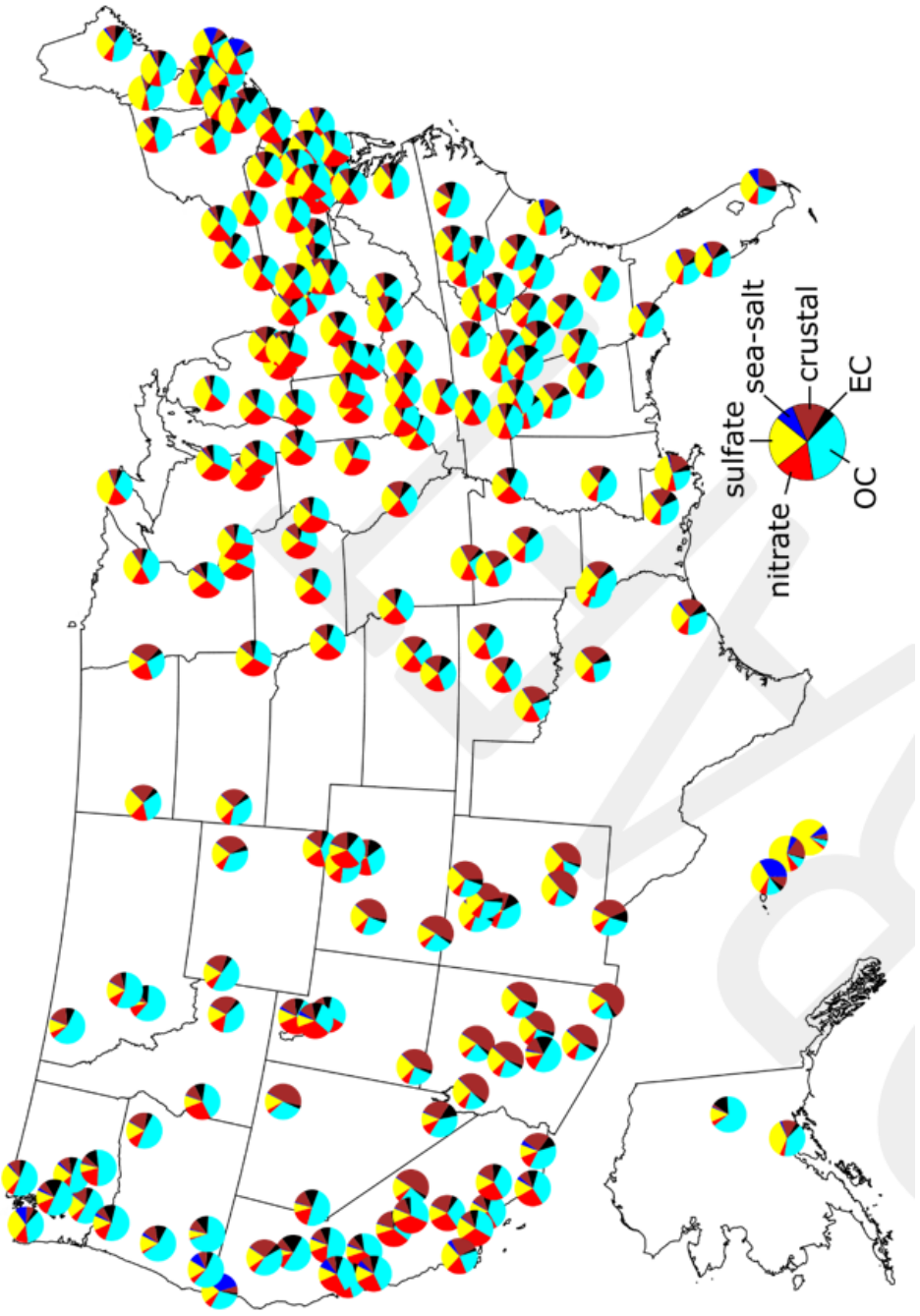
(Stanier et al., 2004). For all 24 European locations, the average upper limit percentage of particles smaller than 0.1 µm ranged from 67 to 85%.

No such large-scale summary of U.S. data is possible, because there are few long-term data on number size distributions in the U.S. Number size distribution data have been reported for an 8-year period from 2002 to 2009 in Rochester, and number concentrations averaged 4,730 cm^{-3} for 0.01 to 0.05 µm particles, 1,838 cm^{-3} for 0.05 to 0.1 µm, and 1,033 cm^{-3} for 0.1 to 0.5 µm (Wang et al., 2011). This corresponds to 90% of total particles smaller than 0.1 µm. This is a larger fraction than the European range, but the lower size limit was 0.01 µm, compared to 0.03 µm for the European network data (Wang et al., 2011). Long-term trends for this period are summarized in Section 2.5.2.1.4. These data can also be compared to earlier observations of particle number concentrations for eight size ranges for a full year from the Pittsburgh Air Quality study (Stanier et al., 2004). Using their data, it is possible to calculate that 90% of the number of particles were also smaller than 0.1 µm and that 98% were smaller than 0.2 µm.

2.5.1.1.6 $PM_{2.5}$ Components

It is useful to distinguish between bulk PM components and more finely speciated components. The term bulk component refers to a large component category like OC, sulfate, or nitrate, which is monitored in networks like CSN or IMPROVE and usually makes up a substantial portion of PM mass. It is also used to differentiate broad categories of components like OC and crustal material, which are considered bulk components, from more finely speciated components like individual organic compounds and elements, which are usually present in lower amounts.

Figure 2-19 shows contributions of sulfate, nitrate, OC, EC, crustal material, and sea salt to $PM_{2.5}$. A major change in $PM_{2.5}$ composition compared to the 2009 PM ISA (U.S. EPA, 2009) is the reduction in sulfate concentrations, resulting in a smaller sulfate contribution to $PM_{2.5}$ mass in 2013−2015 compared to what was reported for 2005−2007 in the 2009 PM ISA, especially in the Eastern U.S. As a result, at many locations sulfate has been replaced as the greatest single contributor to $PM_{2.5}$ mass by organic material or nitrate. This long-term trend demonstrating a reduction in sulfate concentrations is described in more detail in Section 2.5.2.1.4.



Source Permission pending: U.S. EPA 2016 analysis of Air Quality System network data 2013−2015.

Figure 2-19 Contributions of sulfate, nitrate, organic carbon (OC), elemental carbon (EC), crustal material, and sea salt to $PM_{2.5}$.

Regional patterns of component contributions to $PM_{2.5}$ in Figure 2-19 are similar to those reported in the 2009 PM ISA (U.S. EPA, 2009). Sulfate and OC are the species with the highest

contribution to total mass in most eastern locations and OC usually makes the greatest contribution to $PM_{2.5}$ mass in the west, although sulfate, nitrate, and crustal material can also be abundant (U.S. EPA, 2009). Urban and rural sulfate are both substantially higher in the East than in the West (Hand et al., 2012c). The highest nitrate concentrations are found in the west, particularly in California, but with some elevated concentrations in the upper Midwest. Larger contributions of OC to $PM_{2.5}$ mass observed in the Southeast and the West than in the Central and Northeastern U.S. are consistent with larger OC concentrations in those regions described in the 2009 PM ISA (U.S. EPA, 2009). The ratio of organic mass to OC mass depends on source and aerosol age, and was discussed in detail in the 2009 PM ISA (U.S. EPA, 2009). Based on speciation data from 15 cities reported in the 2009 PM ISA, EC contributed a smaller fraction of $PM_{2.5}$ mass than sulfate, nitrate, or OC, but consistently accounted for 4−11% of $PM_{2.5}$ (U.S. EPA, 2009).

Nationally, higher urban than rural OC and EC concentrations were reported by (Hand et al., 2013) and differences in urban and rural seasonal patterns for OC and EC were also observed. They also reported the highest rural OC and EC concentrations were in the Northwest and Southeast (Hand et al., 2012c). On average, OC and EC concentrations were both more uniformly distributed in the eastern U.S., but more localized in the West, with the highest urban concentrations in the West during fall and winter (Hand et al., 2013). However, EC concentrations were more consistent across cities regardless of region in the 2009 PM ISA (U.S. EPA, 2009). In the Southeastern U.S., annual average primary OC concentrations were estimated to exceed annual average secondary OC concentrations, but secondary OC could exceed primary OC at rural sites during the warmest months, and secondary OC concentration also showed little difference between urban and rural sites (Blanchard et al., 2013).

A large fraction of organic PM can be water soluble (Mwaniki et al., 2014). During the summer CalNex 2010 campaign (Kelly et al., 2014), water soluble $PM_{2.5}$ was at a maximum in the morning and in the evening in the San Joaquin Valley of California. In the same study, nitrate was present at higher concentrations than sulfate or ammonium, averaging 0.8 $\mu g/m^3$ and there were hourly average concentrations greater than 25 $\mu g/m^3$ during the winter 2013 DISCOVER-AQ campaign (Kelly et al., 2018).

Fine soil concentrations are higher in the Southwest than in other parts of the U.S., and also exhibit seasonal patterns for urban and rural sites (Hand et al., 2012c). High PM concentrations in urban desert areas were associated with a substantial contribution from crustal material from both coarse and fine PM (Wagner and Casuccio, 2014). Soil related PM also contributes substantially to $PM_{2.5}$ in populated areas of other parts of the world (Satsangi and Yadav, 2014). The pattern of higher crustal material contributions to $PM_{2.5}$ in drier areas of the Western U.S. can also be seen in Figure 2-19 with the examples of Phoenix and Denver.

There are a few new results to add to the body of literature on elemental composition, concerning both ambient observations and sources. In Southern California the most abundant elemental species was sulfur, followed by Si, Fe, Ca, and Al, with soil related elements accounting for 51% of total elemental

mass measured. New research to investigate sources further explored the importance of brake wear, lubricating oils, gasoline and diesel combustion, secondary sulfates, sea salts, and biomass burning as sources of trace elements (Na and Cocker, 2009). New research on atmospheric iron indicate that extent of aqueous solubility of iron present in PM is related to sulfur content of the PM (Oakes et al., 2012b). In Atlanta, iron concentrations exhibit considerable fluctuation, and reach up to 300 to 400 ng/m^3 for a few hours at time, (Oakes et al., 2012b). In Atlanta Fe(II) accounted for between 5 and 35%, or an average of about 25% of total soluble iron (Oakes et al., 2012a). In rural samples copper and zinc were found to be mainly present as sulfates and also nitrates in $PM_{2.5}$ in rural samples, but copper and zinc compounds found in larger particles were similar to copper and zinc compounds found in soil (Osan et al., 2010).

2.5.1.1.7 $PM_{10-2.5}$ Components

It was noted in the 2004 AQCD (U.S. EPA, 2004) that concentrations of most elements differed between $PM_{2.5}$ and $PM_{10-2.5}$, but that concentrations of some metals were similar between the two size fractions. It was also noted that this contrasted with earlier years with less controlled combustion, when Pb and other metals were much higher in $PM_{2.5}$.

Components of $PM_{10-2.5}$ are not routinely monitored like they are for $PM_{2.5}$, and information on $PM_{10-2.5}$ composition is largely limited to specific local studies. In the Southeast, OC and nitrate made similar fractional contributions to $PM_{2.5}$ and $PM_{10-2.5}$, but there was much less sulfate and EC in $PM_{10-2.5}$ than $PM_{2.5}$, and much more major metal oxides (U.S. EPA, 2009). In Los Angeles, crustal material and trace elements accounted for 47.5% of total reconstructed coarse PM mass, with secondary ions (sulfate, nitrate, ammonium, 22.6%) and organic matter (19.7%) also making important contributions, and elemental carbon was a less significant component, accounting for less than 2% of the mass (Cheung et al., 2011). Los Angeles crustal materials had low water solubility, but Ba and Cu were modestly water soluble and activity due to reactive oxygen species was most highly associated with water soluble elements, V, Pd, Cu and Rh in Los Angeles (Cheung et al., 2012a).

In the desert southwest, crustal material is the dominant component of $PM_{10-2.5}$, sometimes accounting for more than half of the mass, followed by organic matter, accounting for 15% (Clements et al., 2014a, 2013). High correlations between $PM_{2.5}$ and PM_{10} indicated that a large component of the fine fraction was derived from dust (Clements et al., 2013). In Denver and Phoenix, $PM_{10-2.5}$ made a greater contribution to total ambient PM_{10} mass than in other cities (U.S. EPA, 2009). PM in Denver has been studied in more detail since then. Coarse PM concentrations were attributed to crustal material, road salt, vehicle abrasion and sulfate (Clements et al., 2014b).

While crustal material often makes the greatest contribution to $PM_{10-2.5}$ mass, the organic fraction also makes a substantial contribution. In the Southeast, organic and elemental carbon accounted for approximately 30% of $PM_{10-2.5}$. Primary biological aerosol particles (PBAP), which consist of microorganisms and fragments of living things, can account for a large fraction of $PM_{10-2.5}$ mass (U.S.

EPA, 2009). These have been measured by treating collected PM with a dye which only reacts with protein containing material (Matthias-Maser et al., 2000). PBAP cannot be distinguished from other types of OC by methods used in monitoring networks. New research on sources of PBAP was summarized in Section 2.3.3. New information on the nature of bioaerosols and biological material associated with particles is well-described in the review by (Froehlich-Nowoisky et al., 2016). PBAP includes living and dead organisms, e.g., algae, archaea, bacteria and viruses, dispersal units, e.g., fungal spores and plant pollen, various fragments or excretions, e.g., plant debris and brochosomes. This class of material can range in size from 1 nm (individual proteins) to 5 millimeters (pollen grains). Summertime aerosols in Phoenix were abundant in biological compounds (e.g., sugars and fatty acids), present almost exclusively in the coarse size fraction (Cahill, 2013).

A pilot study on $PM_{10-2.5}$ species monitoring was carried out to develop target species, evaluate analytical methods and field performance, and to assess sampling and operational issues for routine measurement of $PM_{10-2.5}$ species (U.S. EPA, 2015). Samples collected in all seasons over a period of 1 year in both Phoenix and St. Louis indicated that soil oxides dominated $PM_{10-2.5}$ mass, with organic matter accounting for 10−20%. Sulfate and nitrate accounted for very little of the $PM_{10-2.5}$ mass, although they were substantial contributors to $PM_{2.5}$ mass. Soil oxides were by far the largest component in both locations throughout the year, except in St. Louis in winter, when soil and organic contributions were similar, but overall $PM_{10-2.5}$ concentrations were considerably lower (U.S. EPA, 2015).

2.5.1.1.8 Ultrafine Particle Components

There was little information on the composition of UFP presented in the 2009 PM ISA, although urban UFP was suspected to be rich in OC and EC, and sulfate was expected to be a substantial contributor in rural areas while new particle formation occurred (U.S. EPA, 2009). New research indicates that motor vehicles are a major, and frequently dominant, source of ultrafine particles in urban environments (Morawska et al., 2008). Chemical composition of these particles are determined by the composition of the used fuel and lubricating oil, driving conditions, and engine after-treatment system, as well as meteorological conditions, but generally PM from these sources consists mostly of agglomerates of solid-phase carbonaceous material, and can also contain metallic ash, adsorbed or condensed hydrocarbons and sulfur compounds, and liquid droplets consisting mainly of hydrocarbons and hydrated sulfuric acid that form very rapidly after the vehicle exhaust leaves a tailpipe (Liu et al., 2015; Saffaripour et al., 2015; Karjalainen et al., 2014; Rönkkö et al., 2014; Fushimi et al., 2011; Gidney et al., 2010; Heikkilä et al., 2009; Johnson, 2009).

The chemical composition of ultrafine particles originating from atmospheric NPF is tied heavily to their growth processes during their atmospheric aging. Direct observations during the period of atmospheric NPF show that the composition of particles originating from NPF is usually dominated by organic compounds, especially in forests (Han et al., 2014; Pennington et al., 2013; Pierce et al., 2012; Pierce et al., 2011), but also in many rural or urban environments (Bzdek et al., 2014; Setyan et al., 2014;

Bzdek et al., 2013; Ahlm et al., 2012; Smith et al., 2008). Exceptions for this pattern are environments exposed to major sulfur emissions, in which sulfate may explain up to about half of the ultrafine particle mass (Vakkari et al., 2015; Crilley et al., 2014; Bzdek et al., 2012; Zhang et al., 2011b; Wiedensohler et al., 2009).

2.5.1.1.9 Reactive Oxygen Species

Particle acidity, oligomer formation and the production of reactive oxygen species (ROS) are interrelated, aqueous phase processes with direct consequence for aerosol concentrations, chemical composition and toxicity (Weber et al., 2016). Polymerization reactions responsible for generating oligomers in atmospheric particles require relatively high concentrations of H^+. The reactive forms of the transition metals that play a central role in production of particle phase ROS primarily exist in low pH aqueous conditions.

Sulfate is often the main acid component of $PM_{2.5}$, and largely determines its acidity. Contrary to expectations, declining SO_2 emissions along with fairly stable NH_3 emissions (see Section 2.3.2.1), have led to little long-term change in pH of $PM_{2.5}$ (see Section 2.5.1.1.6). Low pH conditions facilitate the formation of oligomers and HULIS in aqueous particles. Upwards of 90% oligomeric/high molecular weight material has been found in SOA formed in the presence of NO_X, including a substantial fraction of organic nitrogen compounds (Nguyen et al., 2011). Humic-like substances and smaller organic compounds have been implicated in the production of particle-phase ROS, along with transition metal ions, especially Cu and Mn (Verma et al., 2015).

The 2009 PM ISA described early chamber work on identifying reactive oxygen species (ROS) in secondary organic PM by Docherty et al. (2005). Under the conditions of their experiment, they produced very high yields (47 and 85%) of organic peroxides by reacting O_3 with α- and β-pinene. Reactive oxygen species include hydroxyl radical, organic peroxides and hydroperoxides. A discussion of the role of particle-phase ROS in human health effects can be found in Section 5.1.1.

Identification of individual components that act as ROS in PM is incomplete and an active area of research. The extent to which an ambient particle can engage in oxidative reactions depends on the concentration of aqueous oxidants, such as the hydroxyl radical (OH), and whether or not reactants capable of producing additional oxidants are present within the particle. Oxidants, in addition to OH, can be taken up from the atmosphere or chemically formed from processes such as photolysis of nitrate, nitrite, or hydrogen peroxide (H_2O_2), or Fenton-type reactions between H_2O_2 and Fe(II) (McNeill, 2015; Arakaki et al., 2013; Ervens et al., 2011; Herrmann et al., 2010). Organic species, such as quinones, can act as transition ion reducing agents, which allow oxidized form of an aqueous transition metal ion to produce more ROS (Shirai et al., 2012). Tuet et al. (2017) found that the identities of available reactive precursors in the particle phase, humidity and the fate the reactive intermediate were important

determinants of particle reactivity. Atmospheric aging (oxidation) of organic aerosols has also been found to be an important indicator of ROS activity of ambient PM (Saffari et al., 2016; Verma et al., 2015).

2.5.1.2 Urban and Neighborhood Scale Variability

2.5.1.2.1 $PM_{2.5}$

Understanding spatial variation at the neighborhood and urban scale is important for interpreting data from community monitors. Because of its longer atmospheric lifetime (see Section 2.2), $PM_{2.5}$ is expected to exhibit less spatial variability on an urban scale than UFP or $PM_{10–2.5}$. In the 2004 PM AQCD (U.S. EPA, 2004) annual average $PM_{2.5}$ concentration differences between monitors within the urban area were compared for 17 urban areas. The difference in concentration between monitors with the highest and lowest concentrations ranged from less than 1 $\mu g/m^3$ (Baton Rouge, LA) to more than 8 $\mu g/m^3$ (Pittsburgh, PA). The difference exceeded 6 $\mu g/m^3$ in 6 of the 17 cities (Pittsburgh, Cleveland, Chicago, Detroit, St. Louis, Seattle), in 5 of which the highest $PM_{2.5}$ concentrations were between 20 and 22 $\mu g/m^3$. In the remaining city (Seattle) concentrations ranged from 6 to 12 $\mu g/m^3$.

The degree of spatial uniformity within urban areas also varied depending on location (U.S. EPA, 2004). Intra-urban spatial variability of $PM_{2.5}$ concentrations was discussed in considerable quantitative detail in the 2009 PM ISA, using a number of comparison statistics (U.S. EPA, 2009). In most metropolitan areas correlations between $PM_{2.5}$ monitoring sites up to a distance of 100 km from each other were greater than 0.75, with the notable exceptions of Denver, Los Angeles, and Riverside (U.S. EPA, 2009). However, while $PM_{2.5}$ concentrations at different sites within an urban area can be highly correlated, significant differences in concentration can occur on a given day (U.S. EPA, 2009).

Several recent publications have addressed urban scale spatial variability. Urban concentrations are often several $\mu g/m^3$ above regional background concentrations. For example, Indianapolis urban concentrations are on average 3.9 to 5. $\mu g/m^3$ higher than regional background (Sullivan and Pryor, 2014). Substantial spatial variation of $PM_{2.5}$ concentrations has been reported for New York City (Matte et al., 2013). Spatial variability was also demonstrated by a study indicating that $PM_{2.5}$ was present at significantly higher concentrations at urban sites than at upwind suburban sites in the greater New York area (Patel et al., 2009). Substantial differences in $PM_{2.5}$ concentrations between neighborhoods was also observed in Los Angeles (Fruin et al., 2014), but not in Boston (Patton et al., 2014). One of the contributing factors was that monitors are closer to each other in Boston, where more uniformity was observed. Sub-10 km spatial variability was identified as a contributor to poor results for satellite estimates of $PM_{2.5}$ from aerosol optical depth (AOD) using a 10 × 10 km grid (Lary et al., 2014; Chudnovsky et al., 2013b). In Indianapolis for time scales shorter than 1-day spatial variability was 2 to 3 times greater than temporal variability (Sullivan and Pryor, 2014). However, for 24-hour measurements

of PM components temporal variability accounted for 90% of the variance in Detroit (Bereznicki et al., 2012).

Spatial variability arises from source proximity, with motor vehicles accounting for 24 to 36% and secondary sulfate for 17 to 35% of $PM_{2.5}$ among different residential monitoring areas in Detroit, MI (Duvall et al., 2012). Diesel exhaust was also identified as a major and variable source of $PM_{2.5}$ in New York City (Patel et al., 2009). Land use regression modeling based on 155 city-wide street-level locations in New York City (Clougherty et al., 2013) indicated that concentrations of $PM_{2.5}$ and other pollutants varied by more than a factor of two, with highest concentrations near midtown Manhattan. They also reported that density of oil-burning boilers along with total and truck traffic density explained more than 80% of $PM_{2.5}$ spatial variability (Clougherty et al., 2013). However, in Dallas $PM_{2.5}$ exposure was only moderately associated with motor vehicles and weakly associated with industrial sources, but strongly associated with population density (Zou et al., 2009). Overall, recent observations indicate that uniform $PM_{2.5}$ concentrations can occur, but that substantial spatial variability is also common.

2.5.1.2.2 PM_{10}

PM_{10} concentrations vary by as much as a factor of five over urban scale distances of 100 km or less and by a factor of two or more over scales as small as 30 km (U.S. EPA, 2009; Alexis et al., 2001). Differences in PM_{10} measurements across 15 cities were summarized in the 2009 PM ISA (U.S. EPA, 2009). PM_{10} concentrations were less well correlated than $PM_{2.5}$, probably because of greater spatial variability of $PM_{10-2.5}$ (see Section 2.5.1.2.3). For monitors less than 4 km apart an average correlation of 0.93 between $PM_{2.5}$ monitors and 0.70 for PM_{10} monitors was observed (U.S. EPA, 2009). Spatial and temporal differences in PM_{10} concentrations have also been predicted from models based on the geographic information system; meteorological and copollutant data for both fine and large spatial scales and distance to road; elevation; and proportion of low-intensity residential, high-intensity residential, industrial, commercial, and transportation land use within 1 km have all been reported to be statistically significant predictors of measured PM_{10} (Blanchard et al., 2014; Paciorek et al., 2009; Yanosky et al., 2009); (Yanosky et al., 2014).

2.5.1.2.3 $PM_{10-2.5}$

As indicated in the 2004 PM AQCD (U.S. EPA, 2004), the shorter lifetime of $PM_{10-2.5}$ leads to lower spatial correlations for $PM_{10-2.5}$ than for either $PM_{2.5}$ or PM_{10} concentrations (U.S. EPA, 2009, 2004). Errors in measurement (see Section 2.4.4) can also contribute to lower spatial correlations of $PM_{10-2.5}$ (U.S. EPA, 2004). Recent observations from several cities indicate that there is often, but not always, considerable spatial variability in $PM_{10-2.5}$ concentrations in urban areas, that they are often related to specific industrial sources, and that concentrations of specific chemical components can be more variable than mass. In Detroit $PM_{10-2.5}$ was 5 $\mu g/m^3$ higher in two industrial areas, and 8 $\mu g/m^3$

higher in an area heavily impacted by traffic than average concentrations in other parts of the city, and not very consistent with central site monitor concentrations (Thornburg et al., 2009). Poor correlations between monitors were also observed in Los Angeles (Pakbin et al., 2010) and between industrial and suburban sites in Cleveland (Sawvel et al., 2015). In Rochester, NY, where major coarse particle sources were road dust and biological particles, considerable heterogeneity in both composition and concentrations were also observed between different sites (Lagudu et al., 2011).

2.5.1.2.4 Ultrafine Particles

As described in Section 2.5.1.1, UFP spatial variability increased with increasing distance between measurements, increasing source variation in the area studied, and increasing particle size within the UFP size range. (U.S. EPA, 2009). Particularly high spatial variabilities have been observed near roads with heavy traffic, where numerous observations of UFP number concentration declining sharply with distance from roadways have been reported (U.S. EPA, 2009).

More recently, spatial variability of UFP was compared between studies of two locations, Los Angeles, CA (Hudda et al., 2010; Krudysz et al., 2009; Moore et al., 2009) and Rochester, NY (Wang et al., 2012). These two studies provide an interesting comparison because the two studies were similar in domain size. The comparison is summarized in Table 2-8. It should be noted that the Los Angeles studies employed SMPS for particle size distribution measurements, while the Rochester study used a FMPS. Both Krudysz et al. (2009) and Hudda et al. (2010) indicated that regionally transported PM from upwind urban areas of Los Angeles lowered spatial variability by acting as a "homogenizing" factor during favorable meteorological conditions. This effect was not noticeable in Rochester, NY (Wang et al., 2012). Nevertheless, significant variability among sites was observed in both studies.

Table 2-8 Comparison between two urban-scale studies of UFP seasonal and spatial variability.

	Los Angeles, CA (Krudysz et al., 2009)	Rochester, NY (Wang et al., 2012)
Area	11 × 11 km, urban	9 × 9 km, urban
Sites	13 sites	12 sites
Instrumentation	SMPS (14−793 nm), CPC (>7 nm)	FMPS (with one SMPS in a fixed site), 5.6 to 560 nm
Levels of average total number concentrations	5,300 to 27,000 particles/cm^3	9,025 (summer), 10,939 (winter), 4,955 (spring), and 14,485 (fall) particles/cm^3
Seasonal variability	Relatively higher levels observed in the fall/winter than in the summer	Relatively higher levels observed in the fall/winter than in the spring; Relatively high 100−500 mode in the summer
Coefficient of divergence (COD)	>0.2 on average for all particles measured, 0.25 to 0.6 for size-dependent average COD	No clear overall pattern
Size-dependency	Number concentrations of smaller particles (<40 nm) differ from site to site, whereas larger particles tended to have similar concentrations at various sampling locations.	No clear overall pattern

Source: Krudysz et al. (2009).

2.5.1.2.5 Chemical Components

A detailed analysis of 15 urban locations in the 2009 PM ISA (U.S. EPA, 2009) indicated a generally fair degree of spatial uniformity in bulk $PM_{2.5}$ components. Exceptions were noted in one or two cities for crustal material, nitrate, elemental carbon, organic carbon and nickel (U.S. EPA, 2009). More recent observations have focused mainly on carbonaceous components across urban areas. Black carbon (BC) concentrations were 2 to 3 times higher at urban locations than at suburban locations in the greater New York area (Patel et al., 2009). There were several reports of higher concentrations of some PM components near roads with heavy traffic than other urban locations. For example, carbonaceous aerosols exhibited substantial intra-urban variability in Detroit, MI and Cleveland, OH that was consistent with local sources, with EC higher at sites adjacent to freeways and busy surface streets (Snyder et al., 2010). Site to site variability in OC was approximately 7% at distances from 0.5 to 4 km, but between 4−27% at distances 4 to 100 km. However, more finely speciated organic components differed by as much as 60% at the 0.5 to 4 km scale and up to 200% at the 4−100 km scale (Snyder et al., 2010). PAHs and steranes

along with OC and EC were found to be higher near roads with heavy traffic than in other urban locations (Xie et al., 2012). Differences of a factor of 2 to 3 between concentrations on major streets and at background locations in the same city in the Netherlands were also observed for chromium, copper, and iron, elements that were mainly present in the coarse fraction, as well as for black carbon and particle number count (Boogaard et al., 2011).

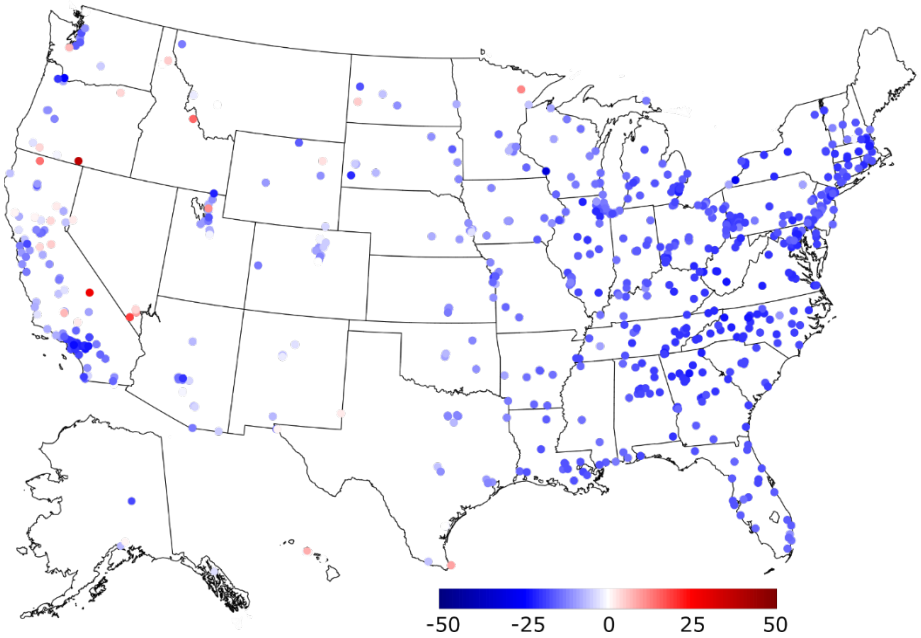
2.5.2 Temporal Variability

2.5.2.1 Regional Trends

Differences in national average concentrations and regional variability between data from immediately prior to this assessment and the 2009 PM ISA (U.S. EPA, 2009) were discussed in Section 2.5.1.1, which demonstrated substantial decreases in PM concentrations since publication of the 2009 PM ISA (U.S. EPA, 2009). This section expands on those observations by exploring long-term trends that extend back as far as 2000, when widespread network measurements of urban $PM_{2.5}$ began, in order to provide more complete assessment of trends.

2.5.2.1.1 $PM_{2.5}$

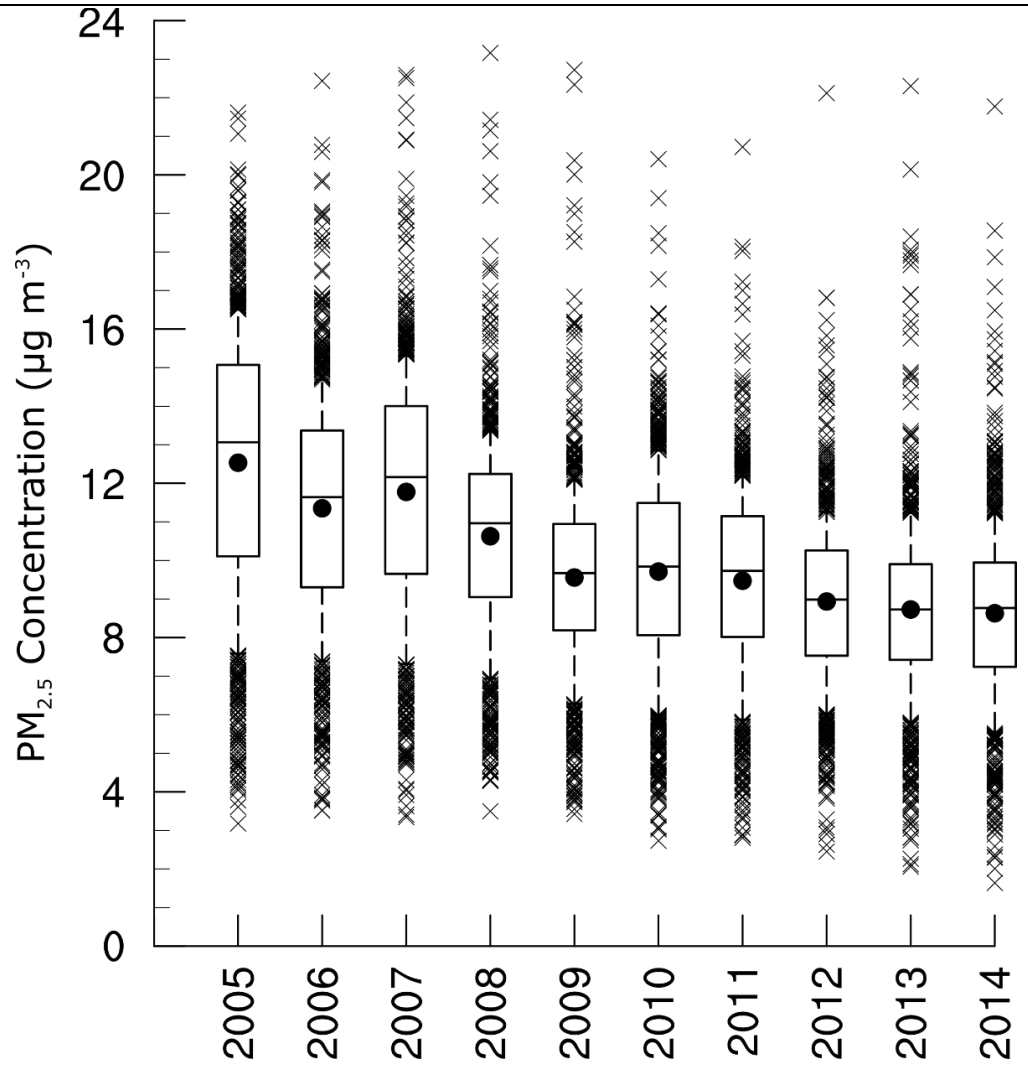
Figure 2-20 show how $PM_{2.5}$ concentrations have decreased substantially at almost all $PM_{2.5}$ monitoring sites between the periods 2003−2005 and 2013−2015, with especially large decreases in the Eastern U.S. Figure 2-21 also shows a decreasing trend of $PM_{2.5}$ concentrations as a time series using national data from network monitoring sites throughout the U.S. Overall, $PM_{2.5}$ concentrations have decreased substantially nationwide since the 2003−2005 period, especially in the Eastern U.S. $PM_{2.5}$ concentrations derived from satellite data also exhibit a decreasing trend, of $-0.39 + 0.10$ μg/m^3 per year averaged over a 1 by 1 degree grid (Boys et al., 2014).



Blue indicates a decrease and red indicates an increase. Percentage increase or decrease is indicated by color intensity of the circle.

Source Permission pending: U.S. EPA 2016 analysis of Air Quality System network data 2003−2005 and 2013−2015.

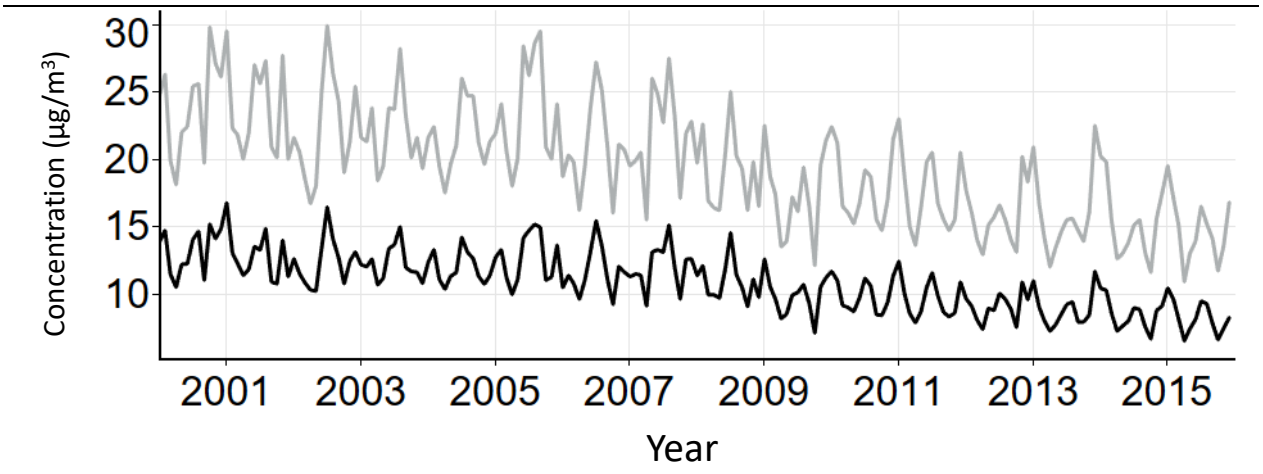
Figure 2-20 Increase or decrease in 3-year annual average $PM_{2.5}$ concentrations between 2003−2005 and 2013−2015.



Source Permission pending: U.S. EPA 2016 analysis of Air Quality System network data 2005−2014.

Figure 2-21 Average $PM_{2.5}$ concentration trends 2005−2014

The predominant downward trends shown in Figure 2-21 are a continuation of the decreasing trend in $PM_{2.5}$ concentration reported in the 2009 PM ISA (U.S. EPA, 2009), in which a 10% decrease in annual average $PM_{2.5}$ concentrations between the 3-year period from 1999−2001 and the 3-year period from 2005−2007 was described. Figure 2-22 shows an overall decrease in monthly and annual $PM_{2.5}$ average and 90th percentile concentrations over the 16-year period from 2000−2015, as well as a steadily shrinking summer peak, across all reporting FRM site-level monitors in the U.S. (Chan et al., 2018). Over this period $PM_{2.5}$ concentration averaged over the entire network decreased by 5 µg/m^3 and 90th percentile concentrations decreased by 9 µg/m^3 (Figure 2-22). It is evident from Figure 2-22 that the sharpest decrease occurred in 2008−2010.

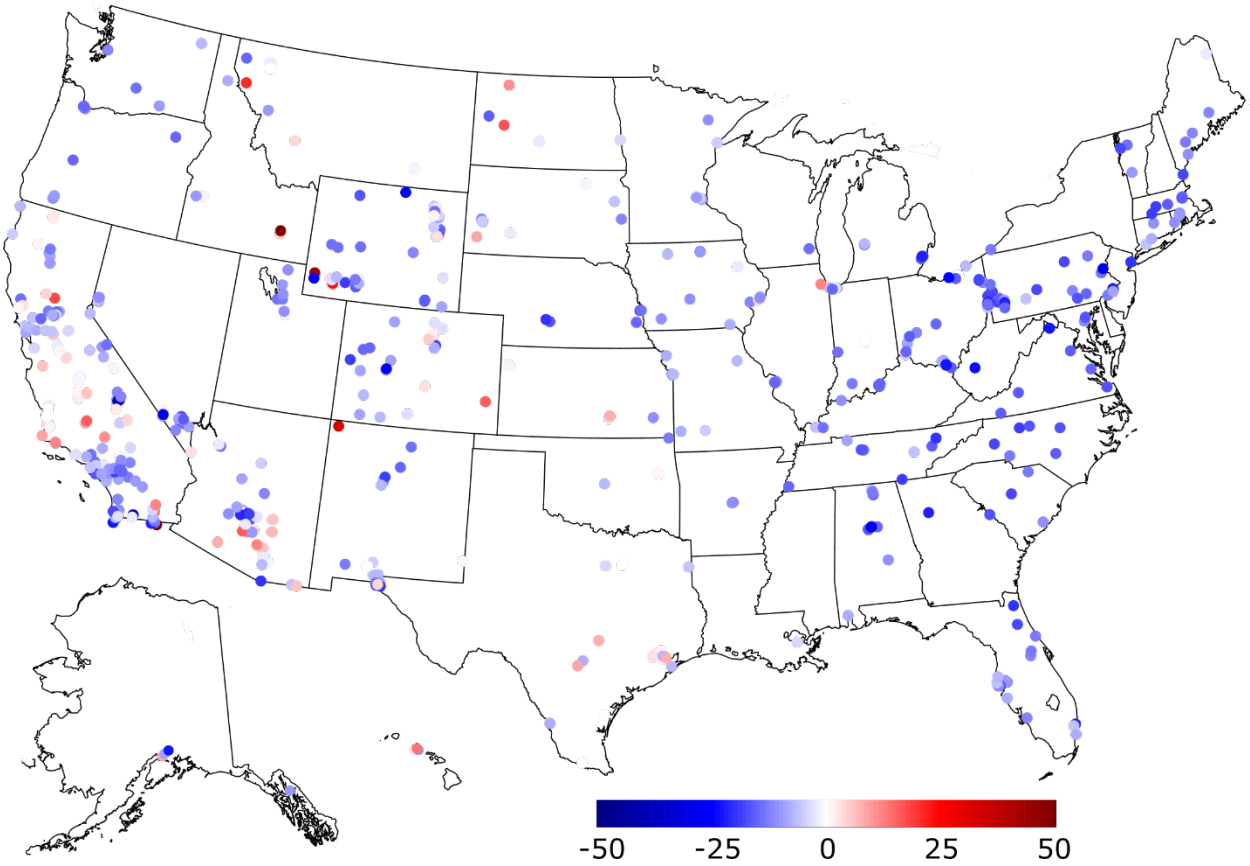


Black = mean, gray = 90th percentile.
Source Permission pending: Chan et al. (2018).

Figure 2-22 Long-term trend in national monthly and annual average $PM_{2.5}$ concentrations (µg/m³) from 2000−2015.

2.5.2.1.2 PM_{10}

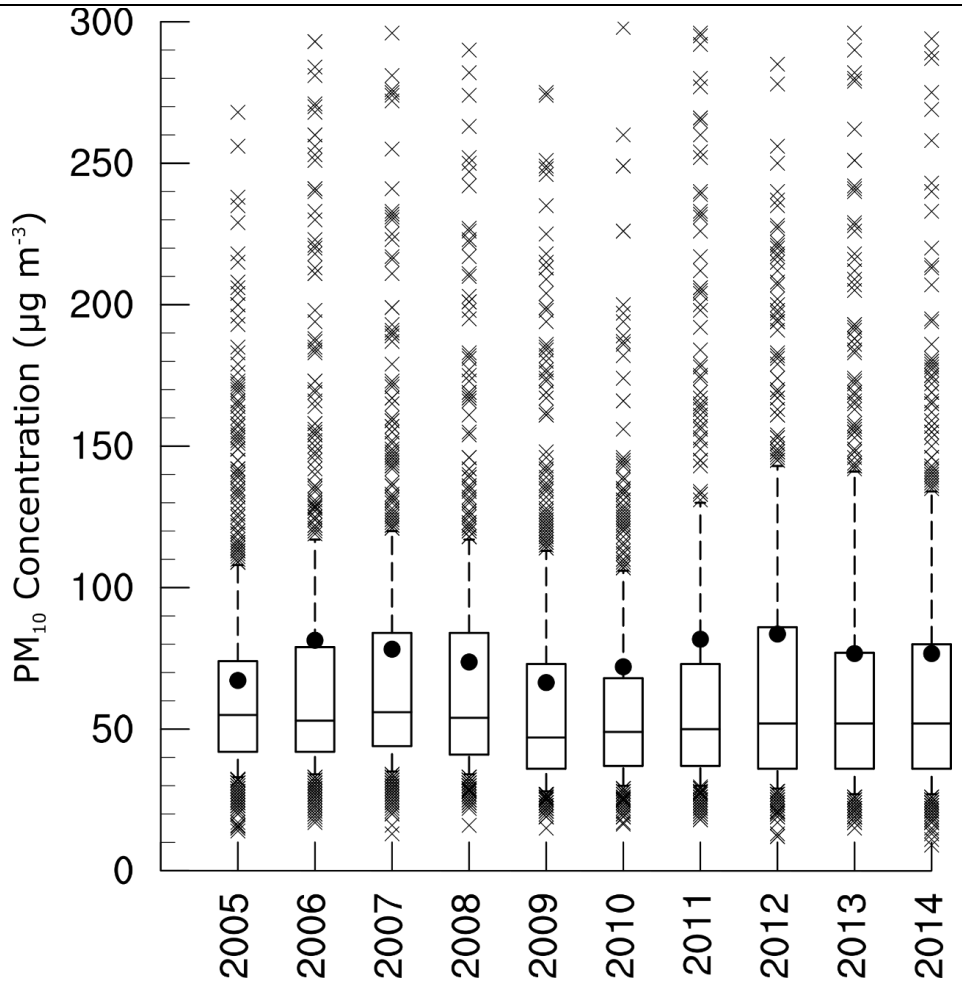
Over the longer term PM_{10} has decreased steadily in several urban areas over the past several decades (U.S. EPA, 2004). Figure 2-23 shows a map of concentration trends in 98th percentile PM_{10} concentrations between 2003−2005 and 2013−2015 and Figure 2-24 shows a time series of national PM_{10} concentrations from 2005−2014. Most sites in the Eastern U.S. show decreasing concentrations over this period, consistent with the data of Table 2-5. However, there are locations in California, the Southwest, the Rocky Mountains, and the Great Plains that exhibit substantial increases in 98th percentile PM_{10} concentrations. The observed decreases in PM_{10} concentrations in many locations are consistent with similar observations for annual average $PM_{2.5}$ concentrations (see Section 2.3.4), reflecting that $PM_{2.5}$ has accounted for the majority of PM_{10} in the Eastern U.S. and a large fraction of PM_{10} throughout the U.S. over the period of decline. However, Figure 2-24 shows no evidence of a nationwide trend of decreasing PM_{10} concentrations in a time series of PM_{10} concentrations from network monitoring sites throughout the U.S.



Blue indicates a decrease and red indicates an increase. Percentage increase or decrease is indicated by color intensity of the circle.

Source Permission pending: U.S. EPA 2016 analysis of Air Quality System network data 2003−2005 and 2013−2015.

Figure 2-23 Increase or decrease in 98th percentile 24-hour PM_{10} concentrations between 2003−2005 and 2013−2015.



Source Permission pending: U.S. EPA 2016 analysis of Air Quality System network data 2003−2005 and 2013−2015.

Figure 2-24 PM_{10} 2nd highest concentration trends from 2005−2014.

2.5.2.1.3 $PM_{10-2.5}$

Long-term concentration trends for urban $PM_{10-2.5}$ are difficult to determine from network data because $PM_{10-2.5}$ monitoring was too recently implemented. However, some NCore stations began $PM_{10-2.5}$ measurements in the mid-2000's and IMPROVE measurements of $PM_{10-2.5}$ have been operating even longer, and although IMPROVE sites are mostly rural, some are collocated with CSN sites. These could be analyzed for long-term trends. In a Los Angeles field study $PM_{10-2.5}$ decreased by 0.39 µg/m^3 from 19 to 15 µg/m^3 for the period 1999 to 2009 compared to 0.92 µg/m^3 for $PM_{2.5}$ over the same period (Cheung et al., 2012b).

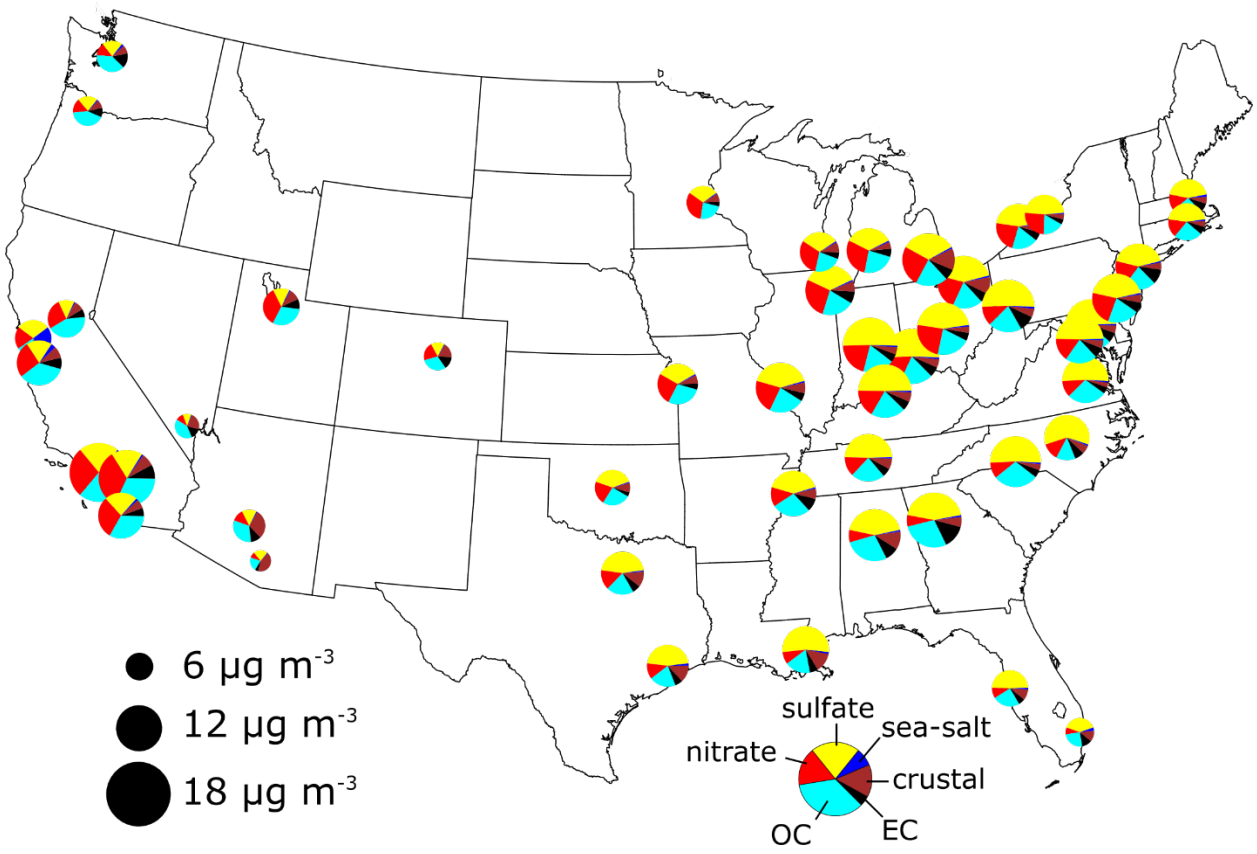
2.5.2.1.4 Ultrafine Particles

Information on UFP concentrations is very limited, confined to very few network monitors that only recently became operational. Data from field studies have been published periodically, but are generally insufficient to assess long-term trends of UFP in any location. One exception is 8 years of UFP data from Rochester, NY, the particle number characteristics of which were summarized in Section 2.5.1.1.5 (Wang et al., 2011). On average over the 8 years that UFP data were collected in Rochester, total particle number concentrations were greater before 2006 than after 2006. This trend was most evident for particles between 0.01 and 0.1 μm. The difference was described as probably due to several changes in local sources due to the 2007 Heavy Duty Highway Rule, a reduction in local industrial activity, and the closure of a nearby coal-fired power plant (Wang et al., 2011).

2.5.2.1.5 Chemical Components

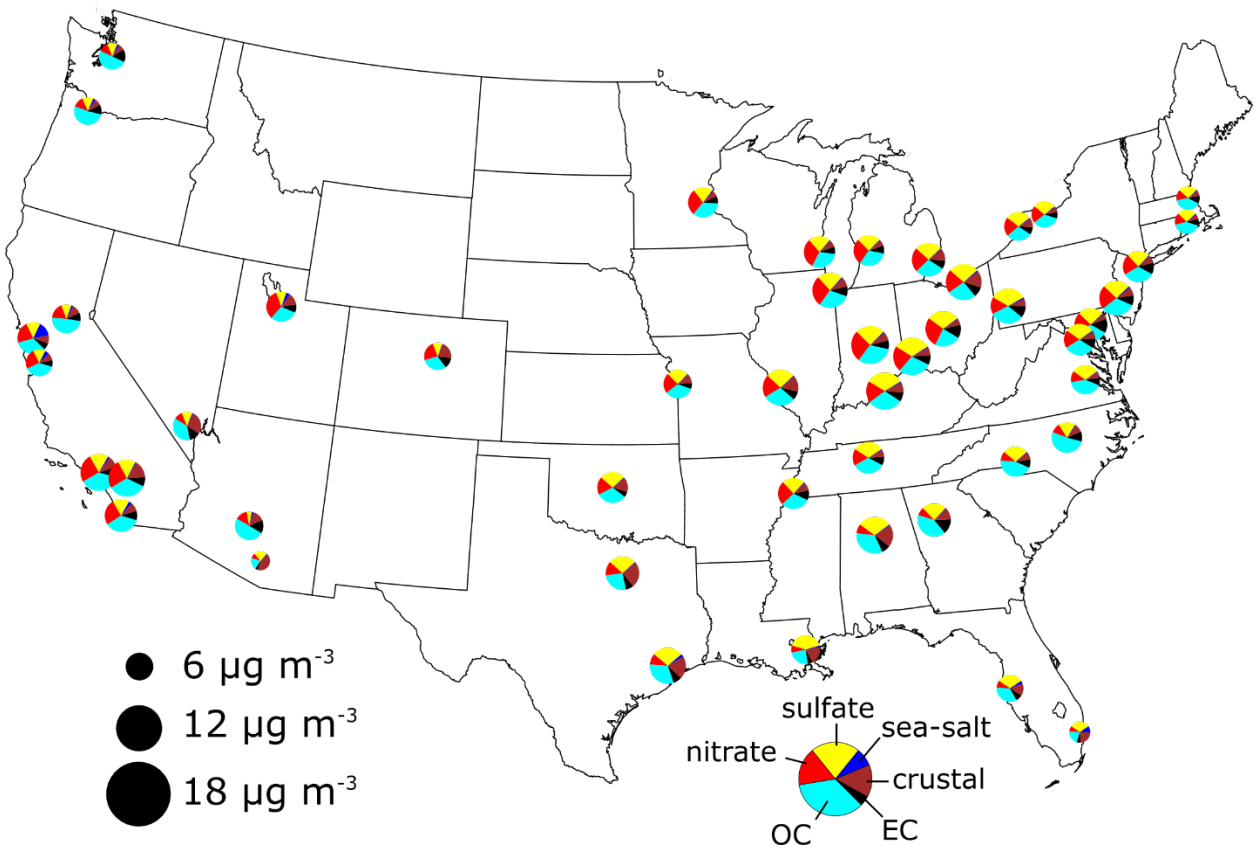
Figure 2-25 and Figure 2-26 show changes in the distribution of bulk $PM_{2.5}$ components, between the 3-year period from 2003−2005 and the 3-year period from 2013−2015. The most noticeable difference is the change in sulfate contribution, which dominates $PM_{2.5}$ mass in the East during the period 2003−2005, but by 2013−2015 it has declined enough that it is no longer the most abundant component in many Eastern locations.

In the 2009 PM ISA (U.S. EPA, 2009), sulfate is described as the most abundant component of $PM_{2.5}$ on a national average, with nitrate, particulate organic matter and sometimes crustal material also contributing substantially to $PM_{2.5}$ mass. The relative abundance of major $PM_{2.5}$ components has changed since the 2009 PM ISA (U.S. EPA, 2009), with lower contributions from sulfate and greater contributions of nitrate and particulate organic matter as a result of the steep decline in SO_2 emissions (see Section 2.3.2.1). The resulting decrease in sulfate concentrations closely follows the recent long-term decrease in $PM_{2.5}$ concentrations described in Section 2.5.2.1.1, and is magnified for monitoring sites in the Eastern half of the U.S., where sulfate has until recently been the most abundant $PM_{2.5}$ components, and where SO_2 emissions have declined the most.



Source Permission pending: U.S. EPA 2016 analysis of Air Quality System network data 2003−2005.

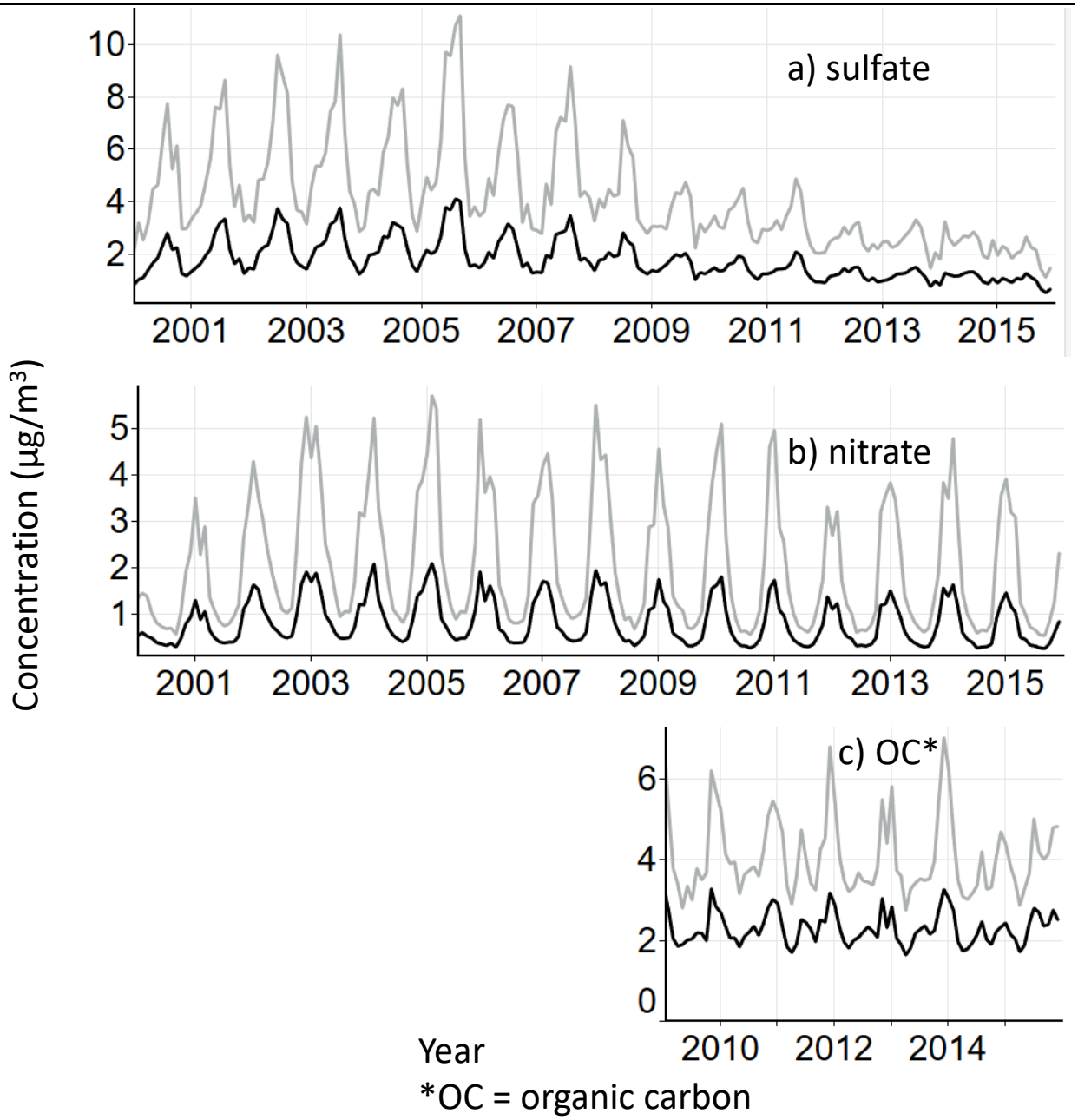
Figure 2-25 Contributions of sulfate, nitrate, organic carbon (OC), elemental carbon (EC), crustal material, and sea salt to $PM_{2.5}$ at selected sites 2003−2005.



Source Permission pending: U.S. EPA 2016 analysis of Air Quality System network data 2013−2015.

Figure 2-26 Contributions of sulfate, nitrate, organic carbon (OC), elemental carbon (EC), crustal material, and sea salt to $PM_{2.5}$ at selected sites 2013−2015.

Figure 2-27 shows $PM_{2.5}$ sulfate, nitrate and OC concentrations from 2000−2015 based on IMPROVE and CSN network data. A steep decline in sulfate concentration is observed, but less change is evident for nitrate and OC concentrations. Like the summer $PM_{2.5}$ maximum (Figure 2-22), the summer sulfate peak also declines to become almost imperceptible toward the end of the period. Based on these observations, it appears that decreases in SO_2 emissions (Section 2.3) have contributed to a substantial decrease in atmospheric sulfate concentrations. The declining sulfate concentrations are also consistent with CMAQ predictions of the sulfate response to decreasing SO_2 emissions. Because sulfate has accounted for such a large fraction of $PM_{2.5}$ mass, the decreasing trend in sulfate concentration is also manifested in lower $PM_{2.5}$ concentrations (Section 2.5.2.1.1) and smaller $PM_{2.5}/PM_{10}$ ratios (Section 2.5.1.1.4). However, sulfate is not the only $PM_{2.5}$ species that exhibited decreasing concentrations over this period, as described below.



Black = mean, gray = 90th percentile.
Source Permission pending: Chan et al. (2018).

Figure 2-27 National monthly concentrations (µg/m^3) of (a) sulfate, (b) nitrate, and (c) organic carbon (OC) from 2000−2015.

Long-term trends in $PM_{2.5}$ component concentrations from the CSN and IMPROVE networks were also recently described in a series of papers (Hand et al., 2013; Hand et al., 2012a; Hand et al., 2012b). In general sulfate has decreased fairly consistently at rural sites at a rate of −2.7% per year from 1992 to 2010 (Hand et al., 2012b). An even steeper decrease in sulfate concentrations has been observed in the most recent years, of −4.6% per year at rural sites from 2001 to 2010 and −6.2% per year at urban sites from 2002−2010 (Hand et al., 2012b). This is similar to the rate of decrease of SO_2 emissions from power plants, and decreases were greater and more linear in the East, where power plant emissions had the greatest contributions to sulfate concentration (Hand et al., 2012b). However, in the winter in the northern and central Great Plains sulfate and nitrate concentrations have increased at a rate of over 5% per year over the period 2000−2010, in spite of decreased nationwide emissions (Hand et al., 2012a), and sulfate increases in spring in some parts of the West were also observed (Hand et al., 2012b). These increases could not be explained by known changes in local or regional emissions (Hand et al., 2012b). In the SEARCH network downward trends in mean annual sulfate concentrations from 1999 to 2010 ranged from -3.7 ± 1.1 to -6.2 ± 1.1% per year. The sulfate reduction was linearly related but not proportional to SO_2 decrease of -7.9 ± 1.1% per year from 1999 to 2010. Over the same period mean organic matter concentration decreased by -3.3 ± 0.8 to 6.5 ± 0.3% per year and elemental carbon by -3.2 ± 1.4 to -7.8 ± 0.7% per year (Blanchard et al., 2013). Total carbon (OC + EC) generally decreased in both urban and rural areas, with the strongest trends in the West (Hand et al., 2013).

For species that are more strongly influenced by local urban sources, trends are manifested more locally, and largely controlled by changes in local source emissions. Al, Fe, and Si decreased in Los Angeles, suggesting successful control of fugitive dust emissions, but Cu declined little, probably indicating similar contributions from brake wear (Cheung et al., 2012b).

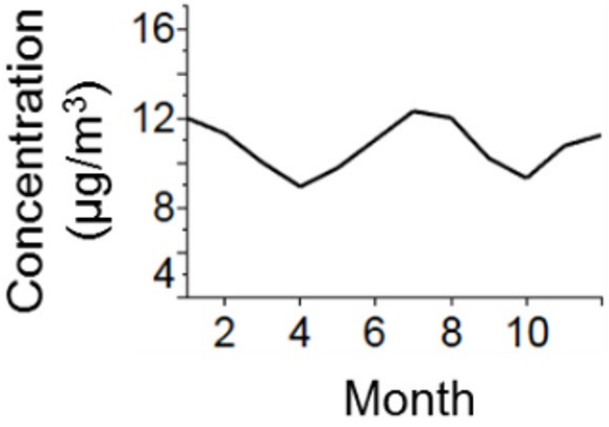
2.5.2.2 Seasonal Variations

2.5.2.2.1 $PM_{2.5}$

Observations described in Section 2.5.2.1.1 indicated that national average $PM_{2.5}$ concentrations and 98th percentile concentrations from 2013−2015 were both higher in winter than in summer (Table 2-4), and observations described in Section 2.5.2.1.1 indicated that monthly average $PM_{2.5}$ concentrations exhibited distinct summer and winter peaks superimposed on a steadily declining national average $PM_{2.5}$ (Figure 2-22). Averaged over all locations and years from 2001−2016, seasonal average $PM_{2.5}$ concentrations were approximately 12 µg/m^3 in summer and winter, but declined to approximately 9 µg/m^3 in the spring and fall (see Figure 2-28).

While monthly average $PM_{2.5}$ concentrations are higher in summer than in winter from 2002−2008, this pattern is reversed from 2009−2015, when monthly average $PM_{2.5}$ concentrations become higher in winter than in summer (see Section 2.5.2.1.1, Figure 2-22). This is a major departure

from previous concentration trends. Observations that the highest seasonal average concentrations occurred in summer in the Eastern U.S. and in winter in the Western U.S. with a few exceptions was already clearly established from 1999−2001 data from the newly operational $PM_{2.5}$ network (U.S. EPA, 2004). These early $PM_{2.5}$ network results were in turn consistent with previous studies carried out prior to its implementation, and were confirmed in the 2009 PM ISA (U.S. EPA, 2009). The observed reduction in summer $PM_{2.5}$ concentrations in the East to the extent that summer is no longer the season with the highest national average $PM_{2.5}$ concentrations is a major development, and is a predictable consequence of successful reduction of SO_2 emissions.



Source Permission pending: Chan et al. (2018).

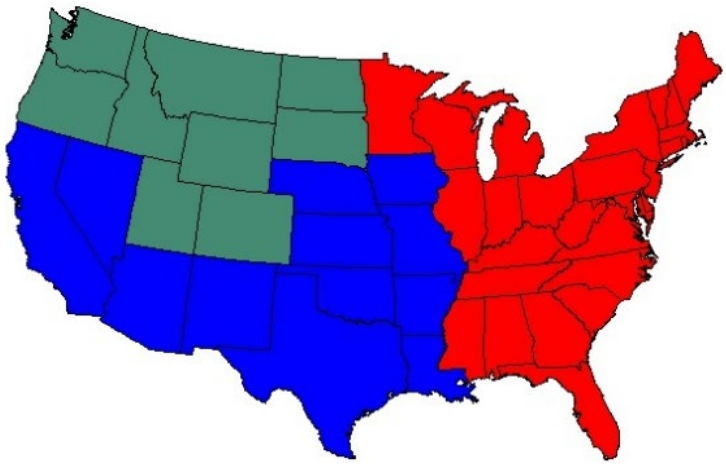
Figure 2-28 National average $PM_{2.5}$ concentration by month 2000−2015.

2.5.2.2.2 $PM_{10-2.5}$

Relatively little had been published on the seasonal variability in $PM_{10-2.5}$ concentrations at the time of the 2009 PM ISA (U.S. EPA, 2009). Figure 2-29 shows three U.S. regions used for comparison of $PM_{10-2.5}$: the U.S. East of the Mississippi and the Northern and Southern portions of the U.S. West of the Mississippi. The regions were divided in this way because previous discussions based on limited data had suggested that PM_{10} was mostly $PM_{2.5}$ in the eastern U.S. and mostly $PM_{10-2.5}$ in the western U.S. (U.S. EPA, 2009, 2004), and these two regions were compared to investigate whether there were also seasonal differences between East and West. However, because results indicated that geographic differences within the western U.S. were greater than observed East-West differences, the western U.S. was further divided into northern and southern portions.

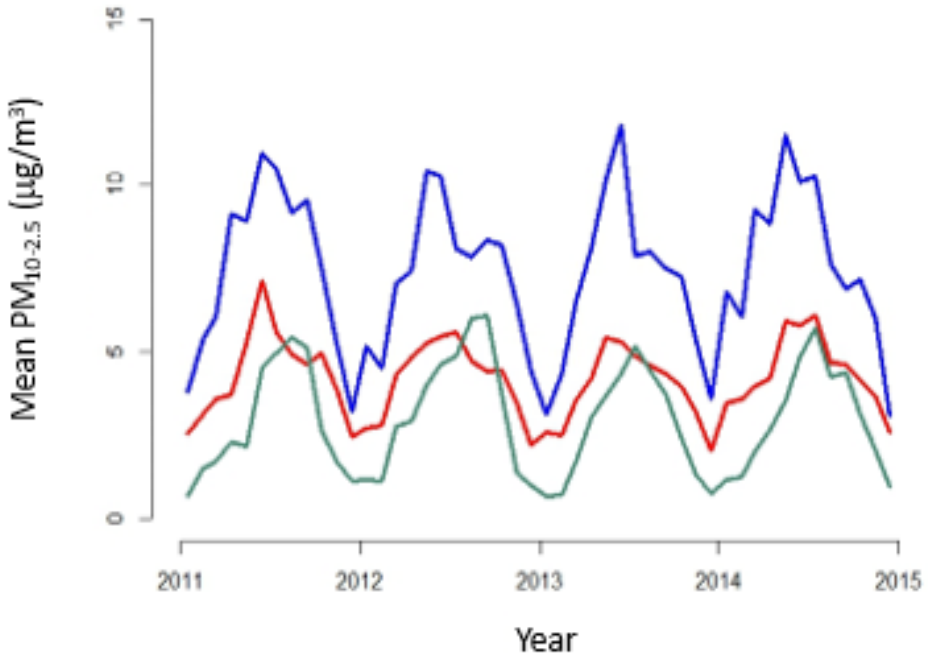
Figure 2-30 shows average concentrations on each day for 4 years from 2011−2014 by region based on data from the IMPROVE network, after dividing the U.S. into these three regions. All regions

display clear seasonal variations, with the lowest concentrations occurring around January and the highest occurring in the summer months. The highest $PM_{10-2.5}$ concentrations are observed in the Southwest/Central region. Concentrations in this region are much higher than concentrations in the East and a seasonal pattern of high summer and low winter concentrations is apparent. By contrast, average concentrations in the Northwest region stretching all the way from the Pacific to the Dakotas were more similar to those in the East, but with a more pronounced seasonal pattern than either the East or the Southwest. These observations indicate that geographic patterns of $PM_{10-2.5}$ concentrations are more complicated than a simple East-West split, but that there are large areas of the Western U.S. where average $PM_{10-2.5}$ concentrations are similar to the Eastern U.S.



Source Permission pending: U.S. EPA analysis of Air Quality System network data 2011−2015.

Figure 2-29 Regions used for coarse PM comparison.



Colors of the lines correspond to the colors of the regions in Figure 2-29, i.e., red is East, green is Northwest, and blue is Southwest/Central.

Source Permission pending: U.S. EPA 2016 analysis of Air Quality System network data 2011−2015.

Figure 2-30 Average daily $PM_{10-2.5}$ concentrations over the 4-year period 2011−2014 collected by the Interagency Monitoring of Protected Visual Environments (IMPROVE) network.

The seasonal differences described in Section 2.5.1.1.3 of highest $PM_{10-2.5}$ concentrations in Spring and Fall and lowest concentration in winter (see Table 2-6) are consistent with other recent observations. In Colorado the highest $PM_{10-2.5}$ concentrations were observed in the Spring and Fall (Clements et al., 2014b). The monsoon period in this region is characterized by high wind events that increase $PM_{10-2.5}$ concentrations due to local wind driven soil, especially at rural sites with agricultural activity (Clements et al., 2014b). In Los Angeles $PM_{10-2.5}$ concentrations were 2−4 times higher in summer than in winter (Pakbin et al., 2010). However, organic coarse PM in Southern California was higher in winter than summer, and mostly was due to soil or biota, especially in "semirural" areas like Riverside and Lancaster (Cheung et al., 2012b).

2.5.2.2.3 Ultrafine Particles

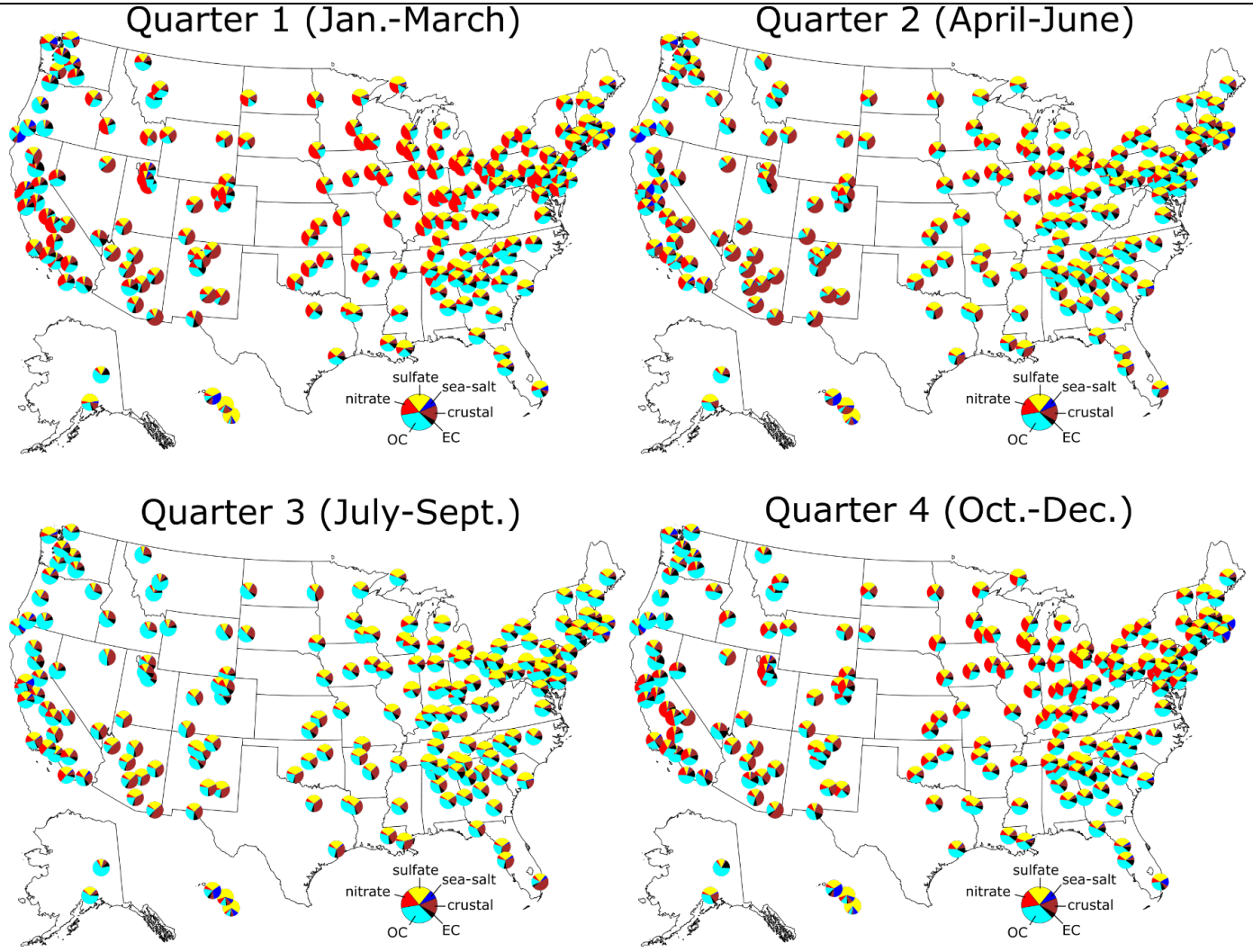
Relatively little has been published about seasonal or hourly differences in UFP concentrations except for localized studies in a few locations suggesting higher concentrations in winter than summer and an inverse relationship between UFP number and temperature (U.S. EPA, 2009). High afternoon concentrations during warmer months were attributed to NPF and high winter and evening UFP concentrations were attributed to lower mixing heights (U.S. EPA, 2009). More recent results indicate urban episodes of high UFP concentrations occur more often in winter than in summer (NYDEC, 2016).

2.5.2.2.4 PM Components

PM composition varies considerably with season. Figure 2-31 shows these changes. Seasonal concentration patterns are for the most part similar to those reported in the 2009 PM ISA (U.S. EPA, 2009) and conclusions from recent analyses of network data (Hand et al., 2013; Hand et al., 2012c) are consistent with patterns that can be observed in Figure 2-31. Sulfate and OC together accounted for the majority of $PM_{2.5}$ mass in many metropolitan areas in the summer, while higher nitrate concentrations were observed in the winter (U.S. EPA, 2009). Urban and rural seasonal variations of ammonium sulfate were similar, and both urban and rural concentrations were substantially higher in the East (Hand et al., 2012c). High winter nitrate concentrations were common in both urban and rural areas, but higher in urban areas (Hand et al., 2012c). Fine soil concentrations, highest in the Southwest, also had similar seasonal patterns for urban and rural sites (Hand et al., 2012c).

The higher OC contributions in fall and winter in the West compared to lower OC concentrations in winter in the Southeast reported in the 2009 PM ISA (U.S. EPA, 2009) are evident in Figure 2-31. EC mass concentration exhibited smaller seasonal variability than OC, particularly in the eastern half of the U.S. Carbonaceous aerosols varied more with season in the West than in the East for both urban and rural sites, although the seasonal patterns were different between Western urban and rural sites (Hand et al., 2013). PBAP often contributes more to PM mass in spring and summer than in fall and winter (U.S. EPA, 2009).

The metals Cu, Fe, Se, Pb, V, and Ni showed less seasonal variability than the sulfate, nitrate, and OC as reported in the 2009 PM ISA (U.S. EPA, 2009). More recently, in Los Angeles, trace element concentrations were higher in drier months of September and October, compared to December and January (Na and Cocker, 2009).



Source Permission pending: U.S. EPA 2016 analysis of Air Quality System network data 2013−2015.

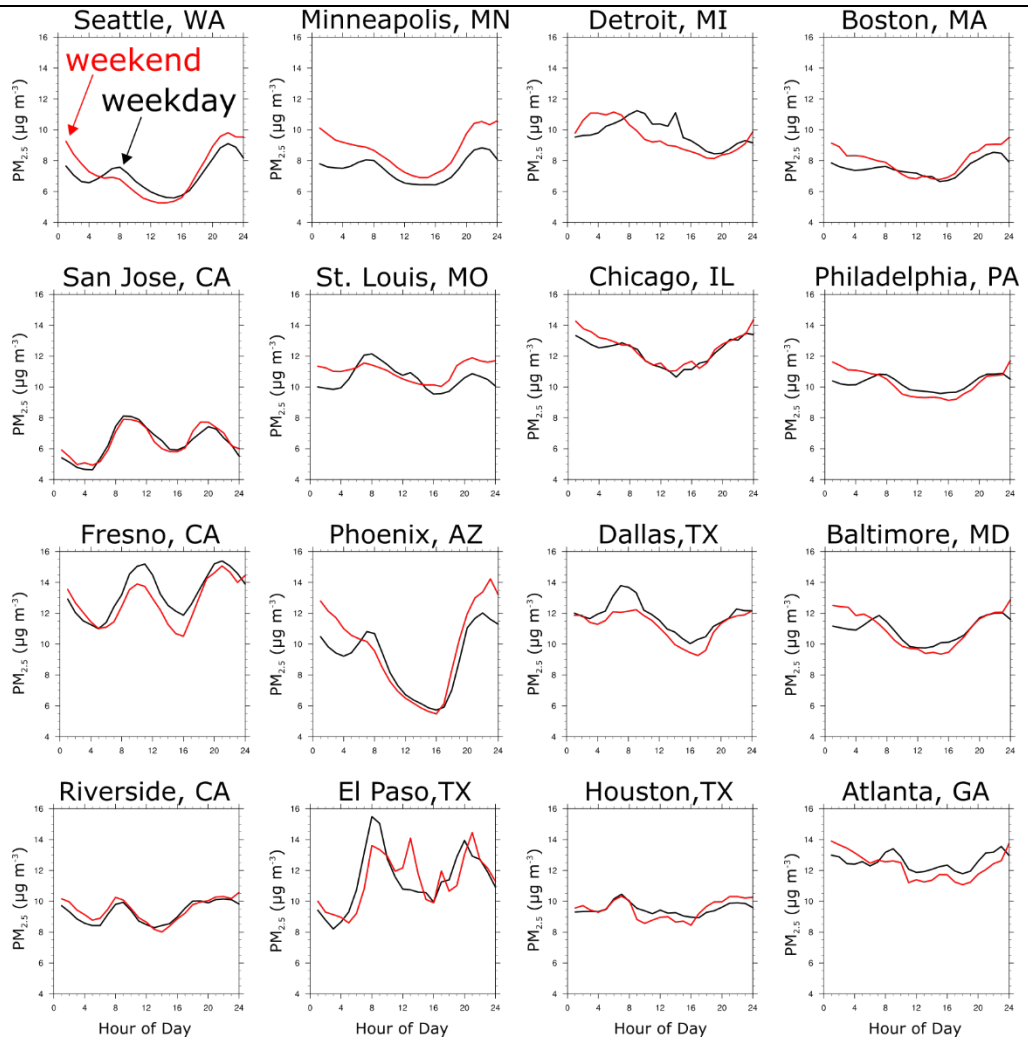
Figure 2-31 Ambient $PM_{2.5}$ seasonal composition 2013−2015.

2.5.2.3 Hourly and Weekday-Weekend Variability

As described in the 2009 PM ISA (U.S. EPA, 2009), hourly $PM_{2.5}$ and PM_{10} measurements are conducted at several hundred network monitoring sites. A two-peaked diel pattern was observed in diverse urban locations and attributed to rush-hour traffic for the morning peak and a combination of rush hour traffic, decreasing atmospheric dilution, and nucleation for the afternoon/evening peak (U.S. EPA, 2009). In most cities, a morning $PM_{2.5}$ peak was present starting at approximately 6:00 a.m., corresponding with the start of the morning rush hour just before the break-up of the planetary boundary layer. Figure 2-32 shows diurnal patterns for multiple cities using more recent data showing rush hour peaks in the morning and evening in most cases, which is consistent with the daily variability in $PM_{2.5}$ concentrations observed in the 2009 PM ISA (U.S. EPA, 2009).

Diurnal variations in $PM_{10–2.5}$ concentrations have also been investigated. In Los Angeles in the summer the highest concentrations of $PM_{10–2.5}$ were observed in midday and afternoon when winds were the strongest. Traffic was responsible for significant resuspension especially during winter nights when mixing heights were lowest at near-freeway sites in urban areas of Southern California (Cheung et al., 2012b).

As described in Section 2.5.1.1.5 (Figure 2-18), for UFP a diel maximum was observed on average during evening hours in diverse geographic locations. An inverse relationship between UFP number and temperature has also been observed, and high afternoon concentrations during warmer months were attributed to photochemical formation and high winter and evening UFP concentrations were attributed to lower mixing heights (U.S. EPA, 2009). Relatively little had been published about hourly differences in UFP concentrations at the time of the 2009 PM ISA except for localized studies in a few locations indicating a diel maximum during evening hours (U.S. EPA, 2009).



Source Permission pending: U.S. EPA 2016 analysis of Air Quality System network data 2012−2015.

Figure 2-32 Diurnal variation of $PM_{2.5}$ concentrations in urban areas

2.5.3 Common Patterns of Particulate Matter Characteristics in the U.S.

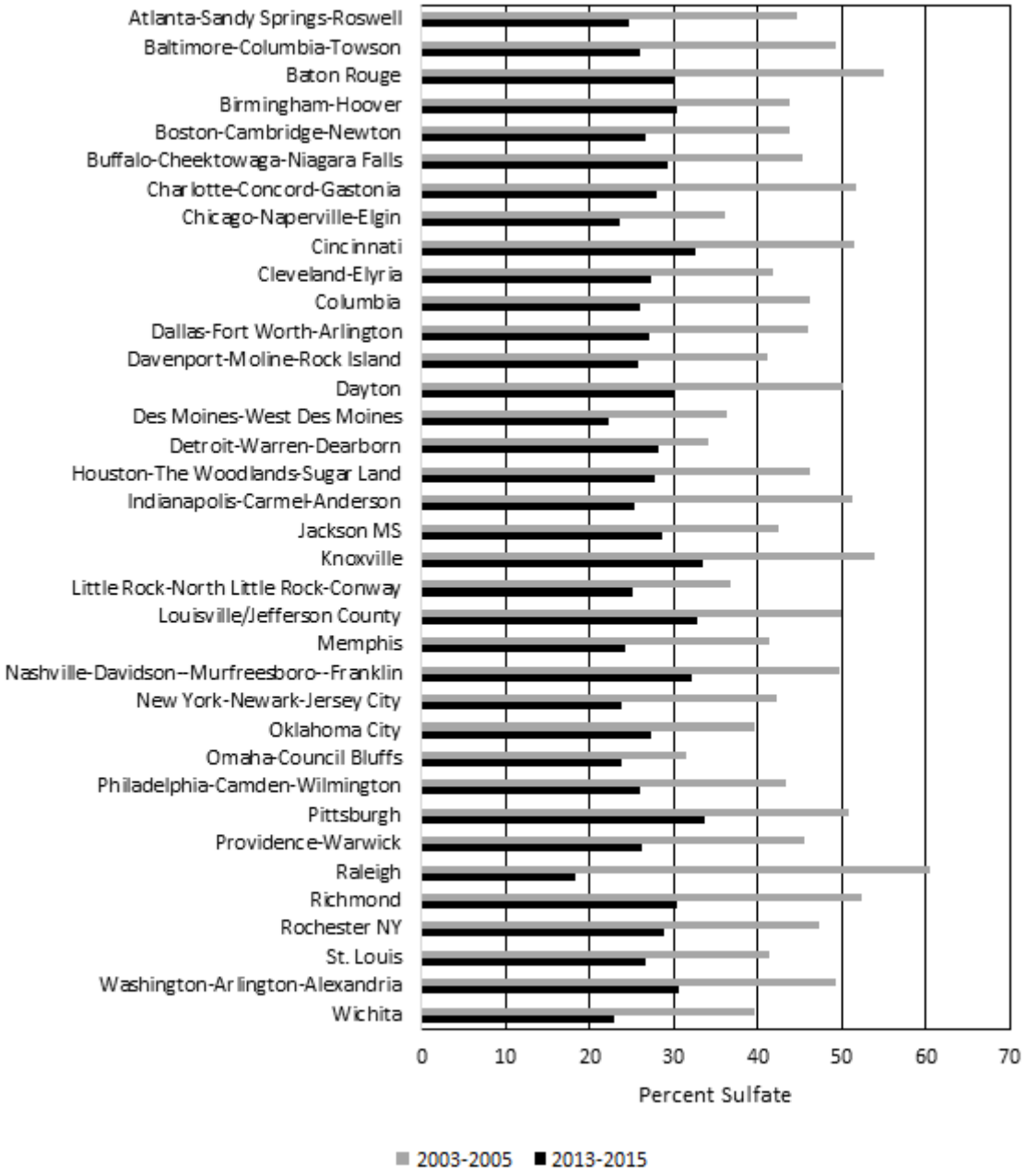
In this section the information on sources, particle size distribution and composition from recent research results and monitoring data are combined to describe common patterns of PM characteristics observed in the U.S. across different regional and seasonal conditions. Historically, $PM_{2.5}$ has been highest in the summer and has been largely accounted for by sulfate over a large area that encompasses most of the Eastern U.S., extending into the Great Plains. Figure 2-33 shows how sulfate concentrations have changed in major urban areas of the Eastern U.S. between 2003−2005 and 2013−2015 based on CSN monitors. At all of the locations shown in Figure 2-33 sulfate was the most abundant component measured for the period 2003−2005, accounting for close to half of the overall average $PM_{2.5}$ mass. In contrast, during the period 2013−2015 sulfate accounted for only about a quarter or a third of $PM_{2.5}$ mass.

For example, the sulfate fraction dropped from 49 to 31% in Washington DC, 51 to 34% in Pittsburgh, 42 to 24% in New York, 43 to 26% in Philadelphia, 44 to 27% in Boston, and 52 to 33% in Cincinnati. In all but five of these locations, mostly in Ohio or the Ohio Valley (Cleveland, Cincinnati, and Dayton, OH, Louisville, KY, Dallas, TX), OC has replaced sulfate as the most abundant component, although OC and sulfate concentrations are very similar in most locations, as shown in Figure 2-31.

In the Eastern half of the U.S., the steep decline in sulfate concentrations has led to major changes in PM composition, seasonal concentration patterns, and size characteristics since publication of the 2009 PM ISA (U.S. EPA, 2009). PM_{10} concentrations in the Eastern U.S. and Midwest previously peaked in summer and was mostly composed of $PM_{2.5}$, with sulfate as the largest single component. More recently, summer concentrations are similar to other seasons, the $PM_{10-2.5}$ and $PM_{2.5}$ fractions are often comparable, and OC is frequently the most abundant single component.

Some finer scale trends within the Eastern U.S. are evident. While OC is becoming the component with the highest concentration throughout the Eastern U.S., in the Southeast annual average OC concentrations are somewhat higher than in the Northeast or Midwest, reaching their highest monitoring concentrations in a large area encompassing most of Alabama, Georgia, and South Carolina (Hand et al., 2011). The origin of summer OC in the Southeast has been intensively studied and is largely SOA due to oxidation of biogenic precursors (Marais et al., 2017; Rattanavaraha et al., 2016; Lewandowski et al., 2013), and urban areas of the Southeast like Atlanta have considerably more biogenic VOC precursors than urban areas of the Northeastern U.S. like New York City (Weber et al., 2007). Integrated modeling and measurement results (Kim et al., 2015), modeling predictions (Marais et al., 2017; Ying et al., 2015), and product concentration measurements (Lewandowski et al., 2013) are also consistent with higher OC concentrations and biogenic SOA at Southeastern sites than in the Northeast or Midwest. OC concentrations in the Southeast are decreasing (Marais et al., 2017).

Another area in the Eastern half of the U.S. stretching from Minnesota and Iowa through Wisconsin, Michigan, Indiana, and Ohio comprises as a region susceptible to high winter nitrate episodes resulting from high emissions of ammonia from animal agriculture combining with atmospheric nitric acid, that lead to mean winter ammonium nitrate concentrations exceeding 4 $\mu g/m^3$ (Pitchford et al., 2009). This region can be distinguished in Figure 2-31 for 2012−2014 by winter nitrate contributions of more than 40% to seasonal average $PM_{2.5}$ mass in Chicago, IL, Minneapolis, MN, Milwaukee, WI, Detroit and Grand Rapids, MI, Indianapolis, IN, Cincinnati and Dayton, OH, Davenport and Des Moines, IA, Omaha, NE, Kansas City, MO and at several other sites in the upper Midwest.



Source Permission pending: U.S. EPA 2016 analysis of Air Quality System network data 2003−2005 and 2013−2015.

Figure 2-33 Sulfate as percentage of $PM_{2.5}$ in eastern urban areas 2003−2005 and 2013−2015.

While substantial differences in PM size distribution, composition, and other characteristics have been reported between the Eastern and Western U.S. (U.S. EPA, 2009), the diversity of PM characteristics across the West makes it more difficult to identify a set of fundamental PM characteristics that applies to the entire region. In interior urban areas, including Salt Lake City, UT, Reno, NV, Boise, ID, Missoula, MT, and Spokane, WA, $PM_{2.5}$ levels are higher under stable conditions on days with snow cover. In Salt Lake City, UT, Reno, NV, and Missoula, MT, most of the highest concentrations were observed on days with high nitrate concentrations enhanced by colder temperatures and higher relative humidity that occur with snow cover (Green et al., 2015). After multiday periods with stable conditions created by snow cover, $PM_{2.5}$ can build up rapidly in layers or in cold air pools. In one case in Salt Lake City $PM_{2.5}$ concentrations increased by 6 to 10 $\mu g/m^3$ per day over a period of several days (Whiteman et al., 2014; Silcox et al., 2011). This area is also subject to episodically high $PM_{10-2.5}$ concentrations from dust suspension.

Closer to the coast, high PM episodes cannot be explained by snow cover and extreme cold, yet some of the highest $PM_{2.5}$ concentrations in Figure 2-13 and Figure 2-14 are in California and concentrations are also highest in winter. In many California locations, a specific combination of conditions appears to be responsible for the highest PM concentrations. High winter $PM_{2.5}$ concentrations were studied intensively over 12 winters and the existence of several simultaneous conditions for at least 2 days duration were required for concentrations to exceed 35 $\mu g/m^3$, including a ridge of high pressure aloft, persistent easterly flow extending up vertically, orographically channeled winds resulting from stability, and enhanced nocturnal cooling under clear sky conditions (Beaver et al., 2010). Ammonium nitrate and organic PM from diverse combustion sources are the main contributors to $PM_{2.5}$ under winter conditions in California (Young et al., 2016; Zhang et al., 2016; Schiferl et al., 2014). Some of the highest 98th percentile concentrations were reported in California and other monitoring sites in the Western U.S. in Section 2.5.1.1.1 (Figure 2-14).

A common characteristic of PM in both California and the dryer areas of the Western U.S. that contrasts with the Eastern U.S. is the higher fraction of PM_{10} accounted for by $PM_{10-2.5}$, with $PM_{10-2.5}$ accounting for most PM_{10} mass in the West, but $PM_{2.5}$ accounting for most PM_{10} mass in the East (see Table 2-7). Populated areas of the Northwest (Western Oregon and Washington) make an exception to this trend. Table 2-7 shows that in both Seattle, WA and Portland, OR, $PM_{2.5}$ accounts for more than 50% of the PM_{10} mass and concentrations are higher in winter than in summer. Wood smoke is a major source of $PM_{2.5}$ in Portland, OR and Seattle, WA (Kotchenruther, 2016; U.S. EPA, 2009), as well as in smaller urban areas in this region.

$PM_{2.5}$ concentrations averaged over the 11-year period from 1998−2008 over the entire contiguous U.S. were reported to be 2.6 $\mu g/m^3$ higher on days under stagnant conditions than for non-stagnant days (Tai et al., 2010). When all U.S. data over a multiyear period are considered, temperature is positively correlated with $PM_{2.5}$ (Tai et al., 2012a; Tai et al., 2012b), especially in the Eastern U.S. (Tai et al., 2012a). Much of $PM_{2.5}$ variability could be explained by cold frontal passages in the East, maritime

inflow in the West, and cyclone frequency in the Midwest (Tai et al., 2012b). Other meteorological conditions that have been reported to enhance PM concentrations include sea breezes (Georgoulias et al., 2009) and drought (Wang et al., 2015).

2.5.4 Background Particulate Matter

The definition of background PM can vary depending upon context, but it generally refers to PM that is formed by sources or processes that cannot be influenced by actions within the jurisdiction of concern. Consistent with other recent NAAQS reviews (U.S. EPA, 2014); U.S. EPA, 2015, 4679035}, there are two specific definitions of background PM of interest: natural background and U.S. background. Natural background is the narrowest definition of background, and it is defined as the PM that would exist in the absence of any manmade emissions of PM or PM precursors. U.S. background PM is defined as any PM formed from sources or processes other than U.S. manmade emissions. Approaches to estimating background PM have evolved over the years. Different approaches for estimating background concentrations in the western and eastern U.S. were taken in the 2004 PM AQCD (U.S. EPA, 2004). Data from IMPROVE monitoring sites in the western U.S. thought to be among the least influenced by regional pollution sources exhibited annual mean concentrations of ~3 $\mu g/m^3$. However, even the most remote monitors within the U.S. can be periodically affected by U.S. anthropogenic emissions, and concentrations observed at the most remote sites in the Eastern U.S. were considerably higher than in the western U.S. In the 2009 ISA (U.S. EPA, 2009), estimates of background concentrations were calculated by CMAQ and classified by region and quarter. All quarterly and annual estimates were less than 2 $\mu g/m^3$, with many <1 $\mu g/m^3$. However, episodic contributions from dust storms or wildfires can be much higher. Further details are given by (U.S. EPA, 2009).

As illustrated by this example, background PM concentrations can be best characterized with chemical transport modeling simulations via source apportionment modeling or estimating what the residual PM concentrations would be were the U.S. anthropogenic emissions entirely removed (i.e., "zero-out" modeling). Unfortunately, there has not been a similar national scale effort to update background $PM_{2.5}$ concentration estimates since the 2009 PM ISA. However, there has been considerable research focused on better understanding the sources and processes that influence background contribution to $PM_{2.5}$ in the U.S.

Background contributions to PM can come from a variety of sources. Natural sources include wind erosion of natural surfaces, volcanic production of SO_4^{2-}; primary biological aerosol particles (PBAP); wildfires producing EC, OC, and inorganic and organic PM precursors; and SOA produced by oxidation of biogenic hydrocarbons such as isoprene and terpenes (U.S. EPA, 2009). However, human intervention can be involved in the formation of SOA. For example, the production of SOA from the oxidation products of isoprene and other biogenic VOC's can be enhanced by the presence of SO_2, NO_X, and other anthropogenic pollutants, accounting for as much 50% of SOA from biogenic VOC's

(Section 2.3.2.3). Other sources of background PM are anthropogenic, principally emissions from outside the U.S. which can be transported into the U.S. The importance of different contributors to background PM varies across the contiguous U.S. (CONUS) by region and season as a function of the complex mechanisms of transport, dispersion, deposition, and re-entrainment.

Background PM can also be viewed as coming from two conceptually separate components: a somewhat consistent "baseline" component and an episodic component. The baseline component consists of contributions that are generally well characterized by a reasonably consistent distribution of daily values each year, although there is variability by region and season. The episodic component consists of infrequent, sporadic contributions from high-concentration events occurring over shorter periods of time (e.g., hours to several days) both within North America (e.g., volcanic eruptions, large forest fires, dust storms) and outside North America (e.g., transport from dust storms occurring in deserts in North Africa and China). These episodic natural events, as well as events like the uncontrolled biomass burning in Central America, are essentially uncontrollable and do not necessarily occur in all years. Section 2.5.4.1 and Section 2.5.4.2 below discuss natural background and intercontinental transport contributions to background PM in the U.S.

2.5.4.1 Natural Background

On average, natural sources including soil dust and sea salt have been estimated to account for approximately 10% of U.S. urban $PM_{2.5}$ (Karagulian et al., 2015). Dust storms are common occurrences in arid regions of the U.S. and the rest of the world. An extreme example is the haboob. During one of these affecting Phoenix in July of 2011, peak hourly average PM_{10} concentrations were >5,000 $\mu g/m^3$ with area wide average hourly concentrations ranging from a few hundred to a few thousand $\mu g/m^3$ (Vukovic et al., 2014). Dust can also make up a substantial fraction of total $PM_{2.5}$ in the Southwestern U.S. This is illustrated in Figure 2-19 (Section 2.5.1.1.6), which shows that at many locations in the Southwestern U.S., crustal material from soil accounts for close to half of the annual average $PM_{2.5}$ mass. Although similar network data do not exist for $PM_{10-2.5}$, the soil contribution to $PM_{10-2.5}$ mass in these locations is likely to be even higher. Dust also accounts for much of the PM that originates from outside the U.S. (Section 2.5.4.2).

Wildfires are a variable contributor to particulate matter emissions. Satellite-based fire detections are combined with ground-based estimates of area burned, fuel availability, and emission factors to quantify PM and precursor emissions at high spatial and temporal resolution (Strand et al., 2012). The gas-phase species emitted from fires can affect oxidation and formation of semivolatile compounds that can condense into the particle phase (Baker et al., 2016). Invasive species, historical fire management practices, frequency of drought, and extreme heat have brought longer fire seasons (Jolly et al., 2015) and more large fires (Dennison et al., 2014). In addition to emissions from forest fires in the U.S., emissions from forest fires in other countries can be transported to the U.S., and transport from Canada, Mexico,

Central America, and Siberia have been documented (U.S. EPA, 2009). According to the U.S. EPA's National Emission Inventory, wildfire smoke contributes between 10 and 20% of primary PM emissions per year (Section 2.3.1), however these emissions are concentrated at the burn area and mostly during the wildfire season, rather than evenly distributed through the year (Sturtz et al., 2014).

Primary biological aerosol particles (PBAP) such as bacteria and pollen can also contribute substantially to $PM_{10-2.5}$ mass in some locations. These are discussed in more detail in Section 2.3.3.

2.5.4.2 Intercontinental Transport

Intercontinental transport contributes 0.05 to 0.15 $\mu g/m^3$ to annual average $PM_{2.5}$ concentrations in the U.S. (Kolb et al., 2010). Large continuous data sets are available to examine the intensity and frequency of intercontinental PM transport events. Ground-based lidar networks and mountain top measurements in Europe, North America, and Asia have been used to establish that intercontinental transport of PM from dust, forest fires, and anthropogenic sources impact local $PM_{2.5}$ and PM_{10} concentrations. Satellites also provide estimates of the amount of PM transported, as well as the altitude at which the transport occurs. Transport at midlatitudes is dominated by westerly winds, which transport East Asian emissions across the North Pacific Ocean to North America. Transport occurs at greater speeds and over longer distances in winter than in summer because the westerly winds are stronger, and greater precipitation in winter in the Western U.S. brings more of the transported PM to the surface. Numerous studies have now documented long-range transport of desert dust from East Asian deserts. Both the frequency of transport events and the overall contribution to PM in the U.S. are reported to be increasing (Kolb et al., 2010; TFHTAP, 2006). By one estimate, 18 Tg/year PM exits Asia between 30 to 60 degrees N latitude, with 4.4 Tg/yr arriving in North America (Yu et al., 2008).

Episodic concentrations as high as 20 $\mu g/m^3$ of PM associated with transport to the U.S. from Asia have been estimated (Jaffe et al., 2005), and $PM_{2.5}$ from Asia has been shown to account for a large fraction total $PM_{2.5}$ in polluted urban air (Jaffe et al., 2003). Over longer time periods, long range transport can make a substantial contribution to local PM concentrations in remote areas like the Arctic. However, in regions with local sources, observed trends in PM are usually more closely related to local emission trends than to long-range transport, and at monitoring sites throughout the U.S. intercontinental influences are small (Henze et al., 2009).

On average, Asian dust contributes typically <~1 $\mu g/m^3$ to $PM_{2.5}$ at remote sites in western states (Creamean et al., 2014). However, transport of Asian dust shows both strong seasonal and interannual variability. Dust emissions are at a maximum in spring, associated with strong winds following cold fronts as the Siberian High extends southward and before there is sufficient vegetation to stabilize the surface. Based on inverse modeling of Asian dust over the period 2005−2012, Yumimoto and Takemura (2015) suggested that dust emissions, transport and deposition are largest during the La Niña phase of the El Niño-Southern Oscillation cycle. They also found that dust emissions were closely related to a strong

meridional pressure gradient and a strong winter monsoon. Husar et al. (2001) report that the average PM_{10} concentration at 25 reporting stations throughout the northwestern U.S. reached 65 μg/m^3 during an episode of Asian dust transport during the last week of April 1998, compared to an average of 10−25 μg/m^3 during the rest of April and May. This was accompanied by visual reports of milky-white discoloration of the normally blue sky in nonurban areas along the West Coast. Satellite data have been especially useful for tracking the trans-Pacific transport of Asian dust. Uno et al. (2011) documented the occurrence of multiple large plumes of Asian dust in April of 2010 that had passed over most of the continental U.S. based on space-borne lidar (the Cloud-Aerosol Lidar with orthogonal Polarization) on board the CALIPSO satellite. Three-dimensional, global-scale CTMs have also been used to estimate intercontinental transport of PM pollution (TFHTAP, 2007) and trans-Pacific transport of mineral dust from Asian deserts (Fairlie et al., 2007).

Transport of dust from the Sahara Desert and the Sahel in North Africa (Prospero, 1999a, b), (Chiapello et al., 2005), (Mckendry et al., 2007) can affect the eastern U.S., while transport of dust from the Gobi and Taklimikan deserts in Asia (Vancuren and Cahill, 2002), (Yu et al., 2008) can exert effects in the western U.S. The ability of African dust to substantively affect PM levels in the U.S. was extensively reviewed in the 2004 PM AQCD (U.S. EPA, 2004) and in the 2009 PM ISA (U.S. EPA, 2009). A multidecade record of African dust reaching Miami indicates that the highest loadings are found in July (Prospero, 1999a, b) with concentrations ranging from ~10 to ~100 μg/m^3. Sample collection began in 1974, before network PM_{10} and $PM_{2.5}$ samplers were developed, and no size cut was specified (Prospero, 1999b). Yu et al. (2015) found that the transport of North African dust across the Atlantic Ocean is strongly negatively correlated with precipitation in the Sahel during preceding year. Dust from Africa has shown a decreasing trend of ~ 10% per decade from 1982 to 2008, based on measurements of aerosol optical depth and surface concentrations in Barbados by Ridley et al. (2014), who also suggest that this decrease is due to a corresponding decrease in surface winds over source regions.

In addition to desert dust, a portion of the PM reaching the U.S. through intercontinental transport is from combustion and industrial sources, and formation of sulfate from SO_2 during transport of air masses to the U.S. from Asia is also well documented. In the Spring in the Northwestern U.S., transport from Asia accounted for 0.16 ± 0.08 μg/m^3 $PM_{2.5}$ sulfate (Heald et al., 2006). Sulfate of Asian origin can account for a large fraction of sulfate in the upper troposphere in western North America, and an increasing fraction of sulfate measured off the northwest coast of the U.S. is of Asian origin. Measurements from an event over the Pacific Ocean were consistent with nearly pure sulfuric acid. Transboundary transport within North America can also be important. Model results suggest that SO_2 emissions in Mexico influence sulfate formation in the U.S. (Henze et al., 2009). Leibensperger et al. (2011) estimated that trans-Pacific transport of SO_2 and NO_X results in a combined increase in background PM[40] in the western U.S. of a few tenths of a μg/m^3.

2.6 Summary

New observations indicate that some fundamental characteristics of atmospheric PM in the U.S. are changing. These range from source emissions and atmospheric formation processes to size distributions, particle composition, and spatial and temporal concentration trends. The most noticeable change in PM or precursor source emissions is the large reduction in SO_2 emissions, mainly from decreased EGU coal combustion. In addition, advances in engine and emissions control technologies have led to continued decreases in automobile emissions. The major urban stationary sources of PM are still industrial processes, construction and road dust, residential wood burning and other fuel combustion, and cooking. The major primary mobile sources are still diesel and gasoline powered highway vehicles as well as off-road vehicles and engines like locomotives, ships, aircraft, and construction and agricultural equipment. $PM_{2.5}$ particles from combustion sources are usually emitted as UFP and grow into larger particles after emission. Secondary $PM_{2.5}$ still accounts for a substantial fraction of the $PM_{2.5}$ mass from both natural and anthropogenic sources (U.S. EPA, 2009). Major $PM_{10–2.5}$ sources are dust suspension, sea spray, and biological materials. Automobile traffic, other combustion sources, and new particle formation are major UFP sources.

Research on atmospheric chemistry has largely focused on better understanding OC sources and SOA formation pathways. Progress in understanding SOA precursors centered on model results of large fractions of SOA from aromatic and monoterpene precursors, observations of gas phase VOC oxidation products continuing to react to form PM, and the discovery of isoprene as a major SOA precursor. Progress related to understanding SOA formation processes was directed toward evidence of cloud processing as well as repeated cycles of volatilization and condensation of semivolatile reaction products as important processes for SOA evolution, investigation of misclassification of SOA as primary organic

[40] PM size was not specified, but secondary PM formed from NO_X and SO_2 is usually nearly all in the $PM_{2.5}$ size range.

aerosol under typical sampling conditions, and observations of greater SOA yields at high NO_X concentrations. Progress in understanding SOA products involved identification of higher molecular weight particle phase oligomers and organic peroxides as an abundant class of reactive oxygen species (ROS) with high oxidizing potential in SOA, as well as observations of abundant organosulfates and organonitrates in SOA.

Major developments in PM monitoring and monitoring capabilities have taken place, and these have had an important impact on our understanding of PM characteristics. For example, before the availability of network data, the 2009 PM ISA was based on literature results and concluded that $PM_{10-2.5}$ concentrations were higher in the Western U.S. than in the Eastern U.S. (U.S. EPA, 2009). The NCore network was implemented in 2011 and now produces multipollutant concentration and data at 78 stations throughout the U.S. Through NCore, more reliable data on $PM_{10-2.5}$ concentrations are available than were possible before. The first years of NCore data reveal a more complicated concentration pattern than a simple East-West split, with the highest $PM_{10-2.5}$ concentrations observed in the Southwest from California to Texas, and in the Central U.S. from Texas and Louisiana as far north as Nebraska and Iowa. In contrast, there are large areas in the Northwest where average $PM_{10-2.5}$ concentrations and $PM_{2.5}/PM_{10}$ are similar to the Eastern U.S. Rapid advances are taking place in UFP measurement technology, but measurements are more method dependent and network monitoring is in its beginning stages. Network monitoring of $PM_{2.5}$ has expanded to include numerous near road monitoring sites.

Annual mean ambient $PM_{2.5}$ concentrations in the U.S. on average are 4−5 $\mu g/m^3$ lower than they were in the last decade, continuing a downward trend described in the 2009 PM ISA (U.S. EPA, 2009). $PM_{2.5}$ concentrations are highest in the San Joaquin Valley, the Los Angeles-South Coast Air Basin of California, and parts of Utah. In the Eastern U.S. there is a region of higher $PM_{2.5}$ concentrations with annual average concentrations greater than 10 $\mu g/m^3$ stretching from Eastern Iowa and Northern Illinois across Indiana, Ohio, and into to Eastern Pennsylvania. While monthly national average $PM_{2.5}$ concentrations were higher in summer than in winter from 2002−2008, this pattern is reversed from 2012−2015, when monthly average $PM_{2.5}$ concentrations become higher in winter than in summer. Summer $PM_{10-2.5}$ concentrations are generally higher than other seasons, but extreme $PM_{10-2.5}$ events appear to be more likely in the spring. PM_{10} reflects characteristic concentration patterns of both $PM_{10-2.5}$ and $PM_{2.5}$, with the highest concentrations in summer. The decrease in $PM_{2.5}$ concentrations has resulted in smaller $PM_{2.5}/PM_{10}$ ratios, and PM_{10} in the East and Northwest is in the range of 50−60% $PM_{2.5}$, while PM_{10} in the Western U.S. is generally less than 50% $PM_{2.5}$. On urban and neighborhood scales, both spatial and temporal variations are strongly influenced by motor vehicle emissions, with the highest $PM_{2.5}$ and UFP concentrations at rush hour, and the highest concentrations of $PM_{10-2.5}$, UFP, and many $PM_{2.5}$ components near roads with heavy traffic.

Recent changes in $PM_{2.5}$ long-term and seasonal concentration trends are consistent with observed changes in $PM_{2.5}$ composition compared to the 2009 PM ISA (U.S. EPA, 2009), the greatest of which is the reduction in sulfate concentrations, resulting in a smaller sulfate contribution to $PM_{2.5}$ mass

in 2013−2015 than in the last decade, especially in the Eastern U.S. As a result, at many locations sulfate has been replaced as the greatest single contributor to $PM_{2.5}$ mass by organic matter. Sulfate and OC are the components with the highest contribution to total mass in most eastern locations and OC usually makes the greatest contribution to $PM_{2.5}$ mass in the west, although sulfate, nitrate, and crustal material can also be abundant. The highest nitrate concentrations are found in the west, particularly in California, but with some elevated concentrations in the upper Midwest. Ammonium concentrations follow both nitrate and sulfate spatial patterns because it is mostly present as ammonium sulfate and ammonium nitrate. Larger contributions of OC to $PM_{2.5}$ mass are observed in the Southeast and the West than in the Central and Northeastern U.S. A large fraction of organic PM can be water soluble. Crustal elements and biological material account for large fraction of $PM_{10-2.5}$ mass. There is still little information on the composition of UFP, but urban UFP is often rich in OC and EC.

Background PM originates from natural and international sources. Natural sources include windblown dust, wildfires, and sea salt. International contributions include intercontinental transport of dust, wildfire smoke, and pollution as well as transboundary transport of these contributors from Canada, Mexico. Background PM usually makes a relatively small contribution to urban annual average $PM_{2.5}$ concentrations. However, it is an important contributor to $PM_{2.5}$ concentrations in the southwestern U.S., and impacts $PM_{2.5}$ concentrations elsewhere on an episodic basis. Background contributions to $PM_{10-2.5}$ can be substantial, as it is generally dominated by dust and sea salt. Less is known about background contributions to UFP.

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CHAPTER 3 EXPOSURE TO AMBIENT PARTICULATE MATTER

Overall Conclusions regarding Exposure to Ambient PM

- Recent and existing evidence indicate that exposure error typically produces *underestimation* of health effects in epidemiologic studies of short-term and long-term PM exposure. Bias away from the null can sometimes occur for long-term exposure studies if a monitor or model underestimates population exposure.
- New developments in PM exposure assessment methods, including hybrid spatiotemporal models that incorporate satellite observations of AOD, land use variables, surface monitoring data from FRMs, and/or CTMs, have reduced bias and uncertainty in health effect estimates by improving the spatial resolution and accuracy of exposure predictions.
- High correlations of $PM_{2.5}$ with some gaseous copollutants necessitate evaluation of the impact of confounding on health effect estimates.
- There is typically more uncertainty for health effect estimates for exposure to $PM_{10–2.5}$ and UFP, because their concentrations tend to be more spatially variable than $PM_{2.5}$ concentrations and concentration data for $PM_{10–2.5}$ and UFP are less frequently available and/or more uncertain.

3.1 Introduction

Assessment of exposure to ambient PM builds from the characterization of concentrations and atmospheric chemistry presented in CHAPTER 2. The primary conclusions from CHAPTER 2 were that $PM_{2.5}$ concentrations continue to decrease over time with few areas exceeding the level of the current NAAQS, sulfates comprise a smaller proportion of total $PM_{2.5}$ throughout the country including in the eastern half of the country, $PM_{10–2.5}$ contributes most substantially to PM_{10} in the southwestern U.S. but is highly variable across urban areas, and substantial uncertainty still exists regarding UFP sources, composition, and concentrations.

This chapter presents new developments in exposure assessment methodology and interpretation of epidemiological study results given strengths and limitations of the exposure assessment data. The chapter describes concepts and terminology relating to exposure (Section 3.2), methodological considerations for use of exposure data (Section 3.3), and exposure assessment and interpretation of epidemiologic study results (Section 3.4). This chapter focuses on the ambient component of personal exposure to PM, because the NAAQS pertains to ambient PM. However, studies using total personal PM measurements or indoor PM concentrations to represent exposure can also inform the understanding of the relationship between exposure and health effects and so are included as supporting evidence if ambient PM exposure can be deduced from the information provided in the studies. This chapter focuses on studies of exposure among the general population. Exposure of groups potentially at increased risk of PM-related health effects, based for example on socioeconomic status and race, is addressed in CHAPTER 12. Intake of PM based on ventilation rate, and in relation to physical activity, is described in CHAPTER 4. The information provided in this chapter will be used to help interpret the evidence for the

health effects of PM exposure presented in the health chapters that follow (CHAPTER 5, CHAPTER 6, CHAPTER 7, CHAPTER 8, CHAPTER 9, CHAPTER 10, and CHAPTER 11).

3.2 Conceptual Overview of Human Exposure

The 2009 PM ISA (U.S. EPA, 2009b) provided a conceptual model of exposure to form a distinction between ambient PM exposure and total personal exposure. This section illustrated that exposure is integrated over time and across the microenvironments in which a person spends time. This section also introduced the concept of an infiltration factor that depends on both penetration of PM indoors and the ventilation and deposition characteristics that influence indoor PM concentration. That discussion is currently updated and presented in Section 3.2.2.

This ISA contains two new sections to orient the reader to concepts relevant to exposure. Section 3.2.1 introduces terminology that is used throughout the chapter when describing exposure assessment studies. Section 3.2.3 highlights facets of exposure assessment that are particularly relevant to PM.

3.2.1 Exposure Terminology

A variety of metrics and terms are used to characterize air pollution exposure. They are described here at the beginning of the chapter to provide clarity for the subsequent discussion.

The *concentration* of PM is defined as the mass of the pollutant in a given volume of air (e.g., $\mu g/m^3$). Concentrations observed in outdoor locations accessible to the public are referred to as ambient concentrations. The term exposure refers to contact at the interface of the breathing zone with the ambient concentration of a specific pollutant over a certain period of time (Zartarian et al., 2005), in single or multiple locations. For example, contact with a concentration of 10 $\mu g/m^3$ $PM_{2.5}$ for 1-hour would be referred to as a 1-hour exposure to 10 $\mu g/m^3$ $PM_{2.5}$, and 10 $\mu g/m^3$ is referred to as the *exposure concentration*. As discussed in CHAPTER 4, dose incorporates the concept of intake into the body (via inhalation).

A location where exposure occurs is referred to as a *microenvironment*, and an individual's daily exposure consists of the time-integrated concentrations in each of the microenvironments visited during the day. Ambient air pollution may penetrate indoors (see Section 3.4.1.1 on infiltration), where it combines with air pollution from indoor sources (*nonambient air pollution*) to produce the total measured indoor concentration. Exposure to the ambient fraction of total indoor concentration, together with exposure to ambient concentrations in outdoor microenvironments such as parks, yards, sidewalks, and bicycles or motorcycles, is referred to as ambient exposure (Wilson et al., 2000). *Total personal exposure to ambient PM* is the concentration of PM emitted from ambient sources or formed in the atmosphere that

is encountered by an individual over a given time. This differs from overall total personal exposure, which may also include exposure to nonambient air pollution. Personal exposure to ambient PM is influenced by several factors, including:

- Time-activity in different microenvironments (e.g., vehicle, residence, workplace, outdoor);
- climate (e.g., weather, season);
- characteristics of indoor microenvironments (e.g., window openings, draftiness, air conditioning); and
- microenvironmental emission sources (e.g., roadways, construction equipment, indoor gas stoves) and concentrations.

Because personal exposures are not routinely measured, the term *exposure surrogate* is used in this chapter to describe a quantity meant to estimate or represent exposure, such as $PM_{2.5}$ concentration measured at an ambient monitor (Sarnat et al., 2000). A *fixed-site monitor* (i.e., a monitor with a fixed position) is a type of *ambient monitor* used to estimate population average exposure concentrations and their trends over neighborhood- and urban-scales for epidemiologic studies.

When surrogates are used for exposure estimation in epidemiologic studies, exposure error or exposure misclassification can result. *Exposure error* refers to the bias and uncertainty associated with using concentration metrics to represent the actual exposure of an individual or population (Lipfert and Wyzga, 1996). Exposure misclassification refers to exposure error that occurs when exposure conditions such as location, timing, or population grouping are incorrectly assigned. *Exposure misclassification* due to exposure assignment methods and spatial and temporal variability in pollutant concentrations may be either differential (i.e., systematic), or nondifferential (i.e., random). *Differential misclassification* refers to the situation where exposure errors differ between groups. An example of differential misclassification is the use of geocoding to estimate air pollution exposure by proximity to roadways, because concentrations decrease with distance from roadways and are different upwind and downwind of a major roadway (Lane et al., 2013; Singer et al., 2004). *Nondifferential misclassification* refers to the situation where exposure characterization has the same probability of being misclassified to a similar degree across all groups.

Exposure misclassification and exposure error can result in bias and reduced precision of the effect estimate in epidemiologic studies. *Bias* refers to the difference between the population-average measured and true exposure, while precision is a measure of the variation of measurement error in the population (Armstrong et al., 1992). Bias toward the null, or attenuation of the effect estimate, indicates an underestimate of the magnitude of the effect, and is characteristic of nondifferential measurement error. Bias away from the null can occur through differential exposure measurement error, such as may occur when an exposed person or group of people are located far from a source that is captured by a fixed-site monitor (Armstrong et al., 1992).

Exposure error has two components: (1) exposure measurement error derived from uncertainty in the metric being used to represent exposure and (2) use of a surrogate parameter of interest in the epidemiologic study in lieu of the true exposure, which may be unobservable. *Classical error* is defined as error scattered around the true personal exposure and independent of the measured exposure. Classical error results in bias of the epidemiologic health effect estimate. Because variation in the measurements tends to be greater than variation in the true exposures, classical error typically biases the health effect estimate towards the null (no effect of the exposure). This would cause the health effect estimate to be underestimated. Classical error can also cause inflation or reduction of the standard error of the health effect estimate. For example, classical error may occur when a fixed-site monitor measuring exposure concentration is imprecise. *Berkson error* is defined as error scattered around the measured exposure surrogate (in most cases, the ambient monitoring measurement) and independent of the true exposure (Goldman et al., 2011; Reeves et al., 1998). Pure Berkson error is not expected to bias the health effect estimate. Berkson error tends not to cause bias in the health effect estimate. For example, Berkson error may occur when personal monitors used in a panel study capture ambient and nonambient exposures, if the objective of the study is to evaluate the effect of ambient exposures on health and the ambient and nonambient exposures are independent of each other.

Definitions for *classical-like* and *Berkson-like errors* were developed for modeled exposures. These errors depend on how exposure metrics are averaged across space. Classical-like errors can add variability to predicted exposures and can bias health effect estimates in a manner similar to pure classical errors, but they differ from pure classical errors in that the variability in estimated exposures is also not independent across space. Szpiro et al. (2011a) defined Berkson-like and classical-like errors as errors sharing some characteristics with Berkson and classical errors, respectively, but with some differences. Specifically, Berkson-like errors occur when the modeled exposure does not capture all of the variability in the true exposure. Berkson-like errors increase the variability around the health effect estimate in a manner similar to pure Berkson error, but Berkson-like errors are spatially correlated and not independent of predicted exposures, unlike pure Berkson errors. Berkson-like error can lead to bias of the health effect estimate in either direction (Szpiro and Paciorek, 2013).

The influence of these types of exposure errors on health effect estimates for specific short-term and long-term exposure study designs is evaluated in Section 3.4.5. This review of the influence of error on exposure estimates used in epidemiology studies informs evaluation of confounding and other biases and uncertainties when considering the health effects evidence in CHAPTER 5, CHAPTER 6, CHAPTER 7, CHAPTER 8, CHAPTER 9, CHAPTER 10, and CHAPTER 11.

3.2.2 Conceptual Model of Total Personal Exposure

A conceptual model of personal exposure is presented to highlight measurable quantities and the uncertainties that exist in this framework. An individual's time-integrated total exposure to PM can be described based on a compartmentalization of the person's activities throughout a given time period:

$$E_T = \int_1^n C_j dt$$

Equation 3-1

where E_T = total exposure over a time-period of interest, C_j = airborne PM concentration at microenvironment *j,* n = total number of microenvironments, and dt = portion of the time-period spent in microenvironment *j.* Total exposure (E_T) can be decomposed into a model that accounts for exposure to PM of ambient (E_a) and nonambient (E_{na}) origin of the form:

$$E_T = E_a + E_{na}$$

Equation 3-2

Indoor combustion, such as cooking, smoking, or candle burning, as well as cleaning, and other activities are nonambient sources of PM (see Section 3.4.1.2, indoor-outdoor [I/O] relationships on indoor PM) that are specific to individuals and result in variable nonambient exposures across the population. Assuming steady-state outdoor conditions, E_a can be expressed in terms of the fraction of time spent in various outdoor and indoor microenvironments (U.S. EPA, 2006; Wilson et al., 2000):

$$E_a = \Sigma f_o C_o + \Sigma f_i F_{inf,i} C_{o,i}$$

Equation 3-3

where f_o = fraction of the relevant time period (equivalent to dt in Equation 3-1) in outdoor microenvironments; f_i = fraction of the relevant time period (equivalent to dt in Equation 3-1) in indoor microenvironments; C_o = PM concentration in outdoor microenvironments; $C_{o,I}$ = PM concentration in outdoor microenvironments adjacent to an indoor microenvironment *i*; and $F_{inf,i}$ = infiltration factor for indoor microenvironment *i*. Equation 3-3 is subject to the constraint $\Sigma_{fo} + \Sigma_{fi} = 1$ to reflect the total exposure over a specified time period, and each term on the right hand side of the equation has a summation because it reflects various microenvironmental exposures. Here, "indoors" refers to being inside any aspect of the built environment, [e.g., homes, schools, office buildings, enclosed vehicles (automobiles, trains, buses), and/or recreational facilities (movie theaters, restaurants, bars)], while "outdoors" refers to outdoor microenvironments (e.g., parks, yards, sidewalks, and bicycles or motorcycles). Assuming steady state ventilation conditions, the infiltration factor (F_{inf}) is a function of the penetration (P) of PM into the microenvironment, the air exchange rate (a) of the microenvironment, and the rate of PM loss (k) in the microenvironment:

$$F_{inf} = \frac{Pa}{(a+k)}$$

Equation 3-4

In epidemiologic studies, the ambient PM concentration, *Ca*, is often used in lieu of outdoor microenvironmental data to represent these exposures based on the availability of data. Thus, it is often assumed that $C_o = C_a$ and that the fraction of time spent outdoors can be expressed cumulatively as f_o; the indoor terms still retain a summation because infiltration differs for different microenvironments. If an epidemiologic study employs only C_a, then it is assumed that exposure to ambient PM, E_a given in Equation 3-3, is re-expressed solely as a function of C_a:

$$E_{\mathrm{a}} = \left(f_{\mathrm{o}} + \Sigma f_{\mathrm{i}} F_{\mathrm{inf,i}}\right) C_{\mathrm{a}}$$

Equation 3-5

Equation 3-5 encapsulates several facets of the relationship between ambient concentration and E_a. First, C_a represents all ambient PM concentrations combined. Measurements and models to quantify C_a may assign one uniform PM concentration in the region of study (e.g., Section 3.3.1.1), or it might be modeled to represent how it varies outdoors across space (Section 3.4.2.2). Second, exposure is related to both concentration encountered and time spent in a given microenvironment. Outdoor exposure is directly influenced by ambient concentration and time spent outdoors. Indoor exposure occurs where infiltration of ambient PM into the envelope of an enclosed space (e.g., building, bus) likely reduces ambient PM exposure by filtering out a fraction of the ambient PM, but the influence of ambient concentration and time of exposure is still present. The components of indoor and outdoor exposure to ambient PM to comprise total ambient PM exposure, E_a. Further combining these factors with human activity level influences dose (Section 4.1.7).

Certain factors influence whether Equation 3-5 is a reasonable approximation for Equation 3-3, including the spatial variability of outdoor PM concentrations due to spatial distribution of sources; meteorology, topography, oxidation rates, and the design of the epidemiologic study. These equations also assume steady-state microenvironmental concentrations. Errors and uncertainties inherent in using Equation 3-5 in lieu of Equation 3-3 are described in Section 3.4. with respect to implications for interpreting epidemiologic studies. Epidemiologic studies often use concentration measured at an ambient monitor to represent ambient concentration; thus α, the ratio between personal exposure to ambient PM and the ambient concentration of PM, is defined as:

$$\alpha = \frac{E_a}{C_a}$$

Equation 3-6

Combining Equation 3-5 and Equation 3-6 yields:

$$\alpha = f_o + \Sigma f_i F_{inf,i}$$

Equation 3-7

where α varies between 0 and 1. If a person's exposure occurs in a single microenvironment, the ambient component of the microenvironmental PM concentration can be represented as the product of the ambient concentration and F_{inf}. Time-activity data and corresponding estimates of F_{inf} for each microenvironmental exposure are needed to compute an individual's α with accuracy (U.S. EPA, 2006). In epidemiologic studies, α is assumed to be constant in lieu of time-activity data and estimates of F_{inf}, which can vary spatially (between homes) and temporally (within a home) based on building and meteorology-related air exchange characteristics.

The conceptual model presented in Equation 3-1 through Equation 3-7 establish a framework for considering the influence of exposure measurement error on statistical models used in epidemiology studies. Exposure measurement error occurs when there is an absence of information for the variables in this framework, so assumptions must be made regarding ambient exposures. If important local outdoor sources and sinks exist but are not captured by ambient monitors, then the ambient component of the local outdoor concentration may be estimated using dispersion models, land use regression (LUR) models, chemical transport models (CTMs), satellite data, or some combination of these techniques, which are described in Section 3.3.2.

3.2.3 Exposure Considerations Specific to PM

The inhalation exposure route relevant for PM is influenced by sources, chemistry, particle size distribution, meteorology, and ambient concentrations, as described in detail in Chapter 2 and briefly summarized here.

The polydisperse size distribution (Section 2.2) and composition (Section 2.3) of PM interact to influence several aspects of exposure. UFP dominates the number concentration (NC) distribution of PM, while $PM_{2.5}$ typically dominates the mass distribution. Combustion via energy production, mobile sources, and industrial processes is the main primary anthropogenic source of UFP and $PM_{2.5}$. Brake, tire, and clutch wear can also contribute to primary UFP, $PM_{2.5}$, and $PM_{10-2.5}$. Secondary production of NO_3^-, NH_4^+, and SO_4^{2-} are also major contributors to $PM_{2.5}$, and the magnitude of those contributions varies by region, time of day, and season. UFP will also grow to the accumulation mode following emissions on time scales of hours to days. Road and construction dust are important anthropogenic sources of $PM_{10-2.5}$ in urban areas, while agricultural dust is an anthropogenic source of $PM_{10-2.5}$ in rural areas. Biogenic $PM_{10-2.5}$ from pollen can also be a substantial contributor to overall $PM_{10-2.5}$.

The size distribution influences transport and dispersion of PM, therefore affecting spatial and temporal variability of PM concentration and hence exposure (U.S. EPA, 2009b). UFP has a short lifetime because it either readily evaporates or undergoes rapid growth into the accumulation mode via

agglomeration of UFP into larger particles, condensation or adsorption of vapors onto UFP, or reaction of gases in or on the particles (Section 2.2). $PM_{2.5}$ will tend to follow the wind unless evaporating, participating in a surface reaction, and/or accumulating to a larger size. Particle growth may enhance deposition. $PM_{10–2.5}$ in dust can settle out of the air at a faster rate than $PM_{2.5}$. Resuspension by vehicle-generated turbulence, tire motion, or other activities may occur for particles of any size but are more likely for $PM_{10–2.5}$, which forms more readily via mechanical generation (Section 2.3.3). As a result, spatial and temporal variability of PM exposure concentration tends to be greater for UFP and $PM_{10–2.5}$ compared with $PM_{2.5}$ (Section 2.5).

Size distribution will also affect what fraction of the ambient air penetrates indoors (U.S. EPA, 2009b). Because $PM_{2.5}$ navigates changes in direction more easily, more $PM_{2.5}$ tends to infiltrate indoors compared with $PM_{10–2.5}$, which impacts onto building envelope surfaces more easily. UFP is more likely to diffuse onto building envelope surfaces compared with $PM_{2.5}$, so it would be expected that a lower proportion of UFP would infiltrate indoors compared with $PM_{2.5}$.

In summary, variability and uncertainties in accounting for PM emissions, chemistry, transport, and dispersion (noted here and described in detail in CHAPTER 2) leads to variability and uncertainties in estimates of exposure concentrations. For PM, uncertainties extend to characterization of the statistical distribution of particles by size and concentration (spatially and temporally). Because they have shorter lifetimes compared with $PM_{2.5}$, spatial and temporal variability is more pronounced for the lower (UFP) and upper ($PM_{10–2.5}$) segments of the particle size distribution compared with the accumulation mode ($PM_{2.5}$). Such uncertainties may complicate estimation of exposure concentrations using models such as CTMs (Section 3.3.2.4) or satellite-based methods where a relationship between $PM_{2.5}$ and surface measurements is derived (Section 3.3.3). Errors associated with these factors are described further in Section 3.4.2, and their influence on epidemiologic study results is considered in Section 3.4.5.

3.3 Methodological Considerations for Use of Exposure Data and Models

This section describes methods for estimating human exposure to PM, along with their strengths and limitations, which are important to understand when developing associations between PM exposure and health endpoints in epidemiologic analyses. The 2009 PM ISA (U.S. EPA, 2009b) and other literature [e.g., Madrigano et al. (2013); Hubbell (2012); Tagaris et al. (2009)] presented information about ambient and personal monitoring, as well as models for data averaging, spatial interpolation, LUR, CTM, and dispersion models. The current section extends that presentation by updating the assessment with discussion of new methodology and a more detailed consideration of features, strengths, and limitations of measurement and modeling techniques for PM exposure assessment.

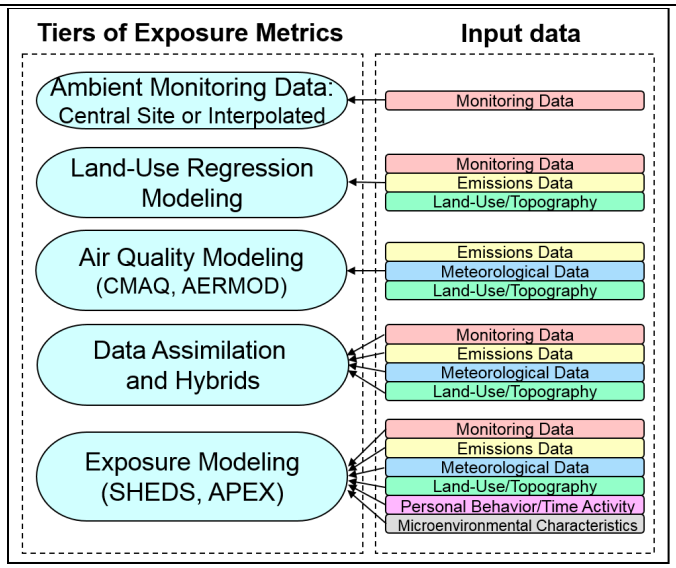
For epidemiologic analyses, accurately assigning air pollutant exposure concentrations to individuals is difficult given the limited spatial and temporal resolution of the available observations.

Applications can vary in scale, from personal (Baxter et al., 2013; Brown et al., 2012; Dons et al., 2012; Kaur and Nieuwenhuijsen, 2009) to national (Fann et al., 2012; Bell et al., 2011b) to global (Lelieveld et al., 2015; Brauer et al., 2012; Lim et al., 2012). In some studies, personal monitoring has been used, but study limitations (e.g., expense, recruiting subjects to participate) typically constrain the size of the population studied in panel studies (Baxter et al., 2013; Ozkaynak et al., 2013; Jerrett et al., 2005a; Sarnat et al., 2000). Thus, methods are employed that use the limited observational data available from ambient air quality monitoring regulatory networks (Solomon et al., 2011) and special, often intensive studies that may be designed to provide data for exposure assessment and/or spatial characterization (Vedal et al., 2013; Hansen et al., 2006; Edgerton et al., 2005; Jerrett et al., 2005b; Butler et al., 2003; Hansen et al., 2003). In addition, health studies are taking advantage of satellite data [e.g., Madrigano et al. (2013); Liu et al. (2009)], mobile monitoring data [e.g., Levy et al. (2014); Bergen et al. (2013)], and models [e.g., Jerrett et al. (2016); Turner et al. (2016); Villeneuve et al. (2015); Pope et al. (2014)].

Modeling PM exposure concentrations can be challenging because PM may contain a mixture of components and is found in a continuum of sizes (Section 2.2). Approaches for modeling PM exposure concentration can generally be used for different sized particles ($PM_{10–2.5}$, $PM_{2.5}$, UFP) and components, though additional considerations may be involved. For example, there are very limited observational data on UFP for cross-validation (Section 2.5); $PM_{2.5}$ composition data from ambient monitoring networks are typically available every few days (e.g., every third or every sixth day) using 24-hour integrated measurements. Different observational techniques for $PM_{10–2.5}$, $PM_{2.5}$, and UFP have different biases and uncertainties, and composition may influence biases and uncertainties within a given size fraction. Some observed components (e.g., OC) are composed of multiple compounds that behave differently in the environment.

There are a range of approaches used to model PM exposure that are applied for specific purposes, and their uses depend upon available data. Ozkaynak et al. (2013) developed a hierarchy of methods based upon complexity, ranging from using ambient monitoring data as an exposure surrogate to human exposure models accounting for time-activity data and microenvironmental exposure concentrations (Figure 3-1). This list can be extended to include source apportionment models. The amount and complexity of model input data increases with increasing complexity of the models. Increasing the complexity of the exposure modeling methods may reduce exposure error in some cases (Sarnat et al., 2013b).

This section includes discussions of surface measurements (including fixed-site and personal monitoring [Section 3.3]), modeling approaches (increasing in complexity from data averaging techniques through microenvironmental models [Section 3.3.2]), and satellite-based methods (Section 3.3.3). Each of these approaches has strengths and limitations, and several new studies discussed in Section 3.3.2.4.3 and Section 3.3.3 blend observations and air quality model results to reduce exposure measurement error. An analysis of the relative strengths and limitations of these methods for application in epidemiologic studies is provided in Section 3.3.5.



Source: Permission pending, Adapted from Ozkaynak et al. (2013).

Figure 3-1 Tiers of exposure models relevant to epidemiology studies and input data types for each exposure model tier.

3.3.1 Surface Measurement

The 2009 PM ISA (U.S. EPA, 2009b) discussed the use of ambient PM concentration data measured at FRMs and FEMs and used as surrogates for PM exposures, and main points are summarized in Section 2.4. The technology for measuring ambient PM at fixed-site monitors has largely stayed the same. More attention is given in Section 2.4.3 to measuring UFP concentrations. New insights to help interpret $PM_{2.5}$, $PM_{10–2.5}$, and UFP concentration data for use in exposure assessment studies are provided in Section 3.4.1.1.

The 2009 PM ISA (U.S. EPA, 2009b) described developments in using personal monitors for exposure assessment. Specifically, developments in light scattering continuous monitoring instrumentation, passive sampling, cascade impactor sampling for $PM_{10–2.5}$ and $PM_{2.5}$, and use of GPS for estimating time-activity were presented. Since then, new developments have been made in active sampling of $PM_{10–2.5}$, $PM_{2.5}$, and UFP. Important developments include reducing the size and increasing portability and battery life of samplers. These are described in Section 3.3.1.2.

3.3.1.1 Ambient Monitoring

Ambient PM data from FRM or FEM from individual sites continue to be used widely in health studies as a surrogate for PM exposure concentration. (Pope et al., 2009; Zanobetti and Schwartz, 2009) provide a number of reasons for the continued use of fixed-site monitor data as exposure surrogates:

(1) instrument error is typically small compared to spatiotemporal modeling error, (2) an ambient monitor may provide a comprehensive set of measurements, (3) the need to capture temporal variation is typically greater than the need to capture spatial variation in short-term exposure studies, and (4) ambient monitor data provide a useful reference for comparing population exposure concentration estimates in long-term exposure studies. The ambient monitor approach is the least data intensive approach among all exposure concentration estimation methods because it only requires data from a single monitor to represent exposures to a large area (on the order of 100 km^2).

Differences in sampler design for $PM_{2.5}$, $PM_{10–2.5}$, and UFP influence the quality of exposure concentration data available for epidemiologic studies of each respective size cut. For $PM_{2.5}$ samplers, quality assurance testing has demonstrated that $PM_{2.5}$ concentration measurements are replicable [(U.S. EPA, 2004), Section 2.4.1.1], lending confidence to their frequent application in exposure assessment studies. In contrast, $PM_{10–2.5}$ exposure concentration has been measured in three ways [dichotomous samplers, differencing using concentrations from collocated PM_{10} and $PM_{2.5}$ monitors, and subtracting area-wide (e.g., county-wide) $PM_{2.5}$ concentration from area-wide PM_{10} concentration] with large differences in quality assurance (Section 2.4.2). It is expected that dichotomous samplers would produce the most accurate measure of $PM_{10–2.5}$ concentration for use as an exposure surrogate, because dichotomous samplers are designed for isokinetic flow appropriate for each PM cut point. However, a systematic study comparing all three methods has not yet been performed. Differences in spatial variability of $PM_{2.5}$ and $PM_{10–2.5}$ (Section 2.5) coupled with low-moderate correlation (Section 3.4.3.1) suggest that area-wide differences would provide the least accurate measure of $PM_{10–2.5}$ concentration for use in exposure assessment studies. UFP is usually measured by condensation particle counters (CPC) (Section 2.4.3.1) and at times by inertial impaction (Section 2.4.3.3). Testing of CPCs has shown that CPCs may operate at 95% counting efficiency. However, concentrations measured by UFP samplers are also more susceptible to negative bias due to larger evaporative losses compared with $PM_{2.5}$ or $PM_{10–2.5}$ concentration measurements. Hence, there is generally higher confidence in $PM_{2.5}$ concentration measurements than in $PM_{10–2.5}$ and UFP concentration measurements used as exposure surrogates.

3.3.1.2 Personal Monitoring

Methods for personal PM monitoring were described in the 2009 PM ISA (U.S. EPA, 2009b). At that time, filter-based personal monitors were used most frequently. Developments at the time of the 2009 PM ISA included size selectivity of personal samples using a Personal Cascade Impactor Sampler that can sample down to a cut point of 250 nm (Singh et al., 2003), a mini-cyclone with the capability of sampling down to 210 nm (Hsiao et al., 2009), and a two-stage cascade impactor for $PM_{10–2.5}$ sampling (Case et al., 2008). A passive monitor had also been adapted for $PM_{10–2.5}$ sampling (Ott et al., 2008; Leith et al., 2007) based on a passive sampler developed earlier that can be used for user-defined size fractions including $PM_{2.5}$ (Wagner and Leith, 2001a, b). Light-scattering detection devices for continuous monitoring, such as the Personal DataRam (pDR, Thermo Scientific, Waltham, MA), the DustTrak (TSI,

Inc., Shoreview, MN), and the SidePak (TSI, Inc., Shoreview, MN) for PM_{10} or $PM_{2.5}$ mass concentration and the P-Trak (TSI, Inc., Shoreview, MN) or personal CPC Model 3007 (TSI, Inc., Shoreview, MN) for UFP count concentration were also described in the 2009 PM ISA. The P-Trak samples between 20 nm and 1 µm, and the CPC samples between 10 nm and 1 µm. However, it is anticipated that the majority of particles are smaller than 100 nm when measuring NC (see Preface). Additionally, the 2009 PM ISA detailed new methodologies used by investigators to enhance personal sampling by incorporating videotape (Sabin et al., 2005) or Global Positioning Systems (GPS) (Westerdahl et al., 2005) into their sampling protocols to estimate personal exposure by using simultaneous measures of exposure concentration and time-activity data. Techniques discussed in the 2009 PM ISA are widely in use, and development of new samplers have largely built upon these techniques. Table 3-1 lists these new techniques with sampling size fraction, speciation, mechanism, and error characteristics.

Table 3-1 New or innovative methods for personal sampling of PM exposure concentrations published since the 2009 PM ISA.

Reference	Active or Passive Sampling	Sampler	Size Fraction	Species	Mechanism	Error Characteristics
Thornburg et al. (2009)	Active	Coarse Particulate Exposure Monitor (CPEM)	$PM_{10-2.5}$, $PM_{2.5}$	NA	Three-stage impactor	$PM_{10-2.5}$: −23% (R^2 = 0.81) $PM_{2.5}$: −3% (R^2 = 0.91) compared with a dichotomous $PM_{10-2.5}$ sampler
Volckens et al. (2016)	Active	Ultrasonic Personal Aerosol Sampler (UPAS)	$PM_{2.5}$	NA	Miniature piezoelectric pump with a cyclone for 2.5 µm size cut plus additional sensors for air flow, sunlight, temperature, pressure, relative humidity, and acceleration	−1.4% compared with a $PM_{2.5}$ FRM
Ryan et al. (2015b)	Active	Personal UFP Sampler (PUFP)	UFP	NA	Water-based CPC plus GPS for location	+16% (R^2 = 0.99)

Table 3-1 (Continued): New or innovative methods for personal sampling of PM exposure concentrations published since the 2009 PM ISA.

Reference	Active or Passive Sampling	Sampler	Size Fraction	Species	Mechanism	Error Characteristics
Nash and Leith (2010)	Passive	Algorithm to modify output from the Wagner-Leith passive sampler to UFP	UFP	Yes	Model of deposition flux developed the passive sampler's size range	6% compared with SMPS
Cai et al. (2014); Cai et al. (2013)	Active	Modification to the Microaethalometer (AethLabs, Berkeley, CA)	$PM_{2.5}$	BC	Reduced humidity and temperature fluctuations through addition of a diffusion dryer	53 ± 238% difference in 1-min readings between the original and diffusion dryer inlet on 97−100% RH day and 5 ± 33% difference between original and diffusion dryer inlet on 65% RH day. The differences reduce to approximately 1% when data are averaged over an hour.
Hagler et al. (2011);Cheng and Lin (2013)	Active	Algorithm to modify output from the Microaethalometer (AethLabs, Berkeley, CA)	$PM_{2.5}$	BC	Introduced a data cleaning algorithm to reduce erroneous fluctuations in the signal (i.e., noise)	Comparison between 1-min data with optimized noise reduction algorithm was comparable to 5-min data averaged with noise
Sameenoi et al. (2012)	Active	Microfluidic electrochemical sensor to detect oxidative potential of PM	Any	ROS	Incorporated DTT assay into Particle into Liquid Sampler (PILS)	Comparison with traditional DTT assay: R^2 = 0.98
Sameenoi et al. (2013)	Active	Microfluidic paper-based analytical device (μPAD) to detect oxidative potential of PM	Any	ROS	Collected $PM_{2.5}$ and PM_{10} on filters, desorbed, then pipetted onto μPAD	Comparison with traditional DTT assay: bias = 10.5%, R^2 = 0.98

Table 3-1 (Continued): New or innovative methods for personal sampling of PM exposure concentrations published since the 2009 PM ISA.

Reference	Active or Passive Sampling	Sampler	Size Fraction	Species	Mechanism	Error Characteristics
Landreman et al. (2008)	Active	Expose rat macrophages to collected aerosol sample to detect oxidative potential of PM	Any	ROS	Collected $PM_{2.5}$ onto filters, desorbed, then pipetted onto a 96-well plate seeded with rat macrophages	Response corresponded to spikes for samples exposed to different numbers of macrophages (not quantitative)

BC = black carbon; DTT = dithiothreitol; ROS = reactive oxygen species.

Prevalent field usage of continuous personal PM monitors using optical techniques necessitates validation of these instruments, since calibration is not possible given that ambient PM does not have replicable optical properties. Wallace et al. (2011) tested the 6 pDR and 14−16 DustTrak (number varied with tests) for $PM_{2.5}$ (with a size-selective inlet), and 14 P-Trak personal samplers for particle number to measure UFP exposure concentrations to establish operational parameters (MDL, bias, precision, drift) for each sampler compared with the median. MDL for the DustTrak and pDR were estimated to be 5 $\mu g/m^3$ and 5.5 $\mu g/m^3$, respectively (not detected for the P-Trak), and relative precision was within 10% for all four monitors. The pDR measurements were 60% higher than collocated personal gravimetric samples from the field tests ($R^2 = 0.7$), and the DustTrak measurements were 164% higher than personal gravimetric measurements ($R^2 = 0.9$). The authors pointed out that the higher readings from the light-scattering instruments relative to the gravimetric measurements are due in part to the lower density of ambient PM relative to the density of the aerosol standard used for laboratory calibration. Another factor Wallace et al. (2011) noted to influence the performance of light-scattering personal PM monitors is relative humidity (RH). High RH results in sorption of water to particles and an increase in volume and mass detected by the instrument. Quintana et al. (2000) found that pDRs produced much higher readings than a gravimetric TEOM instrument when RH was above 85%, but that pDR readings tracked the TEOM readings relatively well at RH values below 60%. Since indoor RH is generally maintained below 60%, the influence of RH is likely to mainly affect outdoor light-scattering measurements, particularly in morning, evening, and overnight hours when RH is highest. Optical personal samplers are subject to errors given the inability to calibrate the monitors for ambient characteristics. The characterization work described above has been done for optical sampling of $PM_{2.5}$, so uncertainties are greater for the $PM_{10-2.5}$ and UFP size fractions. Instrument error and replicability and the factors that affect them must be evaluated for each use in panel studies.

3.3.2 Modeling

At the time of the 2009 PM ISA (U.S. EPA, 2009b), fine-scale exposure prediction models were still relatively nascent in their development. Methods reviewed include time-weighted microenvironmental models and stochastic exposure models for estimation of PM exposure and dispersion models, LUR, and GIS-based modeling approaches for estimation of PM exposure concentration, and attention was given to the models' limitations in adequately capturing spatial variability of PM concentration, particularly for more variable UFP and $PM_{10-2.5}$. Since the 2009 PM ISA, more approaches to spatial averaging of concentrations used for estimating exposure concentrations (Section 3.3.2.1), and new developments in spatiotemporal interpolation of exposure concentration surfaces (Section 3.3.2.2), LUR (Section 3.3.2.3), and dispersion models (Section 3.3.2.4.2) have appeared in the peer-reviewed literature. Additionally, there has been growing use of chemical transport models (CTMs) in exposure assessment studies (Section 3.3.2.4.1) in recent years. Table 3-2 provides an overview of the modeling approaches discussed in this section.

The models discussed in the following sections are typically validated by the study authors using surface monitoring data, but model validation is not performed consistently across the literature. Table 3-3 lists performance measures that have been utilized in the recent PM exposure modeling literature. Model performance is typically evaluated for bias or error using both absolute and relative (or normalized) metrics.

Table 3-2 Comparison of models used for estimating exposure concentration or exposure.

	Type of Model						
Factors[a]	**Data averaging**	**IDW/ Kriging**	**LUR/ ST**	**CTM and Hybrid**	**Dispersion**	**Satellite and Hybrid**	**Microenvironmental**
Type of model	C	C	C	C	C	C	E
Distance from source	X	X	X	X	X	X	X
Emission rate			X	X	X	X	X
Terrain or land use			X	X	X	X	X
Dispersion				X	X	X	X
Chemistry				X	X	X	X

Factors[a]	Type of Model						
	Data averaging	IDW/ Kriging	LUR/ ST	CTM and Hybrid	Dispersion	Satellite and Hybrid	Microenvironmental
Human activity							X
Infiltration							X
Inhalation							X

C = concentration model, CTM = chemical transport model, E = exposure model, IDW = inverse distance weighting, LUR = land use regression, ST = spatiotemporal models.

[a]Factors that may be available in each model are checked.

Table 3-3 Statistical measures used for air quality model performance evaluation.

Performance Measures	Definition[a]
Mean bias (MB)	$\frac{1}{N}\sum_{i=1}^{N}(P_i - O_i)$
Mean error (ME)	$\frac{1}{N}\sum_{i=1}^{N}\lvert P_i - O_i\rvert$
Root mean square error (RMSE)	$\sqrt{\frac{1}{N}\sum_{i=1}^{N}(P_i - O_i)^2}$
Coefficient of determination (R^2)	$\frac{\left\{\sum_{i=1}^{N}\left(O_i - \overline{O}\right)\left(P_i - \overline{P}\right)\right\}^2}{\sum_{i=1}^{N}\left(O_i - \overline{O}\right)^2 \sum_{i=1}^{N}\left(P_i - \overline{P}\right)^2}$

[a]P_i and O_i are prediction and observation at the ith monitoring site, respectively; N is the number of monitoring sites.

3.3.2.1 Data Averaging

Averaging measurements from all monitors in a study area is frequently used to mitigate some of the errors associated with using data from a single ambient monitor to estimate exposure concentrations for a population. There are many averaging approaches in use to provide more representative exposure concentration estimates than those derived from a fixed-site ambient monitor. For example, Strickland et al. (2011) compared nearest fixed-site monitor concentrations of $PM_{2.5}$ and $PM_{2.5}$ components (SO_4^{2-}, OC, EC) averaged over 24 hours with concentrations averaged over three monitors (unweighted). They found that $PM_{2.5}$ and $PM_{2.5}$–SO_4^{2-} mass concentrations were within 8% of each other, with strong correlations between the concentration obtained by a fixed-site monitor and with that obtained by a population-weighted average Spearman $R = 0.969$. Reported $PM_{2.5-OC}$ concentrations had a Spearman correlation of $R = 0.847$, but more spatially varying $PM_{2.5-EC}$ had a Spearman correlation of $R = 0.831$. Goldman et al. (2012) had similar findings when comparing nearest monitor with unweighted averaging. Strickland et al. (2013) compared unweighted averages across monitors with concentrations measured at fixed-site monitors and concentrations estimated to be the "true" exposure concentrations at grid cells within the study domain. The fixed-site monitor produced $PM_{2.5}$ concentrations with the largest biases of −31.3%, in comparison with the unweighted average (−9.0%). Biases for $PM_{2.5}$ components (SO_4^{2-}, NO_3^-, NH_4^+, EC, OC) were similar for both the fixed-site monitor and unweighted average. In the unweighted averaging technique studied by Strickland et al. (2013), temporal variability may be dampened, leading to Berkson errors. As described below, more spatial heterogeneity inherent to the exposure concentration field implies greater Berkson errors.

Spatial averaging techniques include area-weighting and population-weighting (Vaidyanathan et al., 2013). Such schemes require some type of spatial modeling of data before averaging. For example, area and population-weighting might involve use of a regression model of PM or PM component concentration and population density, land use, or emission estimates to develop exposure concentration estimates at grid locations. Concentrations for census tracts, zip codes, or counties can then be averaged and weighted by the associated areas or populations. In such schemes, the objective of the spatial modeling is to develop more representative area or population estimates.

Population-weighted averaging is designed to reduce bias in the health effect estimate by giving greater weight to the locations where more people live. As part of the study referenced above, Strickland et al. (2013) compared population-weighted averages across monitors with concentrations measured at fixed-site monitors and concentrations estimated to be the "true" exposure concentrations at grid cells within the study domain. The population-weighted average produced $PM_{2.5}$ concentrations with biases of −8.1% in comparison with the true $PM_{2.5}$ exposure concentrations. Biases for $PM_{2.5}$ components (SO_4^{2-}, NO_3^-, NH_4^+, EC, OC) were similar for both the fixed-site monitor and unweighted average. Strickland et al. (2011) compared nearest fixed-site monitor concentrations of $PM_{2.5}$ and $PM_{2.5}$ components (SO_4^{2-}, OC, EC) averaged over 24 hours with concentrations averaged using population-weighted averages. They found that $PM_{2.5}$ and $PM_{2.5}$–SO_4^{2-} mass concentrations were within 8% of each other, with correlations

among the three spatial representations ranging from Spearman $R = 0.963-0.995$. Reported $PM_{2.5-OC}$ concentrations had Spearman correlations of $R = 0.891$, but more spatially varying $PM_{2.5-EC}$ had Spearman $R = 0.804$. Goldman et al. (2012) had similar findings when comparing nearest monitor, unweighted, and population-weighted averaging. These results suggest that population-weighted averaging may provide a small improvement over unweighted averaging for estimation of exposure concentration.

Spatial averaging approaches may influence exposure measurement error (Goldman et al., 2010) and associations between short-term $PM_{2.5}$ exposure and health outcomes (Goldman et al., 2012). In the latter study, the authors noted improved population-weighted R^2 values (relative to the fixed-site ambient monitoring method) between exposure concentration metrics estimated using data averaging methods and the simulated "true" ambient concentration field. For example, the R^2 values increased from 0.25 for a fixed-site ambient monitoring method to approximately 0.38 for data averaging methods.

Various methods can be chosen for temporal averaging, such as straight arithmetic averaging or methods that account for site-specific variability and that also account for the lack of some observations during the period. Temporal averaging is used to estimate exposure concentrations over different time intervals. Hourly and daily measures are averaged to provide metrics of interest (e.g., daily, weekly, monthly, seasonal, and annual). Darrow et al. (2011) tested different averaging intervals and found that 1-hour daily max $PM_{2.5}$ concentrations had high correlation with 24-hour average (Spearman $R = 0.82$) and moderate correlations (Spearman $R = 0.75$ and 0.68) with commuting time (7:00–10:00 and 16:00−19:00) and daytime (8:00−19:00) average $PM_{2.5}$ concentrations, respectively. As with the development of spatial averages, the objective of temporal averaging is to minimize error that might be introduced due to missing data from a time-series, so that diurnal, weekly, seasonal, or annual trends can be well characterized.

Spatial and temporal averaging methods provide a mechanism for interpolating where data are missing over space or in a time-series, respectively. The literature shows that averaging techniques produce some bias when compared with true exposure concentrations, but averaging techniques do present an improvement over using data from a single fixed-site monitor.

3.3.2.2 Spatial Interpolation Methods

The single fixed-site ambient monitor and methods that average concentration data across monitoring sites in an area both lead to exposure concentration estimates with no spatial variation. When spatially resolved estimates of PM exposure concentration are desired, a variety of approaches are available for two-dimensional interpolation of observations ranging from smoothing techniques (described here) to statistical modeling techniques involving additional data (Section 3.3.2.4). Various spatial interpolation methods exist that use multiple monitors to provide spatially varying fields. Such

methods include: inverse distance weighting (IDW), inverse distance squared weighting (ID2W) (Hoek et al., 2002), and kriging (Mercer et al., 2011; Whitworth et al., 2011).

IDW, in which ambient PM concentration at a receptor point is calculated as the weighted average of ambient PM concentration measured at monitoring locations, is a commonly used simple interpolation method [e.g., Tai et al. (2010)]. Several variations of IDW have been used to estimate exposure based on ambient PM concentration surfaces. The weighting factor is an inverse function of distance between the receptor and the monitor. For example, Brauer et al. (2008) and MacIntyre et al. (2011) estimated exposure to ambient $PM_{2.5}$ and other industrial pollutants within 10 km of point sources using an IDW sum of ambient $PM_{2.5}$ concentration and the three closest monitors within 50 km. Often, the weighting factor is the inverse distance raised to some power, and a higher power is applied to increase the weight on monitors that are closer to the receptor. Rivera-González et al. (2015) applied an ID2W model and compared the results with a citywide average, use of the nearest monitor, or kriging for development of an ambient $PM_{2.5}$ concentration surface. The results from IDW were correlated with the other city-wide averaging, nearest monitor, and ordinary kriging (Pearson R = 0.83−0.99), and the mean ambient $PM_{2.5}$ concentration estimated with IDW was within 5% of the mean computed with the other methods. Neupane et al. (2010) compared estimates of the ambient $PM_{2.5}$ concentration surface calculated using IDW with a $PM_{2.5}$ concentration surface calculated using both bicubic spline interpolation. Bicubic spline interpolation produced a lower mean ambient $PM_{2.5}$ concentration and larger IQR compared with IDW. Because there is no reference value in these studies, it is difficult to conclude that IDW presents any substantial improvement in prediction accuracy compared with other methods. These findings indicate that the results of IDW are comparable to methods that average concentrations across monitors and to methods that smooth concentration surfaces when estimating $PM_{2.5}$ concentration.

Kriging is a set of well-established methods that use observed covariance for geostatistical interpolation [e.g., Beelen et al. (2009)]. Recent developments have been made to improve kriging techniques. Pang et al. (2010) developed a space-time Bayesian Maximum Entropy (BME) model and compared it with ordinary kriging (OK). OK assumes linearity between data points, and it also assumes that the data are normally distributed. BME is not restricted to linearity or normality and so can draw on different sources of information, such as space-time relationships between variables and probability distributions describing the concentration dataset, to address missing data. Pang et al. (2010) found that estimation errors were 2−4 times larger for OK compared with BME. The ability to apply nonlinear models to address missing data thus provide BME-kriging approaches greater accuracy in modeling $PM_{2.5}$ concentration surfaces.

Berkson-like error in the estimated exposure concentration may arise from smoothing inherent to spatial interpolation models, such as IDW and kriging (see Section 3.2.1 for definition of Berkson-like error). The potential for Berkson-like error may be evaluated by cross-validation across receptor locations distributed over space, and the statistical performance of spatial interpolation methods may vary from study to study. When an interpolation model is fit using a relatively sparsely distributed monitoring

network, Berkson-like errors in estimated exposure concentration can be substantial (Alexeeff et al., 2015; Whitworth et al., 2011). All of the spatial interpolation approaches will produce spatially smoothed pollutant exposure concentration fields from monitoring data. However, spatial and temporal variabilities not captured by monitors are also not captured by these approaches.

If the quantity of data is small in each given site, or if the quality of the data obtained at the monitors is low, then classical-like error may arise (Szpiro et al., 2011a). If there are few observations, all of the interpolation methods suffer. This includes kriging, which depends on developing a variogram. With few observations at the monitoring locations, there is limited information to determine the functional coefficients used for kriging (e.g., the nugget, sill, and range). Weighting schemes for the interpolation models may amplify these errors (Wong et al., 2004).

3.3.2.3 Land Use Regression and Spatiotemporal Modeling

Direct spatial interpolation of PM exposure concentration and methods that employ static parameters to capture spatial variance can lead to excessive spatial autocorrelation when spatial variability of PM is high (Krewski et al., 2009). $PM_{2.5}$ tends to have less spatial heterogeneity than $PM_{10-2.5}$ or UFP (Section 3.4.2) given secondary production (U.S. EPA, 2009b), but high concentrations can still occur near primary sources. Statistical approaches that utilize data that vary over space and time can address this limitation. Geographic information system (GIS) models are being used to incorporate land use, emissions data, and geographic covariates into PM exposure concentration estimates. Two types of models are covered in this section, LUR and spatiotemporal models. LUR models regress observed PM concentrations on land use (and sometimes additional geographic) covariates and then use the model to predict exposure concentrations where PM is not measured (Hoek et al., 2008a; Ryan and Lemasters, 2007). Spatiotemporal models tend to incorporate kriging or autocorrelation into the response variable, which is then fit to the land use and geographic covariates [e.g., Sampson et al. (2013)].

3.3.2.3.1 Land Use Regression

LUR is an empirical approach to estimate exposure concentrations, often at very high resolution in more densely populated locations, by relating observed concentrations to the detailed information on land use. The basic approach is to develop an equation, via regression, relating observed pollutant concentrations (Hoek et al., 2008a; Ryan and Lemasters, 2007) to land use characteristics and other inputs:

$$Y(s_i, t_j) = \beta_0(s_i, t_j) + \sum_k \beta_{1,k}(s_i, t_j) X_k(s_i, t_j) + \epsilon(s_i, t_j)$$

Equation 3-8

Here, $Y(s_i,t_j)$ is the observed concentration at location (monitor) s_i (where i is a monitor location) and time t_j, β_0 and $\beta_{1,k}$ are the regression coefficients (intercept and slopes that are potentially spatially and temporally varying, but may also be constant in time and space), X are the independent variables (e.g., land use or meteorological parameters that may vary in time and/or space), k is the index indicating type of land use, and ϵ is the residual error term. β_0 is also called the additive bias and $\beta_{1,k}$ the multiplicative bias. Other forms of LUR models are also used. While the regression equation often is linear in the independent variables (as shown above), it can include nonlinear and mixed terms, particularly if there is specific knowledge of the relationship between a concentration and a variable that would suggest a specific functional form. The resulting regression equation can then be used to predict exposure concentrations at other times (t) and locations (s) where observations are not available.

Recent studies demonstrate typical LUR model performance, performance evaluation, and variability between cities. Eeftens et al. (2012) evaluated the application of LUR models in 20 cities in Europe for $PM_{2.5}$, PM_{10}, $PM_{2.5}$ absorbance, and $PM_{10-2.5}$. First, the models for the various cities had substantially different independent variables used in the final models, as well as coefficients associated with similar independent variables, demonstrating the location-specific nature of the models. Second, the in-sample R^2 of the various city models varied between 35 and 89% for $PM_{2.5}$ and between 32 and 81% for $PM_{10-2.5}$. Evaluation using a leave one out cross-validation (LOOCV) produced R^2 levels of 21 to 79% for $PM_{2.5}$ and 3 to 73% for $PM_{10-2.5}$. R^2 was not consistent between each city. Wang et al. (2014) expanded on the same model for $PM_{2.5}$ in thirty-six European cities. They found a LOOCV R^2 of 81% (RMSE = 2.38 $\mu g/m^3$) for cities where the model was fit. However, Wang et al. (2014) tested transferability of the model to areas where the model was not fit, and R^2 dropped to 42% (RMSE = 1.14 $\mu g/m^3$). Estimation of $PM_{10-2.5}$ in the LUR can be accomplished using the difference between the PM_{10} and $PM_{2.5}$ LUR models, since each model was trained using PM_{10} and $PM_{2.5}$ concentration data. However, low LOOCV R^2 for $PM_{10-2.5}$ in select cities may have been related to how measured $PM_{10-2.5}$ concentration was calculated for the validation dataset. If reference $PM_{10-2.5}$ concentration was calculated by the difference of two collocated monitors rather than by a dichotomous sampler, flow rate differences could cause some error in the reported $PM_{10-2.5}$ concentrations. If $PM_{10-2.5}$ was calculated by the difference between concentrations measured by PM_{10} and $PM_{2.5}$ monitors that were not collocated, then errors would likely be larger.

Several features of LUR have the potential to limit the accuracy of modeled exposure concentrations. Beckerman et al. (2013a) noted that two major limitations with LUR are variable selection and how to best deal with unbalanced repeated measures, potentially involving arbitrary decisions in the model building process. They used a generalized linear model with a deletion/substitution/addition machine learning algorithm to model $PM_{2.5}$, resulting in an out-of-sample R^2 of 0.65 based on fivefold cross-validation (n-fold cross-validation means that 1/n of the data are reserved for validation with the rest used for model training, and the process is repeated n times). The ability of an LUR method to relate air pollutant concentrations to specific land uses, and thus estimate high resolution exposure concentration fields, is directly dependent on having sufficient numbers of observations in time and/or space to develop

the regression equation with reasonable uncertainties in each of the coefficients (Wang et al., 2014). The sparseness of the routine monitoring networks may incur Berkson-like error in the exposure estimates. More intensive studies may be conducted where additional monitoring data are available (sometimes called saturation monitoring if the additional monitors lead to extensive spatial coverage). Saturation sampling can also lead to introduction of classical-like error in the exposure predictions if different measurement methods are used and differences in the methods are not fully understood (Vedal et al., 2013; Levy et al., 2010).

A related weakness of LUR is its limited generalizability when the monitor and study participant locations are different. The developed regression equations are usually restricted to the study region (typically city-scale) alone and may not be directly applied to another region, due largely to the empirical nature of LUR (Wu et al., 2011; Jerrett et al., 2005a). Local PM data are required to calibrate LUR models, and measurements must be available that estimate the spatial patterns of exposure concentrations. For example, Patton et al. (2015) found during estimation of UFP exposure concentrations in Boston urban neighborhoods that models fit to one neighborhood did not necessarily provide robust estimates of particle NC for another neighborhood, and acceptable model performance required calibration with local data. Hoek et al. (2008a) also reviewed the performance of the LUR model regarding their application for $PM_{2.5}$ given differences between where the model was fit and where it was used for predictions. R^2 values for the developed LUR models for $PM_{2.5}$ ranges from 0.17 to 0.69, with substantially lower out-of-sample R^2 in evaluation (0.09−0.47, with fewer studies performed evaluation/cross-validation). This suggests that comparing performance statistics between cities, even when using one method (in this case, LUR) can yield very different performance and that using cross-validation reduces performance, but to a degree that is not predicable from the full model R^2. This work was extended by Wang et al. (2015) to show the association between the LOOCV R^2 and a health outcome (forced vital capacity: FVC). For models of $PM_{2.5}$, Wang et al. (2015) note that cross-holdout validation, where the model is rebuilt after removing data from a site and retraining the model using the same variables, may be more appropriate than traditional LOOCV for assessing LUR performance, particularly when there are a small number of training sites, because it makes use of all data in the model evaluation process instead of leaving out a portion of the data. In summary, LUR models can have relatively good validation ($0.4 < R^2 < 0.7$), even for spatially variable $PM_{10–2.5}$, but good validation will only occur when the model is used to predict concentrations in the same geographic area where it was fit.

Although LUR models have been used to estimate long-term (e.g., annual) average PM exposure concentrations within large metropolitan areas by using variables such as road type, traffic count, land cover, and topography (Gulliver et al., 2011; Hoek et al., 2008a) and can be applied to current or historical conditions (Hystad et al., 2013), LUR has been used less frequently for time-series exposure studies. Land use variables (e.g., elevation, road-type, distance to road, land cover) usually do not vary in time. Temporal variation in the model is gained by including both the available observations and other temporally-varying inputs, such as meteorological parameters. As part of the New York City Community Air Survey (NYCCAS) in which $PM_{2.5}$ samples were collected from 150 sites across the five boroughs of

New York City, Ross et al. (2013) built a LUR for application in a birth defects exposure study and developed a temporal adjustment procedure to increase the temporal resolution of $PM_{2.5}$ exposure concentration estimates to 2 weeks. This was accomplished by multiplying an LUR derived for one year by the ratio of 2-week averages to annual averages. Validation of the method using data from a second year of measurements produced out-of-sample R^2 of 0.83 (R^2 = 0.88 if two outliers were removed from the dataset). Dons et al. (2013) aimed to fit a LUR model of black carbon (BC) concentration to hourly data for a time-activity exposure study. However, they observed that many variables became insignificant when inputting hourly data into an annual model. Dons et al. (2013) instead built a LUR for hourly data using static and dynamic variables in different models. They found that LOOCV R^2 varied from 0.13 to 0.78. Higher R^2 but also higher RMSE were observed during the late morning to evening hours for the model with dynamic variables. These studies demonstrate that LUR can be extended to study temporal variability of $PM_{2.5}$ and BC, but caution must be used for application in time-series studies since model accuracy is sometimes low.

Recently, LUR has been applied to predict spatial distribution of $PM_{2.5}$ components. As part of the NYCCAS study, Ito et al. (2016) speciated the collected $PM_{2.5}$ samples and built a LUR model to predict $PM_{2.5}$ components concentrations across New York City. The temporal adjustment described above from Ross et al. (2013) was applied in the Ito et al. (2016) study, as well. LOOCV was used to test the models, and models for $PM_{2.5}$ mass and several components (Ca, Ni, V, and Zn) produced $R^2 > 0.8$. Several other components produced R^2 in the range of 0.6−0.7 (Cu, Fe, K, S, and Si), and others produced $R^2 \leq 0.5$ (Al, Br, Mn, Pb, and Ti). Spatial coefficient of variation (CV) was calculated for each component model, and high spatial variability did not always correspond to low LOOCV. For example, Ni had a spatial CV of 0.70 and LOOCV R^2 of 0.85, while Mn had a spatial CV of 0.68 and LOOCV R^2 of 0.36. The LUR models were then applied to a source attribution analysis in which 50–1,000 m buffers were placed around sources, and then annual average concentrations for each component modeled by the LUR were compared to the sources within those buffers.

In summary, new developments for LUR include adaptation of LUR models for short time resolutions and for spatially variable size fractions (UFP, $PM_{10-2.5}$) of PM and $PM_{2.5}$ components (e.g., Ca, Cu, Fe, K, Ni, S, Si, V, Zn). At the same time, several studies have improved characterization of errors and uncertainties in LUR modeling and how best to quality assure those models. Several studies drew attention to poor validations produced when LUR models were fit to one geographic area and then applied to another. Similarly, lack of spatial correlation between predicted concentrations at the model receptors and actual exposure concentrations of study participants can lead to Berkson-like error, and incompatibility of methods to model and measure PM can lead to classical-like errors (see error type definitions in Section 3.2.1).

3.3.2.3.2 Spatiotemporal Modeling

A GIS-based spatiotemporal model provides a useful tool for large-scale spatiotemporal analysis. GIS-based mapping such as kriging utilizes the covariogram for statistical smoothing but may lead to invalid spatial features due to insufficient data for characterizing spatial variation. Generalized additive models that describe regional and small-scale spatial and temporal (monthly) gradients (and corresponding uncertainties) were developed for $PM_{10-2.5}$ and $PM_{2.5}$ over the U.S. for 1998−2007 for use in health studies (Yanosky et al., 2014). Model validation was higher for $PM_{2.5}$ (out-of-sample $R^2 = 0.77$, normalized mean bias factor, NMBF = −1.6%) compared with $PM_{10-2.5}$ (out-of-sample $R^2 = 0.52$, NMBF = −3.2%). Bias increased and precision decreased for $PM_{10-2.5}$ compared with $PM_{2.5}$. Spatial covariates, including elevation, urbanized land use within 1 km, county-level population density, distance to roadways of moderate to heavy traffic, and point-source emissions density were all determined by the authors to be important predictors of $PM_{2.5}$, although the authors did not present data for the relative contribution of each variable to the model. Yanosky et al. (2009) developed spatially and temporally resolved concentration fields of $PM_{2.5}$ and $PM_{10-2.5}$ to be used as exposure concentration estimates in long-term exposure studies for the northeastern and Midwestern U.S. Out-of-sample R^2 for the $PM_{2.5}$ model was 0.77 with precision of 2.2 $\mu g/m^3$ for 1999 to 2002, compared with out-of-sample R^2 for the $PM_{10-2.5}$ model of 0.39 with precision of 5.5 $\mu g/m^3$. The IDW method was applied as an alternative to compare with a semiempirical model. For a $PM_{2.5}$ concentration field developed for 1999 to 2002, cross-validation results for IDW show reasonable performance with out-of-sample $R^2 = 0.60$ (and cross-validation results for IDW were not available for $PM_{10-2.5}$).

Recent studies have attempted to estimate spatially resolved $PM_{2.5}$ exposure across larger regions of the U.S. for application in epidemiologic studies. For example, Sampson et al. (2013) developed a model combining universal kriging that builds from regional partial least squares regression LUR models with categorical variables describing land use, population, emissions, vegetative index, roadway type, impervious surfaces, and proximity to features. Results of cross-validation with 10-fold cross-validation produced out-of-sample $R^2 = 0.52−0.63$ at the national scale and $R^2 = 0.84−0.88$ at the regional scale. Keller et al. (2015) applied this model to $PM_{2.5}$ and BC prediction in the six MESA Air cities (Baltimore, MD, Chicago, IL, Los Angeles, CA, New York City, NY, St. Paul, MN, and Winston-Salem, NC) and obtained out-of-sample R^2 of 0.82−0.91 for $PM_{2.5}$ and 0.79−0.99 for BC (using both AQS and MESA Air monitors for cross-validation). Bergen et al. (2013) applied a similar method for four $PM_{2.5}$ components: EC, OC, silicon, and sulfur, and the out-of-sample R^2 ranges from 0.62 to 0.95. Kim et al. (2015) examined $PM_{2.5}$ component networks for suitability of the data inputs for applying spatiotemporal models for PM component exposure concentrations, and they found that the Chemical Speciation Network (CSN) and Interagency Monitoring of Protected Visual Environments (IMPROVE) networks were too sparse to fit the model. They found that the greater density of the National Particle Component Toxicity (NPACT) study network, set up outside study participants' homes, would be needed to fit the model. Additionally, differences among the three networks with respect to averaging times, quality assurance, and pump flow rates, complicates the ability to combine networks into one database for fitting the model.

Recent developments in spatiotemporal modeling have enabled modeling of larger geographic regions and to overcome some of the limitations of kriging. In some cases, these models have been fit with good accuracy and precision. However, differences in model calibration in different regions introduce model errors, and sparse networks have been found insufficient for model fitting.

3.3.2.4 Mechanistic Models

Improvements in computational resources have led to mechanistic models (see Section 2.4.7 for a description) that are more amenable to exposure assessment studies, because they provide finer spatial resolution over larger domains and can include more components, more sources, and longer time periods compared with previous versions of CTMs (Garcia-Menendez et al., 2015; Ivey et al., 2015; Li et al., 2015; Turner et al., 2015; Hu et al., 2014d; Burr and Zhang, 2011; Civerolo et al., 2010; Wagstrom et al., 2008). Such models computationally solve the atmospheric-diffusion-reaction equations that describe the transport and physical and chemical transformations of pollutants (Seinfeld and Pandis, 2006). Turbulent diffusion is typically treated by using atmospheric dispersion coefficients or diffusivities. Mechanistic models may be used to characterize exposure concentrations where monitoring data are limited or not available.

3.3.2.4.1 Chemical Transport Model Applications for Exposure Concentration Estimation

CTMs commonly utilized for exposure concentration modeling in the U.S. include the Community Multiscale Air Quality (CMAQ) model, Particulate Matter-Comprehensive Air Quality Model with Extensions (PM-CAMx), and the University of California at Davis/California Institute of Technology (UCD/CIT) CTM (Gaydos et al., 2007; Byun and Schere, 2006; Kleeman and Cass, 2001; Russell et al., 1988) at the urban-to-regional scales and global models such as the Goddard Earth Observing System CTM (GEOS-Chem) and Comprehensive Air Quality Chemistry Model (CAM-Chem) (Garcia-Menendez et al., 2015; Bey et al., 2001). The European Air Pollution Dispersion and Chemistry Transport Model (EURAD-CTM) has been used in Europe for PM and related exposure concentration modeling (Weinmayr et al., 2015; Nonnemacher et al., 2014), and GEM-MACH is being used in Canada (Peng et al., 2017). More specialized models may also be used to model specific sources, such as forest fires (Rappold et al., 2014).

CTMs are typically applied over grid sizes of 1 km or more, depending upon the application (while grid resolutions of less than 10 km are used over urban areas, continental scale applications typically are done at about 10−40 km, and global scale applications with larger grids yet). Nested grids are used to achieve a range of resolutions in many applications (Isakov et al., 2007; Byun and Schere, 2006; Zhang et al., 2004). In some applications, CTMs are coupled directly (i.e., on-line) to a meteorological model to provide meteorological fields, commonly WRF and CMAQ (Mathur et al.,

2010). Inputs include meteorological parameters (e.g., wind speed and direction, temperature, relative humidity, etc.) throughout the vertical layers of the atmosphere up to and including portions of the stratosphere and source emissions. The model outputs are the pollutant concentrations, and how they vary in space and/or time (Figure 3-1). The resulting fields are then used for epidemiologic studies and other studies of air quality. The ambient concentration fields are also used as inputs to microenvironmental models for estimating exposure (Baxter et al., 2013; Jones et al., 2013; Georgopoulos et al., 2005; Burke et al., 2002).

CTM models have been used for estimation of exposure concentrations, including for use in epidemiologic studies, both in North America and abroad (Ostro et al., 2015; Weinmayr et al., 2015; Anenberg et al., 2014; Marshall et al., 2014; Nonnemacher et al., 2014; Silva et al., 2013; West et al., 2013; Lim et al., 2012; Tagaris et al., 2010). For studies covering a large geographic area, CTM models can provide location-specific estimates without gaps in coverage. Issues with using CTM models relevant for exposure assessment studies are discussed below. Hu et al. (2015) used the UCD/CIT model to develop a 9-year set of simulated pollutant concentration fields, which were then used by Ostro et al. (2015) to assess the associations of $PM_{2.5}$ and UFP with health in a cohort epidemiologic study. When evaluating the model against monitoring data, they observed low error for $PM_{2.5}$ mass compared with error for individual components, such as SO_4^{2-}. In general, errors were higher when matching observations and simulated values on a daily basis compared with monthly and annual averaging periods, suggesting that model results are more accurate over longer averaging times. They did not report RMSEs or R^2. They noted one advantage of using model results over ambient monitoring was the availability of PM component concentrations every day, versus one out of three. Hou et al. (2015) extended the application of CMAQ to the study of human health effects by using the emissions input data to calculate the sensitivity of $PM_{2.5}$ concentrations to EGU and non-EGU emissions from four regions of the U.S. The sensitivities were then used to estimate changes in mortality as a function of $PM_{2.5}$ exposure concentrations and sensitivity of mortality to regional EGU and non-EGU emissions. Bravo et al. (2012) simulated $PM_{2.5}$ over the eastern U.S. using a 12 km× 12 km grid with a normalized mean bias of 2.1% over the course of a year. However, $PM_{2.5}$ concentrations were underestimated by up to 27% in summer and by up to 32% in late fall. In a related study, Mannshardt et al. (2013) compared results using observations and CMAQ-estimated exposure concentration fields in a study of $PM_{2.5}$ and O_3 associations on emergency hospital emissions in three counties of New York City for 2002−2006. CMAQ was run for the eastern U.S. using 12 km grids and used as input to a human exposure model, SHEDS-PM.

Results from CTMs can be biased and subject to various errors due to inputs and model parameterizations, but factors leading to simulation errors continue to be identified and reduced [e.g., Yu et al. (2014); Barsanti et al. (2013); Baek et al. (2011); Foley et al. (2010)]. For example, PM chemistry modules in CMAQ have been added and revised to address limitations in modeling secondary organic PM formation and nitrate chemistry. Nonetheless, biases and errors persist that may have weekly and seasonal trends due to limitations in emission inventory specifications and chemical and meteorological inputs, respectively. Nolte et al. (2015) compared MOUDI measurements of PM size distribution with

predictions of size distribution (ranging from 0.05 to 20 μm) for several PM components (SO_4^{2-}, NO_3^-, NH_4^+, Na^+, Cl^-, Mg_2^+, Ca_2^+, K^+) at different sites. Nolte et al. (2015) observed discrepancies between the modeled and monitored size distributions where the emissions data were not accurate. Typically, where data were omitted from the NEI, modeled size fractions were negatively biased so that exposure concentrations would be underestimated for those size fractions. Differential bias may also be observed across regions in space. Many such biases can be corrected for using adjustment factors based on comparisons of simulation results with observational data.

The dearth of ambient UFP observations, given that necessary instrumentation is not standard to routine monitoring networks (Section 2.4.5), has limited development and validation of CTMs at this size fraction. UFPs are derived from both direct emissions as well as atmospheric nucleation, and they coagulate on shorter time scales than larger particles (Section 2.3.4). Their concentrations can vary rapidly, and there is an observed steep spatial gradient in NC near sources, e.g., within a few hundred meters of highways (Karner et al., 2010; Zhou and Levy, 2007), suggesting finer resolution modeling should be used when using models to estimate exposure fields for UFPs. The lack of emissions information on UFPs also complicates CTM development. Hu et al. (2014a) and Hu et al. (2014b) developed source-based CTMs to predict $PM_{0.1}$ mass concentration surfaces for estimation of exposure concentrations that were used in an epidemiologic study by Ostro et al. (2015). The model included emissions, advection, diffusion, wet deposition, and dry deposition, but it omitted gas-to-particle phase chemistry, gas-to-particle phase conversion, nucleation, and coagulation. Hu et al. (2014b) used a 4 km × 4 km grid, which creates uncertainties because it is larger than the spatial scale over which UFPs evolve. They noted the need for either fine grid resolution or a subgrid scale model such as large eddy simulation to capture finer-scale dynamics. Hu et al. (2014b) reported Pearson $R = 0.92$ for comparison of $PM_{0.1}$ mass concentration predictions with measurements and Pearson $R = 0.94$ for comparison of $PM_{0.1}$ EC mass concentration predictions with measurements. Bias was not reported, but the authors noted that model performance degrades for $PM_{0.1}$ mass concentration >4 μg/m^3 or <1 μg/m^3 and for $PM_{0.1}$ EC mass concentration >1 μg/m^3 or <0.2 μg/m^3. Using SEARCH data to evaluate CMAQ performance for application in epidemiologic studies, Park et al. (2006) found that CMAQ did not capture UFP dynamics well, finding biases of an order of magnitude and more in NC. Elleman and Covert (2010, 2009a), and Elleman and Covert (2009b) also found that CMAQ did not accurately predict UFP numbers. They linked the biases to the treatment of particle nucleation, emissions estimates, and how the size distribution is captured. Stanier et al. (2014) developed a nonlinear, Lagrangian trajectory model designed to capture the size distribution of UFPs, and applied it to simulate UFPs in the Los Angeles area for a period when more detailed observations existed. They were able to reproduce NC within a factor of two 94% of the time at the four sites being used in the evaluation. In a comparison of 12 different nucleation parameterizations, Zhang et al. (2010a) found that the predicted NC of Aitken mode particles can vary by three orders of magnitude. These recent efforts illustrate that the large uncertainties in UFPs are still a great limitation in applying CTMs to model UFP exposure concentration.

Several new developments in CTM have made the technology more amenable for application in exposure assessment, such as improvements to the model through bias correction methods. However, several limitations still exist, including large grid sizes, uncertainties regarding emissions inputs, and uncertainties in modeling UFP. Specific modeling decisions must therefore be evaluated when CTMs are employed in epidemiologic studies.

3.3.2.4.2 Dispersion Modeling Applications for Exposure Concentration Estimation

Dispersion modeling has been performed to develop relatively fine resolution PM exposure concentration fields (Jerrett et al., 2005a). Dispersion models describe the relationship between emissions, meteorology and the resulting pollutant concentrations using algebraic relationships (e.g., the Gaussian Plume Equation), but they typically have limited ability to model chemistry (if any) (Holmes and Morawska, 2006). Examples of dispersion models include AERMOD, Research LINE-Source Model (or R-LINE), Community LINE-source Model (C-LINE), and California LINE Source Dispersion Model (CALINE) (Barzyk et al., 2015; Snyder et al., 2013; Cimorelli et al., 2005; Perry et al., 2005; Benson, 1992).

Model intercomparison has more recently focused on near-road dispersion modeling. Heist et al. (2013) conducted an intermodel comparison of AERMOD, CALINE, ADMS, and R-LINE for tracer (SF6) dispersion and found that the more recently developed ADMS and R-LINE exhibited lower error and better validation compared with CALINE and AERMOD. The models were each compared with results from a tracer study in Idaho Falls, ID (for open field and constructed barrier conditions) under different convective mixing conditions and near Highway 99 in Sacramento, CA and showed that ADMS, R-LINE, and both versions of AERMOD performed better than the CALINE models for both sites (Table 3-4). ADMS and R-LINE were further compared for near-neutral, weakly stable, convective, and moderately-to-strongly stable convective mixing conditions. At low concentrations (<1 pbb), both models exhibited a tendency for positive bias except for the moderately-to-strongly stable conditions, where both models exhibited some negative bias with more scatter. Chen et al. (2009) tested the performance of three dispersion models, CALINE4, CAL3QHC and AERMOD, at Sacramento, CA and London, U.K. regarding their application in modeling near road $PM_{2.5}$ concentrations. All three models produced R^2 values ranges from 0.85 to 0.90 comparing with measurement data (without adding background concentrations) in Sacramento, CA. However, the models perform less well at London, U.K. with R^2 value at around 0.03 without background concentrations due to the influence of street canyons on receptor performance.

Dispersion models are typically applied over smaller domains (near-source to urban) than CTMs (urban to global). For example, AERMOD is designed for simulating "near source" dispersion from point and area sources, and is most useful for assessing source impacts within 20 km of the source (Silverman et al., 2007), although it has been evaluated for distances up to 50 km for certain applications (Perry et al.,

2005). R-LINE is used for line source modeling, and was originally evaluated by Snyder et al. (2013) for distances of 200 m, though applications have applied it to urban scale (Batterman et al., 2014). While AERMOD is designed to simulate point and area/volume sources, it has been used to estimate the impacts of road networks by approximating road segments as area or volume sources (Isakov et al., 2014; Chen et al., 2009). Rowangould (2015) proposed a new dispersion modeling method for urban environments by breaking the city into coarse and fine grid cells (depending on the roadway density) and modeling dispersion from roadway sources in each roster in parallel. No validation was presented in the Rowangould (2015) paper.

Table 3-4 Comparison of dispersion models with data from a tracer study in Idaho Falls, ID and a near road study in Sacramento, CA and an UFP study in Somerville, MA and Chinatown in Boston, MA.

	Idaho Falls, ID		Sacramento, CA		Somerville, MA		Boston, MA	
Model	NMSE	*R*	NMSE	*R*	NMSE	R^2	NMSE	R^2
CALINE3	NR	NR	2.26	0.29	NR	NR	NR	NR
CALINE4	1.94	0.76	0.86	0.47	0.06	0.54	0.02	0.78
AERMOD-V	1.26	0.84	0.28	0.77	0.11	0.57	0.02	0.81
AERMOD-A	1.25	0.82	0.31	0.72	NR	NR	NR	NR
ADMS	1.14	0.88	0.20	0.78	NR	NR	NR	NR
R-LINE	0.96	0.85	0.34	0.75	0.13	0.58	0.02	0.81

NMSE = normalized mean squared error; NR = not reported, *R* = correlation (not specified if Pearson or Spearman); R^2 = coefficient of determination.

Sources: Data reproduced with permission of Heist et al. (2013); data reprinted with permission from Patton, AP, Milando, C, Durant, JL, Kumar, P. Assessing the suitability of multiple dispersion and land use regression models for urban traffic-related ultrafine particles. Environ Sci Technol. 2017;51:384-392. Copyright (2017) American Chemical Society. (Patton et al., 2017).

Several studies have used dispersion models at urban or neighborhood scales to estimate exposure concentrations. For example, Isakov et al. (2014) applied both AERMOD and R-LINE in Detroit, MI to estimate exposure concentrations to $PM_{2.5}$, EC, OC and pollutant gases at homes and schools of children with asthma participating in the Near Road Exposure of Urban Air Pollutants Study (NEXUS). CMAQ and kriging of observations were used to define regional air pollutant levels. Comparison between model results and measurement show reasonable performance with Pearson *R* range from 0.78 to 0.94 (daily average $PM_{2.5}$ concentrations) at different monitor sites. Simulated concentrations of PM are often used in conjunction with other estimates of regional PM because dispersion models are the more limited in spatial extent and so not designed for PM transport over large distances. For example, in an Atlanta application

(Dionisio et al., 2013; Sarnat et al., 2013b), a variety of approaches were used to estimate exposure concentrations. One approach used AERMOD to model impacts of traffic emissions and added the resulting concentrations to background concentrations (developed from observations) to construct a high-resolution PM field for use in an epidemiologic study. Sarnat et al. (2013b) used the fine-scale resolution to help identify potential health disparities linked to socioeconomic status that were not apparent when using a single fixed-site monitor. Maroko (2012) used AERMOD to simulate $PM_{2.5}$ impacts from point sources in the New York City area to assess environmental justice issues. Dispersion models can also be used to simulate components of PM, assuming that they do not undergo a chemical reaction in the atmosphere. For example, Colledge et al. (2015) used AERMOD to estimate particulate manganese exposure in two Ohio towns.

A recent development in dispersion modeling is the inclusion of UFP when modeling PM dispersion in the vicinity of a road. Patton et al. (2017) evaluated CALINE4, R-LINE, and AERMOD for UFP transport near roads in the greater Boston, MA area (Somerville, MA and Chinatown, within Boston). They found similar performance among all three models (Table 3-4). Stanier et al. (2014) recognized that it is challenging to model UFP emitted from mobile sources, because the UFP size distribution rapidly evolves upon emission from vehicle tailpipes. They fit emissions factors based on existing data for cruising and acceleration of heavy-duty and light-duty vehicles, estimating across a size distribution down to 7 nm and correcting for coagulation and deposition. The emissions factors were incorporated into a dispersion term in the model. Modeled particle NC was compared with measured concentration at two sites within the Los Angeles, CA metropolitan area and showed underestimation of the model (below a factor of 1:2) at one location and modeled data within a factor of two at the other site. Stanier et al. (2014) propose that the model is suitable for estimating spatially resolved UFP exposure concentrations on a daily basis.

Dispersion modeling continues to be used in exposure assessment studies, often in conjunction with CTMs to provide fine-scale spatial resolution. Recent improvements have been made in modeling dispersion of traffic-related air pollution and applying dispersion models at urban scales. However, dispersion models are still limited when applied in dense urban environments since dispersion models are not designed to deal with complex built topography (Kakosimos et al., 2010), and they are limited in their ability to represent UFP transport because they are not designed to capture size-specific UFP dynamics (Stanier et al., 2014).

3.3.2.4.3 Hybrid Approaches

Although spatiotemporal and LUR models have been applied to estimate long-term (e.g., monthly and annual) spatially-resolved ambient PM exposure concentrations, these techniques are typically not as successful for short-term (e.g., hourly and daily) applications as they do not include the impacts of changing source emissions and meteorology. PM data from ambient monitors provide accurate information on temporal trends at monitoring sites but little information on spatial patterns.

Emissions-based models provide spatial information consistent with emissions, chemistry, and meteorology but subject to limitations in the accuracy of these inputs as well as in the ability of models to simulate air pollution physical and chemical processes. "Hybrid" approaches that combine observational data with emissions-based model results are being developed and used to provide better estimates of single component and mixtures along with estimates of the associated uncertainties. These approaches range from rescaling model results to correction for known biases to combining observational and simulation data and optimizing spatiotemporal exposure concentration estimates.

Fusion of Model Outputs for Exposure Concentration Estimation

As noted above, CTMs by themselves typically have spatial resolution of 4 km or greater due to computational limitations, but they provide regional variations in PM (and PM component levels) and capture the formation of secondary PM, while dispersion models provide near-source impacts with a finer resolution. Given these complementary characteristics, it is natural to couple them (though care must be taken to not double count emissions) (Isakov et al., 2009).

Several recent studies have merged CMAQ with dispersion models. For example, Beevers et al. (2013) combined CMAQ results with the ADMS (a dispersion model) in London, England. They found that the combination could capture the spatial and temporal variations in air quality, with a mean bias of 0.6 $\mu g/m^3$ when comparing the model to monitors at five sites. Similarly, Zhai et al. (2016) combined R-LINE results with CMAQ-data fusion fields to estimate $PM_{2.5}$ exposure concentration fields for Atlanta, GA for a birth cohort study, with Pearson $R^2 = 0.72$ between the model and monitoring data with LOOCV normalized RMSE = 0.50 and normalized mean bias of 12%. A combined AERMOD-CMAQ application to New Haven, CT, was conducted (Lobdell et al., 2011; Isakov et al., 2009) to develop local scale (census block level) PM exposure concentrations in a base year (2001) and future years (2010, 2020 and 2030 to assess pollutant control programs). They noted the uncertainties due to model inputs, with coefficients of variation (standard deviation of concentration/mean concentration) ranging from 10−70% within different census tracts, but no estimates of model uncertainty with respect to $PM_{2.5}$ were provided. They linked their results to the HAPEM (Ozkaynak et al., 2008) and SHEDS (Isakov et al., 2009) exposure models, as described further in Section 3.3.4.

Another method of addressing the low spatial resolution of a CTM is to combine the model results with dispersion model results and LUR modeling output for exposure concentration. Wang et al. (2016) combined CTM with LUR using a hierarchical spatiotemporal modeling technique in which the 2-week average LUR-derived $PM_{2.5}$ concentration is modeled as a function of spatiotemporal trends and spatiotemporal residual terms, where the trend terms can be decomposed into an average and a spatially-varying trend (Keller et al., 2015). Wang et al. (2016) incorporated the CTM predictions into the spatially-varying trend term. The advantage of combining these two models is that the CTM is a mechanistic model employing principles of transport, dispersion, and atmospheric chemistry with finer temporal resolution (daily for this study), while the LUR offers fine-scale spatial resolution. The LUR

was fit to fixed-site $PM_{2.5}$ monitoring data in AQS and from the MESA Air study and incorporated a variable for long-term average concentration derived from the CAL3QHCR near-road line source dispersion model. Wang et al. (2016) found that addition of the CTM to the spatiotemporal model of Keller et al. (2015) only produced a marginal improvement in the prediction ability of the model for capturing $PM_{2.5}$ exposure concentrations. Di et al. (2016b) combined GEOS-Chem simulations, based on a 28 km × 25 km grid, with land use and meteorological variables to improve resolution to 1 km × 1 km across the northeastern U.S. Di et al. (2016b) compared the model results with monitoring data when the GEOS-Chem model was used alone and when it was combined with land use and meteorological variables. Out-of-sample R^2 for $PM_{2.5}$ improved from 0.47 for GEOS-Chem alone to 0.85 for the hybrid model. Out-of-sample R^2 ranged from 0.13−0.33 for $PM_{2.5}$ components (EC, OC, NO_3^-, SO_4^{2-}, NH_4^+, dust, sea salt) for GEOS-Chem alone, and R^2 improved to 0.41−0.83 across the $PM_{2.5}$ components for the hybrid model.

Fusion of Chemical Transport Model Predictions with Surface Observation Data

To take greater advantage of the strengths of observational data and model simulations, various data fusion approaches have been developed and applied. Such model-data fusion approaches used in estimating exposure concentration fields for health studies have frequently used CMAQ.

Downscaling approaches have been used frequently in recent years to correct biases in CTM output. Berrocal et al. (2009) proposed a downscaling approach combining monitoring and CMAQ modeling data to improve the accuracy of spatially resolved O_3 model data. Specifically, a Bayesian model was developed to regress CMAQ model estimates of O_3 concentration on monitoring data, and then the regression model was used to predict concentrations using the CMAQ model results as an input field. Although the downscaling method was originally developed for to model O_3 concentration, this technique has since been applied for modeling $PM_{2.5}$ concentration surfaces and found to have low NMB (0.95%) with mean correlation between model output and monitoring data of 0.97 (Bravo et al., 2017). Berrocal et al. (2010) extended the approach to include two pollutants (ozone and $PM_{2.5}$) in a single modeling framework. Predictive mean absolute error (PMAE) for $PM_{2.5}$ concentration in the bivariate model was 2.3 $\mu g/m^3$, compared with observations at 65 monitoring sites. PMAE for $PM_{2.5}$ was 2.4 $\mu g/m^3$ for the comparison of the single-pollutant model with the monitoring sites. Berrocal et al. (2012) also added smoothing processes that incorporate spatial autocorrelation and correction for spatial misalignment between monitoring and modeled data. Bentayeb et al. (2014) applied a similar data assimilation method in which local measurements and elevation data were combined with CTM output in a geostatistical forecasting model. This algorithm was applied for $PM_{2.5}$, PM_{10}, NO_2, SO_2, C_6H_6, and O_3. For the years 1989−2008, correlation between assimilated $PM_{2.5}$ concentration and local observations at 2 km resolution ranged from Pearson $R = 0.12$ to 0.85, with correlations decreasing with year. Bentayeb et al. (2014) explained the low correlations by a small number of $PM_{2.5}$ monitoring stations producing anomalous data and low correlations between emissions and concentration data.

Bias correction methods are variations on downscaling that have been developed to address spatiotemporal bias in the CMAQ model. For example, Crooks and Oezkaynak (2014) developed a statistical method of spatiotemporal bias correction of $PM_{2.5}$ mass and its major components for CMAQ fields. The correction uses speciated data from ambient monitors. Mass conservation for $PM_{2.5}$ observations constrains the sum of the $PM_{2.5}$ components' concentrations in locations without speciation monitors. The Crooks and Oezkaynak (2014) method is similar to downscaling methods in that it is a calibration method, but it corrects to the grid-scale rather than receptor points. The method was developed for use in an epidemiologic study investigating the association between $PM_{2.5}$ component ambient concentrations and birth outcomes throughout the state of New Jersey based on 1-month averages, so the focus was on addressing seasonal bias trends rather than daily biases. The bias-corrected CMAQ results were more accurate than the original CMAQ output (calculated as mean bias and RMSE using monitored concentrations as a reference), and a cross-validation study found that predictions improved when enforcing mass conservation. Comparison between the bias-corrected CMAQ and other downscaling or bias correction methods was not provided. Hogrefe et al. (2009) used a combined model-observation approach to estimate historic gridded fields of $PM_{2.5}$ mass and component concentrations, with corrections varying by component, season, and location. $PM_{2.5}$ mass concentration had a median bias of −0.3 $\mu g/m^3$ and median RMSE of 7.5 $\mu g/m^3$ compared with monitor values. Hogrefe et al. (2009) reported high relative biases and larger uncertainties for nitrate and organic carbon, compared with sulfate and ammonium. This was especially pronounced at remote IMPROVE sites, compared with urban CSN sites that have more monitors. Although more development is needed, these methods present additional options for applying CTMs for modeling $PM_{2.5}$ species.

A hierarchical Bayesian model (HBM) to predict daily $PM_{2.5}$ exposure concentrations for use in the Environmental Public Health Tracking Network has been developed through a CDC-EPA collaboration. This model integrates U.S. EPA monitor data with CMAQ simulation results to generate daily $PM_{2.5}$ concentration and error fields for a 36 km grid across the conterminous U.S. and for a 12 km grid across an eastern portion of the U.S. (Vaidyanathan et al., 2013; McMillan et al., 2010). In the application of HBM over a section of the eastern U.S., McMillan et al. (2010) found that the mean squared error using the HBM field was similar to a field developed using kriging, though the HBM outperformed kriging by 10−15% for bias. They found that 59% of the validation data was captured in the kriging prediction intervals as compared to 80−90% when using HBM. For the U.S.-wide application at 36 km resolution, the HBM method had Pearson *R*'s ranging from 0.91 to 0.94, depending upon the method used to impute the CMAQ data (Vaidyanathan et al., 2013), while the 12 km application over the eastern portion had Pearson *R*'s of 0.84 to 0.86.

Data fusion methods sometimes include fusing CTM modeling results with observations for exposure predictions. Chen et al. (2014) evaluated an observation-CMAQ fusion for population air pollution exposure assessment using an inverse distance weighting method on observation-CMAQ differences, concluding that data fusion improved the estimation of population-weighted average exposure concentrations. On average, $PM_{2.5}$ mass was estimated to be negatively biased by about 30%,

and individual components had a range of positive and negative biases from −150 to 100%. Nitrate and OC tended to see the largest biases and errors. After data fusion, the bias for $PM_{2.5}$ was near zero. Performance for individual components was similarly improved. Friberg et al. (2016) also fused CMAQ results to observations in a study focused on $PM_{2.5}$ exposures in Georgia. In this study, daily spatial exposure concentration fields for $PM_{2.5}$ mass, $PM_{2.5}$ components, and various gases were constructed from two blended fields. For one field, the temporal variance is driven by observations, while the spatial structure is driven by the annual mean CMAQ fields. The second field is constructed by scaling daily CMAQ simulated fields using mean observations to reduce bias. The final step blends the two fields based on using the temporal variance. The method intentionally does not force the fields to the observations at each monitor as they can be impacted by local emissions. The original CMAQ application for $PM_{2.5}$ was biased low about 12% with an RMSE of about 50% and an R^2 of 0.3. Typically, performance for individual $PM_{2.5}$ components was not as good. After applying the data fusion, the bias was almost totally removed, the RMSEs were about 20% for $PM_{2.5}$ and most PM components (though NO_3^- and EC were substantially higher), and the R^2 was about 0.92 (similar to individual components, though R^2 for EC was about 0.8). The method was tested using a 10−fold cross validation. In this case, the $PM_{2.5}$ R^2 was 0.75 and the RMSE was 30%.

Data fusion techniques have been tested in several other locations. Friberg et al. (2017) compared the fused CMAQ with original CMAQ model runs for five cities (Atlanta, GA, Birmingham, AL, Dallas, TX, Pittsburgh, PA, and St. Louis, MO) and found that the RMSE for $PM_{2.5}$ ranged from 2.21 to 3.76 μg/m^3 for the fused CMAQ, compared with 6.93 to 7.86 μg/m^3 for the original CMAQ.Huang et al. (2018) applied this method to North Carolina. In addition to doing the traditional 10-fold cross-validation, they also used spatial grouping of the 10% of monitors being removed to account for monitor clustering. In this case, the simulated $PM_{2.5}$ from the base CMAQ application had an RMSE of 6.3 μg/m^3 and an R^2 of 0.3, while after data fusion the RMSE decreased to 1.8 μg/m^3 and R^2 improved to 0.95. They also conducted 10-fold cross validation, both with and without (i.e., randomly withheld) spatial grouping. Finally, they compared the CMAQ-based data fusion fields with fields developed using a Bayesian-based method incorporating aerosol optical depth (AOD) from satellite data and found that the CMAQ-based approach performed slightly better (e.g., R^2 of 0.97 vs. 0.90 for AOD) using all of the data. The application of the same method in multiple locations shows that performance varies by domain.

Hybrid approaches can involve merging CTMs with dispersion and/or LUR models, merging CTMs with observational data, or some combination therein. Hybrid approaches improved CTM validation for $PM_{2.5}$ mass concentration when CTM was merged with either models or observational data. However, validation was not as good for $PM_{2.5}$ mass components, possibly due to the sparseness of validation data and limited data for $PM_{2.5}$ component emissions.

3.3.3 Satellite-based Methods for Exposure Concentration Estimation

At present, spatiotemporal methods for predicting exposure concentration based on satellite observations have been applied primarily to $PM_{2.5}$ using AOD information supplied by various satellite-based instruments [see Section 2.4.4 and (Lin et al., 2015; Hu et al., 2014c; van Donkelaar et al., 2014; Lee et al., 2012a; Mao et al., 2012; Liu et al., 2009)]. Satellite data (Section 2.4.5), obtained twice per day over the U.S., has been used in recent exposure assessment studies to estimate exposure concentrations in rural regions where monitoring is not conducted, to improve estimates of spatial variability in exposure concentrations, and to cover larger geographic regions. For example, Hystad et al. (2012) used a composite satellite image of AOD over the years 2001 to 2006 to estimate $PM_{2.5}$ exposure concentration across Canada, which includes urban and rural areas. The authors adjusted the satellite data by annual average $PM_{2.5}$ (or estimated $PM_{2.5}$ based on TSP measurements prior to $PM_{2.5}$ measurements, which began in 1984) and then used the study cohorts' residential locations to estimate their exposures based on their residential histories and exposure concentrations corresponding to those locations. Hystad et al. (2012) noted that incorrect assignment of exposure based on failure to account for movement between residences over time and space through this method resulted in 50% of individuals being classified in the wrong $PM_{2.5}$ exposure quintile. Prud'homme et al. (2013) computed the correlation of $PM_{2.5}$ exposure concentration predicted at a residential location with the nearest fixed-site monitor and found that the correlation decreased from $R = 0.74$ (not stated if Pearson or Spearman) when the home was within 1 km of the monitor and decreased to 0.60 for distances of 30−40 km between the home and the monitor. This result implies that the $PM_{2.5}$ exposure concentration predicted using AOD is a better predictor of exposure concentration within a given grid cell compared with exposure concentrations further away.

Errors in the relationship between $PM_{2.5}$ and AOD are related to variation in retrieval due to resolution of the satellite image and variation in meteorology, topography, and reflectance (Section 2.4.4). Hu (2009) calculated the correlation between surface $PM_{2.5}$ and AOD at 877 monitoring sites across the U.S. and found that average correlation east of the 100°W longitude line was Pearson $R = 0.67$, compared with Pearson $R = 0.22$ west of the 100°W longitude line. Negative correlations between $PM_{2.5}$ and AOD were calculated at several sites west of the 100°W longitude line but at only three locations east of the 100°W longitude line. van Donkelaar et al. (2010) also noted this discrepancy between satellite data quality in the eastern and western U.S. They used population-weighting to determine national and global estimates of exposure concentration. Population density happens to be lower in mountainous parts of the western U.S., where the highest biases in AOD were noted.

Improving the relationship between AOD and surface PM observations to estimate exposure concentrations has led to the use of more advanced statistical methods for fusion of satellite data with CTM output and surface data in recent years. Satellite-based exposure concentration models now use AOD and other information (e.g., direct pollutant observations, meteorology, and land-use). For example, van Donkelaar et al. (2012) applied a smoothed bias correction to satellite-derived $PM_{2.5}$ exposure

concentrations by first applying a 90-day moving average to the AOD prior to fitting $PM_{2.5}$ concentration estimates, and then smoothing the $PM_{2.5}$ exposure concentration field using IDW. The bias correction alone reduced the positive bias in the estimate to +29% with an estimated uncertainty of 54%. This is compared to the uncorrected $PM_{2.5}$ exposure concentration estimate, which had a bias of 97% with an estimated uncertainty of 67%. Incorporation of smoothing reduced the bias further to +14% with an uncertainty of 42%. An LUR approach to derive spatiotemporal pollutant fields accounts for the complexities in the AOD-PM relationships, including spatially and temporally varying conditions (Lee et al., 2016; Hu et al., 2014e; Ma et al., 2014; Chudnovsky et al., 2012; Hystad et al., 2011). Similar to LUR models, the approach is to develop a regression relationship between the observed $PM_{2.5}$ and AOD that includes the AOD field available from satellite observations and, potentially, other variables (e.g., those used in traditional LUR modeling). The regression coefficients can vary in time and space.

Not accounting for spatial and temporal variability in the relationship between $PM_{2.5}$ and AOD may lead to poor model performance (Hu et al., 2014d). Liu et al. (2009) recommended use of a two-stage general additive model including land use variables, with a stage one temporal model and stage two spatial model, so that the temporal and spatial variability are both addressed by the model, with an out-of-sample R^2 of 0.78, which was close to the model fit R^2 of 0.79 (stage one model-fit $R^2 = 0.77$, stage two model-fit $R^2 = 0.73$). Given the large spatial and temporal coverage of satellites, a large number of observations are typically available to develop the model. Additional spatial variation, particularly at scales finer than the resolution of the satellite observations, is provided by using fine scale land use variables. Lee et al. (2011) also recognized that the relationship between $PM_{2.5}$ and AOD is governed by time varying parameters affecting the vertical profile, the temporal variability of surface $PM_{2.5}$ over the course of a day. They developed a day-specific mixed effects model with random intercepts and slopes to quantify the relationship between surface $PM_{2.5}$ measured by surface monitors and AOD over New England in 2003. They assumed that temporal variability in properties that most strongly affect this relationship are much larger than their spatial variability over the domain of interest. In their model, the AOD fixed effect represents the average effect of AOD on $PM_{2.5}$ for all study days and the AOD random effects explain the daily variability in the $PM_{2.5}$-AOD relationship. Since some ground-based $PM_{2.5}$ monitors are located near strong sources, but Moderate Resolution Imaging Spectroradiometer (MODIS) samples represent an average over a 10 km × 10 km grid, an additional site specific random effects term is added to correct possible bias. Site specific out-of-sample R^2 varied from 0.87 to 1.0 with precision ranging from 8.8 to 38.6% for measured mean $PM_{2.5}$ at 26 urban sites (range: 9 to 19.5 $\mu g/m^3$).

Satellite observations of AOD have also been incorporated into hybrid modeling approaches. For example, Beckerman et al. (2013b) combined LUR, based on AOD observations, GEOS-Chem model output, land use data, and surface measurements of $PM_{2.5}$ concentration, with BME to predict $PM_{2.5}$ concentrations. BME was added to the model to improve spatiotemporal variability at scales smaller than the satellite's spatial resolution. Beckerman et al. (2013b) did not observe a substantial added benefit to including satellite data in an LUR model that also drew from land use data, surface measurements of $PM_{2.5}$ concentrations, and GEOS-Chem simulations. In this study, $PM_{2.5}$ concentrations were predicted

throughout the contiguous U.S. using an LUR-BME with and without satellite data. The LUR with inclusion of satellite data produced an out-of-sample R^2 of 0.27 compared with R^2 of 0.05 without inclusion of satellite data. When BME was incorporated in the LUR to interpolate between spatiotemporal residuals from the training model, out-of-sample R^2 improved to 0.79. R^2 was the same for the simulations both including and excluding satellite data. Using a similar hybrid satellite-modeling approach, Lee et al. (2012a) found that during the period 2000−2008 in the New England region of the U.S., a densely populated study domain with high traffic areas, $PM_{2.5}$ exposure concentrations were predicted with an out-of-sample R^2 value of 0.83 and a mean relative error of 3.5%. Chang et al. (2014) describe a statistical downscaling approach that incorporates LUR models utilizing AOD and statistical techniques for combining air quality data sets that have different spatial resolutions. In cross-validation experiments for a 3-year time period over the southeastern U.S., the model performed well (out-of-sample $R^2 = 0.78$ and RMSE = 3.61 μg/m^3 between observed and predicted daily $PM_{2.5}$ concentrations), with a 10% decrease in RMSE attributed to the use of AOD as a predictor. Validation of hybrid models has been inconsistent across studies.

Recent studies have tested the effect of satellite image resolution on $PM_{2.5}$ mass concentration predictions. Hu et al. (2014c), using a two-stage model, compared the more traditional MODIS AOD at 10 km resolution with a Multiangle Implementation of Atmospheric Correction (MAIAC) algorithm at 1 km in the Southeastern U.S. and found that, when using 10-fold cross-validation, the out-of-sample R^2 was slightly lower for the 1 km MAIAC observations (0.67 vs. 0.69), though the R^2 for model fitting was the same (0.83). This can be contrasted against Chudnovsky et al. (2013), discussed in Section 2.4.4 Alexeeff et al. (2015) also used the 1 km MAIAC fields to estimate exposure concentration fields, comparing their results to fields developed using kriging. They found that using the MAIAC-based fields had a higher cross-validation than kriging, and that the low out-of-sample R^2 yielded biases in areas with lower covariance in the concentration field. Lv et al. (2016) used MODIS AOD and a statistical method similar to Chang et al. (2014) in an application in China. It is discussed here in terms of how the evaluation was performed. Using all data (no withholding), the R^2 was 0.78 and the normalized mean error was 0.27. When they used a random leave 10% out procedure, the method led to an R^2, normalized mean error (NME) and RMSE of 0.68, 0.26 and 21.40 μg/m^3, respectively (like $PM_{2.5}$ concentrations, RMSE is much higher in China than in the U.S.). Using a process where monitors were removed after being grouped by city led to somewhat worse performance: 0.61, 0.28 and 23.53 μg/m^3, respectively. This suggests that method and application evaluations should use cross-validation methods that consider spatial groupings of monitors as a more stringent evaluation approach.

Recent efforts have fused satellite data with LUR model results and surface observations to maximize available data for estimation of exposure concentrations. Kloog et al. (2011) built a three-stage regression model using surface measurements as the response variable and including MODIS-derived AOD, land use variables, and a daily calibration $PM_{2.5}$ concentration from surface measurements to estimate $PM_{2.5}$ exposure concentration on a 1 km × 1 km grid across New England, and Kloog et al. (2012a) extended the model across the Mid-Atlantic states. When AOD was available, the

cross-validation out-of-sample R^2 was 0.83 for New England and 0.87 for the Mid-Atlantic states; when AOD was unavailable, cross-validation out-of-sample R^2 was still 0.81 for New England and 0.85 for the Mid-Atlantic states. When running the model for the two regions combined, Kloog et al. (2012b) found cross-validation out-of-sample R^2 was 0.81 for the total model of $PM_{2.5}$ and 0.81 for the LUR stage of the model. Kloog et al. (2014) built upon this method by first calibrating the AOD on daily measurements of $PM_{2.5}$ and adjusting for land use and meteorological variables for the Northeastern U.S. (New Jersey to Maine) for 2003−2011. Where AOD data were available, this model was used to predict $PM_{2.5}$ exposure concentration. The second model used the AOD−$PM_{2.5}$ calibration to predict AOD, which was then input into the regression model for a 1 km × 1 km grid. Finally, a 200 m × 200 m resolution prediction was developed by taking the residuals at each monitoring site and regressing them against the fine-scale resolution predictors to estimate fine-scale $PM_{2.5}$ exposure concentration. The models were built separately for temporal and spatial variables, and each had an average cross-validation out-of-sample $R^2 = 0.87$.

Similar to BME, machine learning approaches can be used to merge satellite observations with land use and other data for prediction of $PM_{2.5}$ mass concentration. For example, Reid et al. (2015) used a machine learning approach to estimate spatiotemporal $PM_{2.5}$ exposure concentration fields over the central region of California during a period of wildfires in the region by building spatiotemporal models using 11 model types from a set of 29 independent variables and selecting the optimal one for each model type. Input data included $PM_{2.5}$ and meteorological predictions from a CTM (WRF-Chem), land use data, and satellite AOD observations [three sets: the Geostationary Operational Environmental Satellite West Aerosol/Smoke Product (GASP) with a resolution of 4 km, the MODIS AOD product with a resolution of 10 km, and a local AOD product developed from MODIS data at a 500 m resolution, $PM_{2.5}$ and meteorological predictions from WRF-Chem, land use data, and distance to the nearest fire cluster]. The data were put in to each of the methods to develop a best model. Ten-fold cross-validation out-of-sample R^2 ranged from 0.387 to 0.803, and RMSE ranged from 1.49 μg/m^3 to 2.03 μg/m^3. It was found that similar model performance (within 1.5% of the RMSE) was achieved using only 13 variables, compared with a model of all 29 variables, with highest out-of-sample R^2 and lowest RMSE. They found that the variable most correlated with the $PM_{2.5}$ observations was the GASP followed by the distance to nearest active fire cluster, then the local AOD product and WRF-Chem $PM_{2.5}$ contributed equally. Di et al. (2016a) used a similar approach for a model of $PM_{2.5}$ exposure concentration across the contiguous U.S. GEOS-Chem simulation results were merged with satellite data for AOD, surface reflectance, and aerosol absorbance index, as well as with surface data from monitors reporting to AQS and data for meteorology and land use. For 2000−2012, out-of-sample $R^2 = 0.84$ with RMSE of 2.94 μg/m^3. The relationship between predicted and measured $PM_{2.5}$ concentrations was approximately linear until measured $PM_{2.5}$ concentrations were above approximately 60 μg/m^3. At that point, the predictions were insensitive to measured $PM_{2.5}$, but limited $PM_{2.5}$ concentration data were available above concentrations of 60 μg/m^3. These studies illustrate that the most important variables change, depending on the scenario modeled and the specific variables included.

Several other studies have devised novel methods to fuse observational data and results from models for estimation of exposure concentrations. Pirani et al. (2014) performed Bayesian spatiotemporal modeling for the assessment of short-term exposure to PM_{10} in London, U.K. using mass concentration measurements and output from the high spatial resolution air dispersion modeling system. They found exposure concentration estimates in urban areas are improved by including city-scale particle component and long-range transport component with covariates to account for residual spatiotemporal variation. Crooks and Isakov (2013) developed a novel method using wavelets to blend CMAQ, AERMOD, and observation fields to capture intra-urban transport of pollutants across a spectrum of spatial scales. They used it to estimate block group and zip code centroid exposure concentrations in Atlanta, GA and found that it captured the concentrations down to scales on the order of 100 m.

Several studies using AOD observations to predict $PM_{2.5}$ have been published in recent years. Progress in this approach includes incorporation of AOD with LUR, BME, and geostatistical modeling approaches that also may include surface measurements. Most applications of these hybrid models were designed to make comparisons across space for long-term exposure studies, where the temporal averages were more stable than for short-term exposure studies. Still, validation results across these studies were inconsistent, so attention must be given to the strengths and limitations of individual exposure models and their appropriateness for a given scenario (e.g., urban vs. rural, where monitoring for use in model training and validation may be sparse in the latter case) rather than assuming that the predicted $PM_{2.5}$ exposure concentration is accurate if it includes satellite data.

3.3.4 Microenvironmental Exposure Modeling

Indoor air exposures to total PM may be measured directly or estimated based on infiltration rates that typically use some level of mass balance model, potentially with chemistry, deposition, and other processes that can affect individual exposure. Inputs to indoor air mass balance models include ambient PM concentrations (observed or estimated), air exchange rates, indoor source emissions, and other factors that can affect the dynamics of pollutants. Such indoor air models are included in integrated exposure models (such as U.S. EPA's Stochastic Human Exposure and Dose Simulation [SHEDS] and Air Pollutants Exposure [APEX] models) or individual models (such as the Exposure Model for Individuals [EMI]), that also incorporate factors such as human activity patterns (Baxter et al., 2013). In Baxter et al. (2013), mean $PM_{2.5}$ exposure estimates obtained from models that considered time spent indoors and indoor-outdoor air exchange rates with no indoor sources were approximately half of the concentrations from ambient monitor measurements.

Personal exposure occurs in multiple microenvironments that people encounter through their daily activities (e.g., indoors, outdoors, in vehicles). Methods have been developed to simulate potential total exposures through such environments by tracking "representatives" of population groups as they move between indoor and outdoor microenvironments, using estimated pollutant concentrations in each

location to develop a time-weighted exposure profile for that population group. How individuals "move" though the different microenvironments is taken from studies of personal activity data [e.g., the Consolidated Human Activity Database, or CHAD (Isaacs, 2014)]. This database has information on sequential patterns of individual activities. This allows simulating not only "average" individual exposures, but also the distribution of exposures for different individuals or population groups over time.

Residential air exchange rate (AER) is a critical parameter for exposure models, such as APEX, SHEDS, and EMI (Breen et al., 2015; U.S. EPA, 2011, 2009a; Burke et al., 2001), with people spending the majority of their time indoors (Section 3.4.2.1). Since the appropriate AER measurements may not be available for exposure models, mechanistic, and empirical (i.e., regression-based) AER models can be used for exposure assessments. Empirical AER models do not consider the driving forces from the wind and indoor-outdoor temperature differences. Instead, a scaling constant can be used based on factors such as building age and floor area (Chan et al., 2005). Single-zone mechanistic models, such as the Lawrence Berkeley Laboratory (LBL) model, represent a building as a single well-mixed volume(Breen et al., 2010; Sherman and McWilliams, 2007; Sherman and Grimsrud, 1980). Recently, the LBL air infiltration model was linked with a leakage area model using population-level census and residential survey data (Sherman and McWilliams, 2007) and individual-level questionnaire data (Breen et al., 2010). Variations on the LBL model were compared with daily AER measurements in North Carolina (Breen et al., 2010) to find mean absolute differences of 40−43%.

The Hazardous Air Pollutant Exposure Model (HAPEM, now Version 6) is a screening level approach for modeling long-term inhalation exposures to ambient air pollutants, including PM. It can take modeled ambient pollutant concentrations as inputs or can use a parameterization of National Air Toxics Assessment (NATA)-generated PM estimates based on the near-road and far-from-road census tract populations (Rosenbaum and Huang, 2007). To develop exposure concentration estimates in microenvironments (e.g., commuting), microenvironmental factors are used to modify outdoor concentrations (e.g., provided by developing ambient exposure concentration fields). HAPEM has been used for nationwide assessments of exposure to sources of specific PM components and other pollutants (Ozkaynak et al., 2008) and, as noted above, coupled with a CMAQ/AERMOD combination (Isakov et al., 2009).

The SHEDS model and APEX model (which is now part of the Total Risk Integrated Methodology, or TRIM-Expo) both simulate individual movements though multiple microenvironments. APEX uses either a mass balance approach or a ratio to estimate in-vehicle or indoor concentrations (Che et al., 2015). Differences in subpopulation sampling methods between APEX and SHEDS produce small differences in predictions for population exposure concentrations (12.2 vs. 12.9 $\mu g/m^3$, respectively). SHEDS includes an activity-dependent ventilation rate to estimate dose. SHEDS-PM (the PM version of SHEDS) has a linear relationship between ambient concentrations and in-vehicle concentrations as well as in offices, restaurants/bars, schools, and stores. When analyzing contributions to exposure based on application of SHEDS-PM with daily $PM_{2.5}$ from CMAQ, Jiao et al. (2012) found that spatial variability

of ambient concentrations within urban areas was not substantial, but inter-individual variability in estimated exposures was substantial. Daily estimates of the ratio of ambient exposure to ambient concentration differed by a factor of 4−5 across the simulated individuals. SHEDS uses time-activity data from the CHAD database. Jiao et al. (2012) noted that there were not sufficient data in the CHAD database to quantify how time-activity patterns varied as a function of sex, region, or season when limited to the three areas studied, although statistically significant differences in time spent indoors or time spent outdoors by sex, region, and season were seen for CHAD data aggregated across large geographic regions. Liu and Frey (2011) proposed a method to estimate in-vehicle $PM_{2.5}$ exposure concentrations that combines using ambient concentrations and a local incremental concentration that accounts for near road enhancements in lieu of assuming a linear relationship between $PM_{2.5}$ concentration measured at fixed-site monitors and exposure concentrations estimated on the road using the CALINE4 dispersion model. Liu and Frey (2011) found that in-vehicle exposures contribute 10−20% of average daily $PM_{2.5}$ exposures. Georgopoulos et al. (2009) linked SHEDS with an environmental risk model (MENTOR) to estimate exposures (and the related risks) for $PM_{2.5}$ in Philadelphia, using a CTM to provide the $PM_{2.5}$ field. For those individuals with the highest 5% of $PM_{2.5}$ exposures, the major microenvironment was indoors, and environmental tobacco smoke was the dominant source. Ozkaynak et al. (2009) evaluated the uncertainty inherent in the coupled model formulation and compared it with a "crude" estimation of uncertainty when the models are run separately and with CMAQ outputs being used for SHEDS inputs. Uncertainty for the crude method was 1.2−4.4 times higher than for the coupled formulation.

The EMI model simulates individual exposure to $PM_{2.5}$ as the aggregate of exposures in multiple microenvironments (Breen et al., 2015). The EMI uses a five-tier system to model individual exposures. AER is predicted in Tier 1 based on surveys and variations on the LBL model for each microenvironment. Infiltration factors are predicted in Tier 2, and those values are used to predict outdoor concentrations infiltrated indoors measured immediately outside each microenvironment and measured at fixed-site monitors in Tier 3. A weighted average of the infiltration factor over time spent in different microenvironments is produced for each individual in Tier 4, and then personal exposures to pollution from directly outside the microenvironment and from the fixed-site concentration measurement are computed in Tier 5 for each individual. Personal monitoring and time-activity surveys are necessary inputs for the EMI. The Tier 2−5 metrics were observed to have approximately 15−25% error (Breen et al., 2018; Breen et al., 2015).

The trade-off between computational accuracy and efficiency in exposure and risk models has received limited discussion in the exposure model literature. Chang et al. (2012) described a simulation process incorporating SHEDS exposure simulation into two risk models: an "exposure simulator" in which an exposure time series was simulated stochastically and then incorporated into an ensemble average risk, and a two-stage "Bayesian" approach in which the computed time series was used as a prior in an exposure model. Risk of mortality (CHAPTER 11) associated with short-term $PM_{2.5}$ exposure was estimated using the exposure simulator model, the Bayesian model, and fixed-site $PM_{2.5}$ concentration as

an exposure surrogate. Little difference was observed between the exposure simulator and Bayesian models, but the exposure simulator was less computationally intensive.

3.3.5 Exposure Assignment Methods in Epidemiologic Studies

Epidemiologic studies use a variety of methods to assign exposures or exposure concentrations to study participants. Study design, data availability, and research objectives are all important factors for epidemiologists when selecting an exposure or exposure concentration estimation method. Common methods for estimating exposure concentrations from monitoring data include using fixed-site ambient monitoring, averaging concentrations from multiple monitors, and selecting the closest monitor to represent population exposure concentration. Investigators may also use statistical adjustment methods, such as trimming extreme values, to prepare the exposure concentration data set. Alternatively, modeling approaches described in Section 3.2.2 (modeling) can be used to estimate more spatially or temporally resolved exposure concentrations when data and resources are available.

Comparison studies have illustrated differences among the methods for producing estimates of exposure concentrations. For example, Dionisio et al. (2013) simulated $PM_{2.5}$ mass concentration, $PM_{2.5-EC}$, and $PM_{2.5}$–SO_4^{2-} exposures or exposure concentrations using different methods including a fixed-site monitor, an AERMOD model, a hybrid model combining regional background estimates with local contributions by AERMOD, and the SHEDS exposure model. The methods differed more with respect to modeling spatial variability (as measured by coefficient of variation) compared with temporal variability, with spatial variability being greater for the AERMOD and hybrid approaches for all three pollutants. Temporal variability was similar across methods for $PM_{2.5}$ and SO_4^{2-} with some difference across methods for EC. Mannshardt et al. (2013) compared use of fixed-site monitor concentration data, exposure concentrations estimated by CMAQ output, and exposures calculated using SHEDS to study respiratory emergency department visits associated with $PM_{2.5}$ exposure in New York County, NY, Queens, NY, and Bronx, NY. They found that the use of the SHEDS model led to a very similar relative risk as using CMAQ but provided additional information that helped reduce uncertainty. The effect estimates associated with exposure modeled by SHEDS and exposure concentration modeled by CMAQ were both higher and more precise than the effect estimate obtained from using fixed-site data as an estimate for exposure concentration. However, Mcguinn et al. (2017) estimated $PM_{2.5}$ exposure concentration and risks of coronary artery disease and myocardial infarction using a fixed-site monitor, CMAQ run with a census tract-level downscaler and with data fusion at 12 km resolution, and a satellite at 1 km and 10 km resolution. They did not find a relationship of model resolution with exposure concentration or with the magnitude of the effect estimates or with precision of the effect estimate for either health outcome studied.

Additional studies have also explored the effect of using different spatial averaging techniques to handle exposure concentration estimates from fixed-site monitoring data. Goldman et al. (2012) and

Strickland et al. (2013) compared exposure concentration estimates for $PM_{2.5}$, PM_{10}, SO_4^{2-}, NO_3^-, NH_4^+, EC, and OC among different methods, including fixed-site monitors, population-weighted averages of the (1) fixed-site monitors, (2) unweighted averages, (3) population-weighted averages, (4) area averages, and (5) a spatiotemporal model that used the pollutants' spatial and temporal autocorrelation structures to estimate exposure concentrations. Taking the spatiotemporal model as a reference, Goldman et al. (2012) found the fixed-site monitor had greater bias in the exposure metric compared with the averaging methods, and that bias increased for more-spatially-variable EC and OC compared with $PM_{2.5}$. These comparisons highlight differences among the methods in their ability to capture variability of exposures or exposure concentrations among study participants. The importance of capturing such variability also depends on the variability of the PM size cut or components.

Comparison of exposure concentration surfaces involving satellite observations have focused on spatial resolutions appropriate for different exposure concentration estimation techniques. Lee et al. (2012b) compared the appropriate averaging distance ranges for $PM_{2.5}$ exposure concentration surfaces estimated using satellite detection and kriging with $PM_{2.5}$ concentration measurements from fixed-site monitors using 6 years of data. Lee et al. (2012b) compared the kriged or remotely sensed data with the surface measurements over distances ranging from 7.6 km to 106.0 km using mean squared error (MSE), mean error, mean absolute error (MAE), Pearson correlation, and Spearman correlation. Lee et al. (2012b) estimated that kriging provided superior exposure concentration estimates when distances from the kriged estimate to the fixed-site monitor were smaller than 98 km while satellite detection provided superior exposure concentration estimates when distances from the remotely-sensed concentration centroid to the fixed-site monitor exceeded 98 km. Jerrett et al. (2016) compared remotely sensed $PM_{2.5}$ exposure concentration surfaces estimated from input by three satellite systems, downscaled CMAQ exposure concentration estimates, a spatiotemporal exposure concentration surface, a LUR model, and a combined LUR-kriging model. The mean and median $PM_{2.5}$ exposure concentrations were similar across methods (range of means: 11.4 to 12.2 $\mu g/m^3$), but the LUR models and one spatiotemporal model (geographically-weighted regression) produced higher variability than the other methods (IQRs range from 3.6 to 5.7 $\mu g/m^3$).

Epidemiologic study design influences the relevance and utility of exposure concentration estimation methods. Methods with high temporal resolution are preferable for short-term exposure studies even if spatial resolution is low, assuming the temporal variability at the site of data collection does not vary substantially across the study area. Fixed-site monitors, with temporal variability matching that of the health dataset, may be appropriate for this case, especially for $PM_{2.5}$ concentration, which tends to be less spatially variable than concentrations of $PM_{10-2.5}$ or UFP. Methods with high spatial resolution are preferable for long-term exposure studies where spatial contrasts are important. Methods that merge data from several sources, such as hybrid methods drawing from a combination of land use variables, satellite observations, CTM model output, and surface measurements, are designed to produce more spatial variability in the PM concentration surface. However, satellite data and CTM model output are not as readily available for $PM_{10-2.5}$ and UFP as they are for $PM_{2.5}$. Table 3-5 summarizes various exposure

concentration estimation methods used in PM epidemiologic studies, appropriate applications, and associated errors and uncertainties. In general, the methods listed in Table 3-5 that model spatial variability more accurately are often used in studies of health effects from long-term PM exposure, because uncertainties in spatial variability will have more of an influence on effect estimates from long-term exposure studies. Similarly, the methods that capture temporal variability are typically used in short-term PM exposure studies, because uncertainties in temporal variability will have more of an influence on effect estimates from short-term exposure studies.

Table 3-5 Summary of exposure or exposure concentration estimation methods, their typical use in PM epidemiologic studies, and related errors and uncertainties.

Exposure Concentration Assignment Method	Description	Epidemiologic Application	Strengths	Limitations	Exposure Errors
Measurement Methods					
Fixed-site monitor [Section 3.3.1.1; Section 2.4.1; U.S. EPA (2009b)]	Typically, the nearest monitor to a receptor location; monitor type varies with particle size: $PM_{2.5}$: A FRM or FEM monitor located at a fixed location to measure ambient PM concentration; $PM_{10-2.5}$: A dichotomous FRM or FEM monitor located at a fixed location to measure ambient PM concentration, collocated PM_{10} and $PM_{2.5}$ monitors used to calculate concentrations by differencing for a given location, or non-collocated PM_{10} and $PM_{2.5}$ monitors used to calculate concentrations by differencing across a city or county; UFP: typically, a CPC to measure particle number concentration.	Short-term exposure studies: surrogate for ambient PM exposure concentration of a population within a city. Long-term exposure studies: surrogate for ambient PM exposure concentration to compare populations within a city or among multiple cities.	Ambient PM concentration measurements undergo rigorous quality assurance	Non-FRM and non-FEM optical instruments cannot be calibrated to ambient conditions, based on differences in size distributions and composition of calibration particles (e.g., Arizona road dust) and ambient PM; measurements of ambient PM concentration made at a fixed location may differ from an exposed individual's true exposure concentration, and no spatial variation is assumed; smaller particles (e.g., UFP) are more susceptible to evaporative losses.	Correlation between outdoor PM concentrations proximal to the receptors and ambient PM concentration measurements typically decreases with increasing distance from the monitor, especially for $PM_{10-2.5}$ and UFP, potentially leading simultaneously to decreased precision and to bias towards the null, as increased noise drives the slope towards zero; errors in $PM_{10-2.5}$ concentrations related to different flow rates used in PM_{10} and $PM_{2.5}$ monitors for the differencing methods; errors in $PM_{10-2.5}$ concentrations due to differences in locations of PM_{10} and $PM_{2.5}$ monitors when the instruments are not collocated. Potential for bias if ambient PM concentration at a receptor location is higher or lower than the ambient PM concentration measured at the monitor, especially for $PM_{10-2.5}$ and UFP; potential for imprecision from assumption of constant PM concentration within some radius of the monitor, especially for $PM_{10-2.5}$ and UFP; errors in $PM_{10-2.5}$ concentrations related to different flow rates used in PM_{10} and $PM_{2.5}$ monitors for the differencing methods; errors in $PM_{10-2.5}$ concentrations due to differences in locations of PM_{10} and $PM_{2.5}$ monitors when the instruments are not collocated.

Table 3-5 (Continued): Summary of exposure or exposure concentration estimation methods, their typical use in PM epidemiologic studies, and related errors and uncertainties.

Exposure Concentration Assignment Method	Description	Epidemiologic Application	Strengths	Limitations	Exposure Errors
Microenvironmental monitor (Section 3.3.1.2)	Typically located in an outdoor or indoor microenvironment to measure ambient PM concentration; $PM_{2.5}$: A FRM or FEM monitor located at a fixed location to measure ambient PM concentration; $PM_{10-2.5}$: A dichotomous FRM or FEM monitor located at a fixed location to measure ambient PM concentration, or collocated PM_{10} and $PM_{2.5}$ monitors used to calculate concentrations by differencing for a given location; UFP: typically, a CPC to measure particle number concentration	Panel studies: PM exposure (e.g., personal or residential samples) within a geographic area	Ambient PM concentration measurements undergo rigorous quality assurance	Non-FRM and non-FEM optical instruments cannot be calibrated to ambient conditions, based on differences in size distributions and composition of calibration particles (e.g., Arizona road dust) and ambient PM; instrument expense may make it difficult to perform sampling simultaneously in multiple environments.	Nonambient PM exposure sampling may lead to bias if appropriate statistical methods are not used for handling biased data.

Table 3-5 (Continued): Summary of exposure or exposure concentration estimation methods, their typical use in PM epidemiologic studies, and related errors and uncertainties.

Exposure Concentration Assignment Method	Description	Epidemiologic Application	Strengths	Limitations	Exposure Errors
Active personal exposure monitor (Section 3.3.1.2)	Air is pulled through a pump and sampled for ambient PM concentration; $PM_{2.5}$ or $PM_{10-2.5}$: air is typically directed through a collection filter on an impaction plate or past an optical detector; upstream hardware (e.g., cyclone) may be used for separating PM by specific size fractions; UFP: typically, a CPC to measure particle number concentration; for BC, PM is typically measured with an aethalometer.	Panel studies: PM exposure (e.g., personal or residential samples) within a geographic area	PM and/or BC concentrations are obtained at the site of the exposed person	Non-FRM and non-FEM optical instruments cannot be calibrated to ambient conditions, based on differences in size distributions and composition of calibration particles (e.g., Arizona road dust) and ambient PM; some monitors can detect a minimum particle size of 0.1 μm and a few others can detect 0.25 μm, but the majority detect over the entire fine PM range; many monitors are noisy.	Nonambient PM exposure sampling may lead to bias if appropriate statistical methods are not used for handling biased data.
Passive personal exposure monitor (Section 3.3.1.2)	PM is captured on a treated substrate via passive exposure for a time period to measure a personal or area sample, and the substrate is analyzed by SEM; concentration is calculated based on a model of passive diffusion flux for $PM_{2.5}$, $PM_{10-2.5}$, or UFP.	Panel studies: ambient PM exposure within a city or among multiple cities	PM concentrations are obtained at the site of the exposed person	Long duration integrated sampling time (e.g., 7 days) does not allow for time-series analysis; diffusion-related losses to the passive sampler hardware have the potential to bias the concentration estimation based both on reduced particle counts and overestimation of flux to the sampling substrate.	Nonambient PM exposure sampling may lead to bias.

Table 3-5 (Continued): Summary of exposure or exposure concentration estimation methods, their typical use in PM epidemiologic studies, and related errors and uncertainties.

Exposure Concentration Assignment Method	Description	Epidemiologic Application	Strengths	Limitations	Exposure Errors
Modeling Methods					
Data averaging (Section 3.3.2.1)	Averaging across multiple monitors during the same time window and within a geographical area such as a city or county, typically using fixed-site monitoring data	Short-term exposure studies: surrogate for ambient PM exposure concentration of a population within a city	Ambient PM concentration measurements undergo rigorous quality assurance; averaging scheme designed for population or trend of interest	Non-FRM and non-FEM optical instruments cannot be calibrated to ambient conditions, based on differences in size distributions and composition of calibration particles (e.g., Arizona road dust) and ambient PM; measurements of ambient PM concentration made at a fixed location may differ from an exposed individual's true exposure concentration, and spatial variation is assumed to be well-represented by the averaging scheme.	Correlation between outdoor PM concentrations proximal to the receptors and ambient PM concentration measurements typically decreases with increasing distance from the monitor, especially for $PM_{10-2.5}$ and UFP, potentially leading simultaneously to decreased precision and to bias towards the null, as increased noise drives the slope towards zero.
	Spatial averaging (area averaging, population-weighted averaging), typically using fixed-site monitoring data	Long-term exposure studies: surrogate for ambient PM exposure concentration, usually within a city or geographic region			Potential for bias if ambient PM concentration at a receptor location is higher or lower than the spatial average, especially for $PM_{10-2.5}$ and UFP; potential for imprecision from assumption of constant PM concentration within some geographic area, especially for $PM_{10-2.5}$ and UFP.

Table 3-5 (Continued): Summary of exposure or exposure concentration estimation methods, their typical use in PM epidemiologic studies, and related errors and uncertainties.

Exposure Concentration Assignment Method	Description	Epidemiologic Application	Strengths	Limitations	Exposure Errors
Inverse distance weighting (Section 3.3.2.2)	Measured ambient PM concentrations are interpolated to estimate ambient PM concentration surfaces across regions; IDW uses an inverse function of distance to monitors	Long-term exposure studies: surrogate for ambient PM exposure concentration, usually within a city or geographic region	High spatial resolution	Over-smoothing based on assumption that ambient PM concentration is constant for a given distance from the source or based on smoothing function between monitors (which is more of an issue for $PM_{10-2.5}$ and UFP).	Potential for negative bias if ambient PM sources are not captured or PM concentration is overly smoothed; potential for positive bias if PM deposition or other loss processes; potential for imprecision from overly smoothed PM concentration.
Kriging (Section 3.3.2.2)	Measured ambient PM concentrations are interpolated to estimate ambient PM concentration surfaces across regions	Long-term exposure studies: surrogate for ambient PM exposure concentration, usually within a city or geographic region	High spatial resolution	Over-smoothing is possible based on smoothing function between monitors (which is more of an issue for $PM_{10-2.5}$ and UFP).	Potential for negative bias if ambient PM sources are not captured or PM concentration is overly smoothed; potential for positive bias if PM deposition or other loss processes; potential for imprecision from overly smoothed PM concentration.
Land use regression (Section 3.3.2.3)	Measured ambient PM concentrations are regressed on local variables (e.g., land use factors); the resulting model is used to estimate ambient PM concentrations at specific locations	Long-term exposure studies: surrogate for ambient PM exposure concentration, usually across a city but sometimes among multiple cities	High spatial resolution	Does not account for emission rates, dispersion, or atmospheric chemistry and may account for meteorology only in terms of wind speed and wind direction, depending on model formulation; has limited generalizability to other locations; uncertainties are highest where training monitors are sparse.	Potential for bias if grid is not finely resolved, if the model is misspecified, or if the model is applied to a location different from where the model was fit.

Table 3-5 (Continued): Summary of exposure or exposure concentration estimation methods, their typical use in PM epidemiologic studies, and related errors and uncertainties.

Exposure Concentration Assignment Method	Description	Epidemiologic Application	Strengths	Limitations	Exposure Errors
Spatiotemporal model (Section 3.3.2.3)	Measured ambient PM concentrations are modeled by a spatial average, spatially-varying covariates, and a spatiotemporal residual; the resulting model is used to estimate ambient PM concentrations at specific locations	Short-term and long-term exposure studies: surrogate for ambient PM exposure concentration, usually across a city but sometimes among multiple cities	High spatial resolution	Does not account for emission rates, dispersion, or atmospheric chemistry and may account for meteorology only in terms of wind speed and wind direction, depending on model formulation; has limited generalizability to other locations; uncertainties are highest where training monitors are sparse.	Potential for bias if grid is not finely resolved, if the model is misspecified, or if the model is applied to a location different from where the model was fit.
Chemical transport model (Section 3.3.2.4.1)	Grid-based ambient PM concentrations are estimated from emissions, meteorology, and atmospheric chemistry and physics	Short-term and long-term exposure studies: surrogate for ambient PM exposure concentration, sometimes within a city but more typically across a larger region	Strengths include accounting for emission rates, mixing height, atmospheric stability, meteorology, atmospheric chemistry, and complex terrain	Limited grid cell resolution (i.e., grid cell length scale is typically 4−36 km); spatial smoothing of local PM emissions sources; UFP not typically modeled; temporal emission allocations (e.g., by hour of weekday, by month, etc.) are generally the same over time.	Potential for bias when grid cells are too large to capture spatial variability of ambient PM exposures, especially for $PM_{10-2.5}$; bias in PM mass concentration and PM components related to underestimation of BC and OC.
Dispersion model (Section 3.3.2.4.2)	Ambient PM concentrations at specific locations are estimated from emissions, meteorology, and atmospheric physics	Short-term and long-term exposure studies: surrogate for ambient PM exposure concentration within a city or geographic region	High spatial and temporal resolution, accounts for atmospheric physics from local emission sources	Very limited representation of atmospheric chemistry or background PM concentrations; input emissions data are sometimes not available (e.g., roads where vehicle counts are not measured).	Potential for bias where the dispersion model does not capture boundary conditions and resulting fluid dynamics well (e.g., in large cities with urban topography affecting dispersion).

Table 3-5 (Continued): Summary of exposure or exposure concentration estimation methods, their typical use in PM epidemiologic studies, and related errors and uncertainties.

Exposure Concentration Assignment Method	Description	Epidemiologic Application	Strengths	Limitations	Exposure Errors
Hybrid approaches (Section 3.3.2.4.3)	Grid-based ambient PM concentrations are estimated from emissions, meteorology, and atmospheric chemistry and physics and bias corrected based on monitoring data	Short-term and long-term exposure studies: surrogate for ambient PM exposure concentration, sometimes within a city but more typically across a larger region	Strengths include accounting for emission rates, mixing height, atmospheric stability, meteorology, atmospheric chemistry, and complex terrain; bias correction improves model results, particularly where biases are large	Limited grid cell resolution (i.e., grid cell length scale is typically 4−36 km); resource-intensive; spatial smoothing of local PM emissions sources; UFP not typically modeled.	Although there is the potential for bias when grid cells are too large to capture spatial variability of ambient PM exposures (especially for $PM_{10-2.5}$; bias in PM mass concentration and PM components related to underestimation of BC and OC), fusing model results with monitoring data helps to minimize exposure errors.
Microenvironmental modeling [e.g., APEX, SHEDS (Section 3.3.4)]	Estimates distributions of micro-environmental PM concentrations, exposures, and doses for populations (e.g., census tracts) based on air quality data, demographic variables, and activity patterns	Short-term and long-term exposure studies; panel studies	Accounts for variability of PM exposures across large populations, accounts for different concentrations in different microenvironments, accounts for location-activity information	Models simulate individuals and their exposures; they do not model actual individuals but simulated representative individuals based on the population being modeled.	Potential for bias when the modeled distributions of ambient PM concentration, indoor:outdoor pollutant ratios, and time-activity patterns differ from the true distributions.

Table 3-5 (Continued): Summary of exposure or exposure concentration estimation methods, their typical use in PM epidemiologic studies, and related errors and uncertainties.

Exposure Concentration Assignment Method	Description	Epidemiologic Application	Strengths	Limitations	Exposure Errors
Satellite-based methods (Section 3.3.3)	Grid-based ambient PM concentrations are estimated from emissions, meteorology, and atmospheric chemistry and physics and bias corrected based on satellite data	Long-term exposure studies: surrogate for ambient PM exposure concentration, sometimes within a city but more typically across a larger region	Strengths include bias correction improves model results, particularly where biases are large	Limited temporal resolution (i.e., based on a daily observation); assume AOD is representative of ground-level $PM_{2.5}$ concentrations; algorithms converting AOD observations to $PM_{2.5}$ concentrations vary regionally; limited grid cell resolution (i.e., grid cell length scale is typically 1−36 km); spatial smoothing of local PM emissions sources; $PM_{10-2.5}$ and UFP not typically modeled.	Although there is the potential for bias when grid cells are too large to capture spatial variability of ambient PM exposures (especially for $PM_{10-2.5}$; bias in PM mass concentration and PM components related to underestimation of BC and OC), fusing model results with satellite data helps to minimize exposure errors.

APEX = air pollutants exposure model; BC = black carbon; CPC = condensation particle counter; FEM = federal equivalent method; FRM = federal reference method; IDW = inverse distance weighting; SHEDS = stochastic human exposure and dose simulation; PM = particulate matter $PM_{2.5}$ = PM with a 50% cut point at 2.5 μm; $PM_{10-2.5}$ = PM fraction captured between 50% cut points of 10 μm and 2.5 μm; SEM = scanning electron microscopy; UFP = ultrafine PM.

3.4 Exposure Assessment and Interpretation of Epidemiologic Study Results

The exposure assignment methods discussed in Section 3.3 inform different PM-health relationships, depending on the method chosen. These relationships include those between ambient concentration and health effects, between exposure concentration and health effects, and between ambient exposure and health effects. The ambient exposure-health relationship is the main relationship of interest for the causal determinations in the ISA, and it can be evaluated using personal monitors, microenvironmental models, or ambient concentration as a surrogate for exposure (Table 3-5). Methods that estimate local exposure concentration, including spatial averaging, LUR, and emissions/transport models inform the exposure concentration-health relationship. Ambient concentration measured at an ambient monitor can be used directly to inform the ambient concentration-health relationship.

The following sections review the available literature to explore how the selection of an exposure metric may influence these relationships. The following discussion focuses on the relationships influencing exposure, such as those between ambient PM concentration and exposure to ambient PM (Section 3.4.1), factors contributing to error in estimating exposure to ambient PM (Section 3.4.2), and the influence of exposure errors on epidemiologic study results (Section 3.4.4). Additionally, this section explores copollutant relationships that may influence interpretation of the health effect estimates for ambient PM exposures (Section 3.4.3).

3.4.1 Relationships Influencing Exposure

This section builds upon discussions from the 2009 PM ISA (U.S. EPA, 2009b) about relationships between ambient PM measured outdoors, ambient PM infiltrating indoors, and resulting relationships between indoor and outdoor ambient PM concentrations and between personal exposure to ambient PM and ambient PM concentration. Summaries of relevant discussions from the 2009 PM ISA are included in Section 3.4.1.1, Section 3.4.1.2, and Section 3.4.1.3.

3.4.1.1 Air Exchange Rate and Infiltration

When concentrations measured at an ambient monitor are used as a surrogate for $PM_{2.5}$, $PM_{10-2.5}$, or UFP exposure, the metric does not account for reduction in exposure concentration related to the process of infiltration indoors. The 2009 PM ISA (U.S. EPA, 2009b) describes how air exchange rate (AER) can influence the infiltration of PM into the building envelope. AER is the airflow into and out of a building and is represented by a in the conceptual model presented in Section 3.2.2. Several factors affect the AER, including weather conditions, building characteristics, and occupant behavior, resulting in

substantial spatial and temporal variations in AER. Deposition is dependent on PM size, where UFP loss can be expected to occur through Brownian diffusion, while $PM_{10-2.5}$ losses may occur through gravitational deposition or impaction. These phenomena were described in Sarnat et al. (2006a) and summarized in the 2009 PM ISA. New developments include characterizing infiltration of UFP, clarification on the factors influencing infiltration, and examination of air conditioning usage or AER as an effect modifier of $PM_{2.5}$ exposure for epidemiologic studies.

Field studies indicate that residential AER values vary by region and season, with substantial variability among different residences. Cao and Frey (2011) observed higher geometric mean AER in New York City (0.64 $hour^{-1}$), where housing stock tends to be older, compared with Harris County, TX (0.37 $hour^{-1}$) and a six-county region of central North Carolina (0.54 $hour^{-1}$). The RIOPA (Relationship Among Indoor, Outdoor, and Personal Air) study measured summer and winter AER in homes in three U.S. cities (Los Angeles, CA, Elizabeth, NJ, and Houston, TX). Median AER values were similar in Los Angeles and Elizabeth (0.87 $hour^{-1}$ and 0.88 $hour^{-1}$, respectively), but lower in Houston (0.47 $hour^{-1}$) (Yamamoto et al., 2010). Isaacs et al. (2013) analyzed seasonal RIOPA and DEARS data and found similar AER for the RIOPA cities and median AER of 0.92 $hour^{-1}$ in winter and 1.46 $hour^{-1}$ in summer. Summer AER was lower than winter AER in Elizabeth (0.88 $hour^{-1}$ vs. 1.07 $hour^{-1}$) and Houston (0.37 $hour^{-1}$ vs. 0.63 $hour^{-1}$). A similar seasonal difference was observed in Windsor, Ontario (0.14 $hour^{-1}$ vs. 0.3 $hour^{-1}$) (Wheeler et al., 2011). In contrast, Los Angeles AER values were higher in summer than winter (1.14 $hour^{-1}$ vs. 0.61 $hour^{-1}$). More prevalent use of open windows in Los Angeles and Detroit, where summertime tends to be less humid than in Elizabeth or Houston, may promote greater air exchange. These differences may grow smaller with the increased prevalence of air conditioning, because air conditioning usage is an important factor in infiltration (Allen et al., 2012). The higher winter AER values in the northern cities of Elizabeth and Windsor may be due to an increased "stack effect" resulting from indoor-outdoor temperature differential (Breen et al., 2014).

Between-city variability in residential building characteristics may explain heterogeneity in associations of $PM_{2.5}$ with risk estimates (Section 11.1.6.3.2). Baxter and Sacks (2014) explored this idea by performing *k*-means cluster analysis of factors related to AER, including percentage of homes with central air conditioning, mean year the home was built, and mean home size, from the American Housing Survey across 94 CBSAs across the U.S. Their analysis produced five clusters, labeled Clusters 1-5 by the study authors. Clusters 2 and 3 had high proportions of air conditioning (72% each), and those clusters primarily spanned the southern U.S. including the southeast and southwest. Homes in these clusters were built, on average, in 1989 and 1970. Cluster 1, which crossed the Northeast, Rust Belt, Pacific coast, and Denver, had slightly more than 1 quarter (27%) of homes with air conditioning, and had smaller homes on average (1,672 ft^2). Clusters 4 and 5 were primarily situated in the Northeast and Rust Belt, had air conditioning in 56 and 19% of homes, and were somewhat larger (2,098 ft^2 and 2,253 ft^2). In the latter three clusters, homes were built on average in 1954, 1959, and 1945. The results of Baxter and Sacks (2014) and Baxter et al. (2017), in a related study of short-term $PM_{2.5}$ exposure and mortality, support the

idea of a regional differences in building characteristics and health effects estimates based on north-south and east-west differences in housing clusters.

Vehicle AERs can be substantially higher than residential AERs, leading to rapid infiltration of on-road pollutants. Many factors affect vehicle AER, including whether windows are opened or closed, vehicle make and model, vehicle age, driving speed, and fan/recirculation setting on the vehicle ventilation system. The combined effect of these factors result in AERs that vary by more than two orders of magnitude, from less than 1 $hour^{-1}$ (approximately equivalent to a typical residential AER) to more than 100 $hour^{-1}$ (Hudda et al., 2011). In a model fit to AER measurements on 59 vehicles driven at three different speeds under recirculation conditions with closed windows, the most important variables were vehicle age, mileage, and speed, plus an adjustment for manufacturer (Fruin et al., 2011). Fan speed and vehicle shape were not influential variables.

More data have since been acquired to estimate F_{inf} for UFP since the Sarnat et al. (2006a) study. Sarnat et al. (2006a) found that F_{inf} reached a maximum for particles of 200 nm size and was sensitive to AER and PM composition. The smallest size they studied was 20 nm. Kearney et al. (2014) estimated daily F_{inf} for PM_1, $PM_{2.5-1}$, and UFP (NC estimated by the authors to have 80% smaller than 100 nm) in Edmonton, Ontario. They studied conditions in winter and summer and observed winter-time median F_{inf} of 0.45 for PM_1 (based on the SO_4^{2-} method) and of 0.19 for UFP (based on P-TRAK portable sampler measurements), a 58% reduction. During the summer, median F_{inf} was 0.79 for PM_1 and 0.51 for UFP, a 35% reduction. In addition to the influence of season, Kearney et al. (2014) also tested building age and ventilation characteristics and found that building age, airflow characteristics in the home, temperature differential, and wind speed influenced F_{inf} for PM_1 in winter, while furnace operation and wind speed influenced F_{inf} for UFP in winter. For summer, only wind speed influenced F_{inf} for PM_1, while portable air cleaner operation and window opening influenced F_{inf} for UFP. Rim et al. (2010) focused on UFP smaller than 100 nm and were able to measure particles as small as 4.4 nm (under open window conditions) and 9 nm (under closed window conditions) in their study of F_{inf} using an SMPS. For open window conditions, F_{inf} = 0.08 for particles in the 4.4−5.1 nm bin. For closed window conditions, F_{inf} = 0.03 for the 9−11 nm bin. For the 55−64 nm bin, F_{inf} was 0.16 for closed windows and 0.47 for open windows. The Rim et al. (2010) study also compared the C_{in}/C_{out} ratio with F_{inf}. Unlike for $PM_{2.5}$ and $PM_{10-2.5}$, the C_{in}/C_{out} ratio was very close in value to F_{inf} for UFP. These findings imply that very little PM in the smallest size fractions infiltrates the building envelope, suggesting that large errors would occur from assuming that concentrations measured at an ambient monitor were representative of indoor exposure to ambient UFP, especially as the particle size decreased.

Indoor air filtration using high-efficiency particulate air (HEPA) filters can reduce F_{inf} as well as indoor total and ambient $PM_{2.5}$ concentrations. Allen et al. (2011) conducted an intervention study by temporarily installing HEPA filters in 25 homes in British Columbia, Canada during winter and early spring. Indoor $PM_{2.5}$ concentrations were 59% lower on average during HEPA filter operation (4.6 vs. 11.2 $\mu g/m^3$). Reductions of similar magnitude were observed for outdoor-generated $PM_{2.5}$

(1.5 vs. 3.5 μg/m^3). Allen et al. (2011) estimated F_{inf} using the recursive method of Allen et al. (2003) and found that the average infiltration of $PM_{2.5}$ was reduced by 41% (0.20 vs. 0.34). These studies show a consistent effect of HEPA filtration in reducing $PM_{2.5}$ infiltration.

Several recent studies suggest that air conditioning may modify the association between $PM_{2.5}$ and health effects. Allen et al. (2012) used $PM_{2.5}$ and questionnaire data from the MESA-Air study to model F_{inf} as a function of air conditioning and heating use, window opening, and window insulation. During the summer, central air conditioning usage was the most important factor in the model, accounting for 80% of the overall model variability (model $R^2 = 0.70$). During the winter, the most important factor was 2-week average outdoor temperature, which accounted for 45% of the overall model variability (model $R^2 = 0.49$). These results suggest that the variability in $PM_{2.5}$ infiltration within and between cities may account for increased variability in estimation of $PM_{2.5}$ exposure and hence attenuation of the health effect estimate. Hodas et al. (2012) considered sensitivity of F_{inf} to $PM_{2.5}$ mass concentration, $PM_{2.5}$ component concentration, proximity to roadways, and income. Generally speaking, F_{inf} was higher when calculated for $PM_{2.5}$ mass concentration rather than individual components. F_{inf} was higher for both those living near roadways and for AER of 0.90 hour^{-1}, which was identified as the "typical" AER for low income homes compared with the general population. Hodas et al. (2012) suggested that variation in F may account for exposure misclassification in cases where variability in AER leads to assignment of incorrect F and for effect modification when conditions such as source proximity and poverty influence F.

Based on results of studies showing how F_{inf} varies under different conditions, Allen et al. (2012) suggested that infiltration could modify the health effect of $PM_{2.5}$ exposure; this idea was explored in other studies. Bell et al. (2009) tested if air conditioning prevalence (i.e., the proportion of homes with air conditioning in a given community as indicated by the American Housing Survey) modified the effect of $PM_{2.5}$ exposure concentration on cardiovascular and respiratory hospital admissions (HA) and of PM_{10} on mortality. Over the course of a year they observed decreases of 30% for the effect of short-term PM_{10} exposure on mortality and of 34% for the effect of short-term $PM_{2.5}$ exposure on cardiovascular HA when any air conditioning was in use. They observed an overall 45% increase in the effect of $PM_{2.5}$ on respiratory HA for those who use air conditioning, but a break-down of their data showed that there was a 75% decrease in effect of $PM_{2.5}$ on respiratory HA during the summer when air conditioning use would be most prevalent. Sarnat et al. (2013a) also explored how AER can be a modifier of the effect of $PM_{2.5}$, NO_X, and CO related to asthma ED visits in Atlanta neighborhoods. Parsing their data by low and high AER (0.25/hour threshold) and poverty level (8.5% threshold), Sarnat et al. (2013a) observed that the majority of locations with high levels of poverty also had high AER. They attributed this observation to old, drafty housing being more prevalent among those in poverty. Larger effect estimates were observed among those with high poverty and low AER, however. When effect modification was tested using an interaction term, a negative effect on ED asthma visits was observed despite increased $PM_{2.5}$ and AER being associated with increased ED visits. These results indicate that air conditioning may modify associations between $PM_{2.5}$ and health effects, but the results are not entirely consistent.

Many of the newer studies of PM infiltration focused on characterizing infiltration of UFP, clarification on the factors influencing infiltration, and examination of air conditioning usage or AER as an effect modifier of $PM_{2.5}$ exposure. UFP infiltration was found to decrease with decreasing particle size, likely due to particle diffusion to surfaces. Many new studies noted differences in infiltration for seasons or between northern and southern cities. Areas with prevalent air conditioning usage tended to have lower infiltration compared with areas where window opening is prevalent. Indoor-outdoor temperature gradients also likely influenced PM infiltration, with particles naturally following the warm-cold gradient. Some recent studies found that air conditioning may also modify the effect of short-term $PM_{2.5}$ exposure and health effects.

3.4.1.2 Indoor–Outdoor Concentration Relationships

The 2009 PM ISA (U.S. EPA, 2009b) largely focused on infiltration of PM in the $PM_{2.5}$ and $PM_{10–2.5}$ size ranges, finding that infiltration of PM indoors decreased with increasing particle size. This section builds on the literature review from the 2009 PM ISA with a focus on relationships between indoor and local outdoor PM concentrations in different size fractions, particularly $PM_{2.5}$ and UFP. Most of the studies published since the 2009 PM ISA that evaluated indoor-outdoor PM relationships were conducted outside the U.S., including studies in Europe, Canada, Mexico, South America, the Middle East, and Asia. Since PM levels, sources, and composition are likely to differ substantially in some areas from those typically encountered in the U.S., this section focuses on North American and European indoor-outdoor studies.

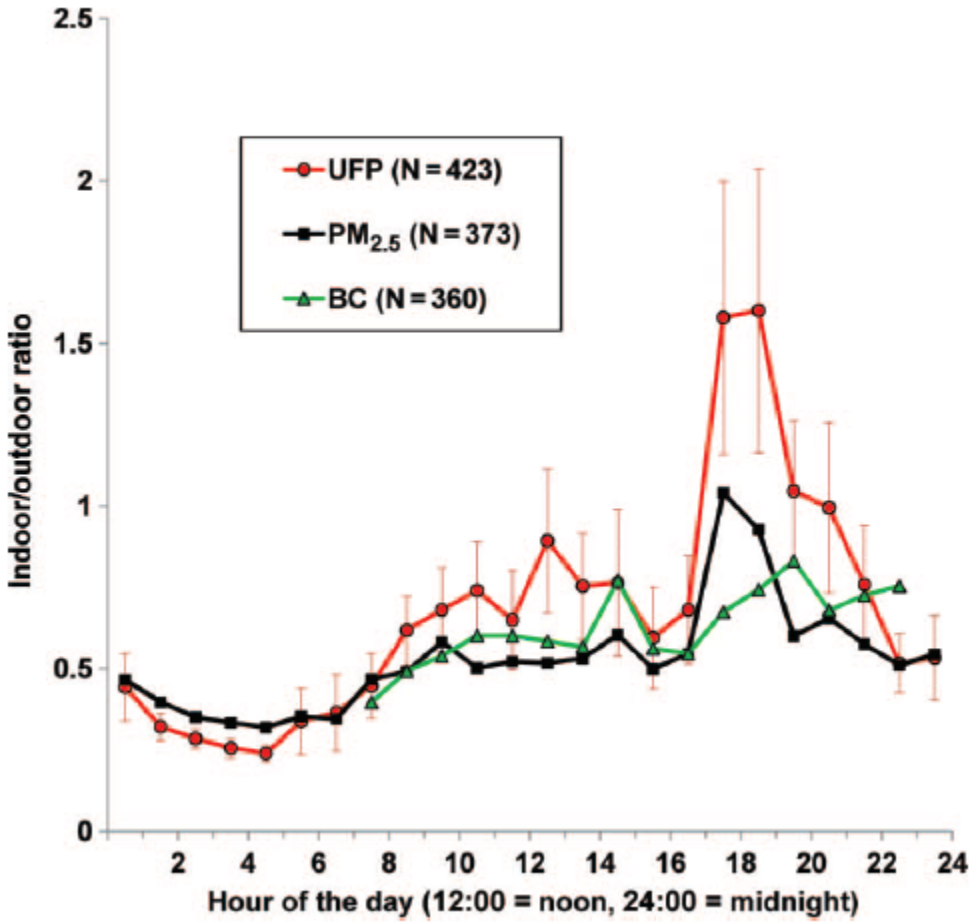
Recent literature has added data to the characterization of indoor-outdoor relationships across the $PM_{2.5}$ and $PM_{10–2.5}$ size fractions. A multicity study in Europe compared indoor and outdoor residential 24-hour average concentrations for NC (7−3,000 nm), $PM_{2.5}$, and $PM_{10–2.5}$ at 152 homes in Helsinki (Finland), Athens (Greece), Amsterdam (the Netherlands), and Birmingham (U.K.) (Hoek et al., 2008b). Median indoor-outdoor correlations for $PM_{10–2.5}$ were the lowest of the three PM metrics in all cities, ranging from 0.10−0.39. In Helsinki and Amsterdam, NC indoor-outdoor correlations were lower than $PM_{2.5}$ correlations (0.41 vs. 0.74 and 0.58 vs. 0.85, respectively), while in Athens and Birmingham, NC correlations were higher (0.80 vs. 0.63; 0.50 vs. 0.35). A common indoor source, gas cooking, was prevalent in both Amsterdam and Birmingham, cities with differing correlation magnitude, and so is unlikely to explain city-to-city differences in correlations. Consistent with observed low correlations, the regression slope of indoor on outdoor concentrations (a measure of infiltration, with a slope less than one indicating less infiltration) was lower for $PM_{10–2.5}$ than the other two PM metrics, ranging from 0.11−0.16. NC slopes ranged from 0.19−0.42 and were lower than $PM_{2.5}$ slopes (range: 0.39−0.48) in Amsterdam, Birmingham, and Helsinki, while the two slopes were roughly equivalent in Athens. Again, infiltration slope results were generally consistent with correlation results, being either both high or both low in a particular city. Buonanno et al. (2013a) reported I/O and the ratio of indoor to fixed-site monitors for three schools in Cassini, Italy and found I/O ranged from 0.63−0.74 while the indoor to fixed-site ratio

ranged from 0.47−1.53. These values are much higher than those reported in the Hoek et al. (2008b) study. Another important finding is that $PM_{10–2.5}$ exhibited the lowest infiltration and indoor-outdoor correlation of the three metrics, with NC and $PM_{2.5}$ infiltration behavior similar to one another. Semmens et al. (2015) measured NC in various size fractions ranging from 0.3−10 µm and found that correlations between indoor $PM_{2.5}$ and various NC size fractions were very high for NC less than 1 µm in size (0.94 and 0.93 for NC 0.3−0.49 µm and 0.5−0.99 µm, respectively). Correlations with $PM_{2.5}$ decreased monotonically for larger NC size fractions, with $PM_{2.5}$–$PM_{10–2.5}$ correlations of 0.46 for NC 2.5−4.99 µm and 0.35 for NC 5.0−9.99 µm. Correlations among indoor NC size fractions were highest for adjacent bins. Collectively, these results indicate that differences in source patterns, spatial concentration heterogeneity, housing stock, meteorology, and other factors contribute to different indoor-outdoor relationships in different urban areas, particularly for NC and $PM_{2.5}$.

Results for indoor-outdoor relationships for $PM_{2.5}$ concentration were not consistent across studies of the effect of season. Several single-city studies in the U.S. and Canada have evaluated indoor-outdoor relationships by season. For example, in Boston, median residential indoor-outdoor slopes for 24-hour average $PM_{2.5}$ were higher in summer than winter (0.74 vs. 0.53) for a panel of 25 participants studied in 2000 (Brown et al., 2008). Hsu et al. (2012) reported correlations between indoor and outdoor (outside residence and fixed-site monitors) concentrations of $PM_{10–2.5}$ and $PM_{2.5}$ in New York City, NY and Seattle, WA. For $PM_{10–2.5}$ in New York City (correlations not reported for Seattle), Spearman $R = 0.20$ for indoor-outdoor and 0.08 for indoor-fixed-site during the summer and Spearman $R = −0.12$ and −0.07 for indoor-outdoor and indoor-fixed-site during the winter. For $PM_{2.5}$ in New York City, Spearman $R = 0.44$ for both indoor-outdoor and indoor-fixed-site in winter and Spearman $R = 0.57$ and 0.53 for indoor-outdoor and indoor-fixed-site in summer. Hochstetler et al. (2011) measured $PM_{2.5}$, EC, and NC inside and outside three public schools in Cincinnati, OH and observed a lower slope and R^2 for $PM_{2.5}$ (I/O slope = 0.24, $R^2 = 0.08$), compared with EC (I/O slope = 0.44, $R^2 = 0.66$) and NC (I/O slope = 0.68, $R^2 = 0.72$). In Windsor, Ontario, Kearney et al. (2011) calculated the indoor-outdoor ratio (I/O) for UFP (20−100 nm), and found wide variation with median I/O of 0.19 (95th percentile: 0.64) and 0.27 (95th percentile: 0.61) for summer measurements for 2005 and 2006, respectively, and 0.25 (95th percentile: 0.45) for winter, 2006 measurements. Kearney et al. (2011) based these numbers on nighttime measurements, when it was assumed that there were no indoor sources of UFP so that I/O approximates F_{inf}; I/O estimates based on recursive and censoring models produced similar results. Daily I/O (not slopes) in Windsor were similar for $PM_{2.5}$ (0.5), BC (0.45), and 20−1,000 nm NC (0.55) at approximately 90 residences, averaging across summer and winter sampling seasons (Wheeler et al., 2011). Hourly I/O for NC were much higher during dinnertime (approximately 1.5), indicating indoor NC sources from cooking (Figure 3-2); this also contributed to a higher daily ratio relative to the other PM metrics. For $PM_{10–2.5}$ in Regina, Saskatchewan, 5-day geometric mean concentrations were lower indoors than outdoors during summer (4.3 vs. 8.8 µg/m^3) in a set of 100 residences, but the opposite was true for a set of 79 residences during winter, with higher indoor concentrations (3.7 vs. 2.5 µg/m^3). The spatial coefficient of variation for outdoor $PM_{10–2.5}$ concentrations was higher in winter than in summer.

Variation in indoor-outdoor relationships among different studies for warm and cold months may relate to different contributions from indoor sources, such as cooking and heating, between cities.

Time of day also influences I/O ratios, as shown in Figure 3-3 for data reported by Wheeler et al. (2011). In addition, Semmens et al. (2015) studied residences relying mainly on wood stoves for heating and found that I/O ratios were approximately 1.0−1.2 (indicating indoor sources) during daytime hours (6 a.m.–10 p.m.), indicating the wood stove or other indoor sources were contributing to indoor PM. Overnight (10 p.m.–6 a.m.) ratios were approximately 0.6. The relatively lower overnight I/O supports the finding that indoor sources were driving the high I/O values during the day.

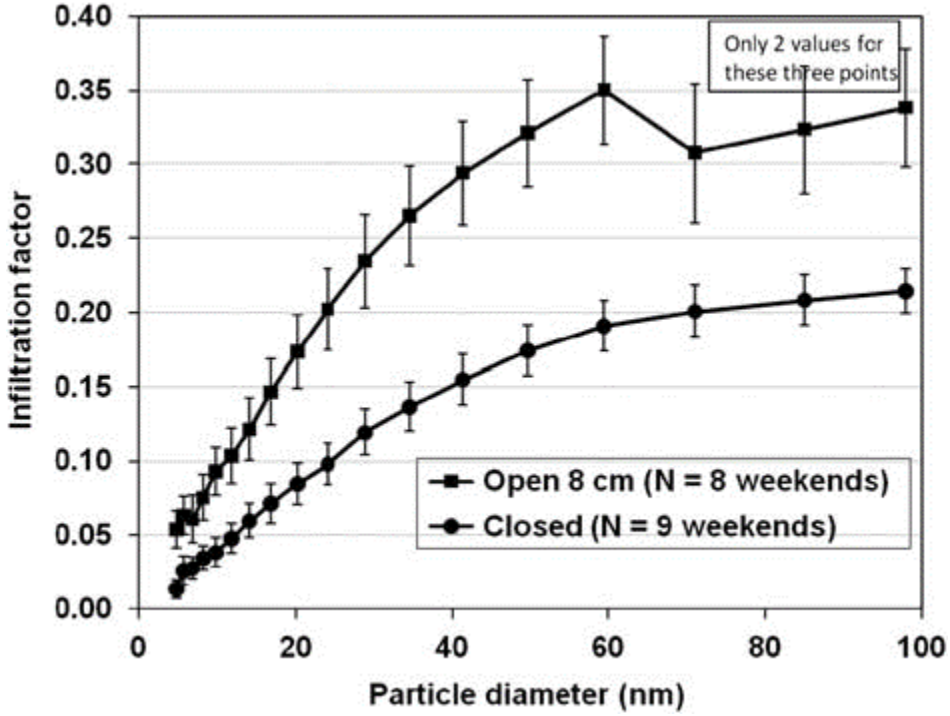


Note: Standard errors are only shown for the I/O for UFP. This figure was reproduced from Wheeler et al. (2011). The figure shows how the indoor-outdoor ratios change with hour of day for UFP, $PM_{2.5}$, and BC. Each type of PM has a peak indoor-outdoor ratio between 17:00 and 20:00. However, the peak indoor-outdoor ratio is much higher for UFP than for $PM_{2.5}$, which is slightly higher than for BC.

Source: Permission pending Wheeler et al. (2011).

Figure 3-2 Indoor-outdoor ratios for UFP, $PM_{2.5}$, and BC measured at 90 residences.

New research on UFP I/O suggest that I/O decreases with decreasing particle size within the ultrafine size range. Indoor-outdoor ratios were calculated for a manufactured house located on the National Institute for Standards and Technology (NIST) campus in Gaithersburg, MD to characterize infiltration to test how I/O varies across UFP size (Wallace and Ott, 2011). I/O generally increased with increasing UFP size (up through 100 nm) for both open and closed window conditions (Figure 3-3). Open window I/O was always higher and had greater variability than closed window I/O. This pattern is consistent with observations by Sarnat et al. (2006a) presented in the 2009 PM ISA (U.S. EPA, 2009b) in which F_{inf} increases with increasing particle size up to about 100 nm. Above 200 nm, Sarnat et al. (2006a) reported that F_{inf} declined with increasing particle size up to 8 µm. Across all experiments, Wallace and Ott (2011) estimated that ambient UFP exposure was responsible for 36% of total UFP exposure and that the contribution of outdoor UFP exposure to total UFP exposure would likely increase in urban environments.



Source: Permission pending Wallace and Ott (2011).

Figure 3-3 Indoor-outdoor ratios for UFP size obtained in a test house on the National Institute for Standards and Technology (NIST) facility for open and closed window conditions.

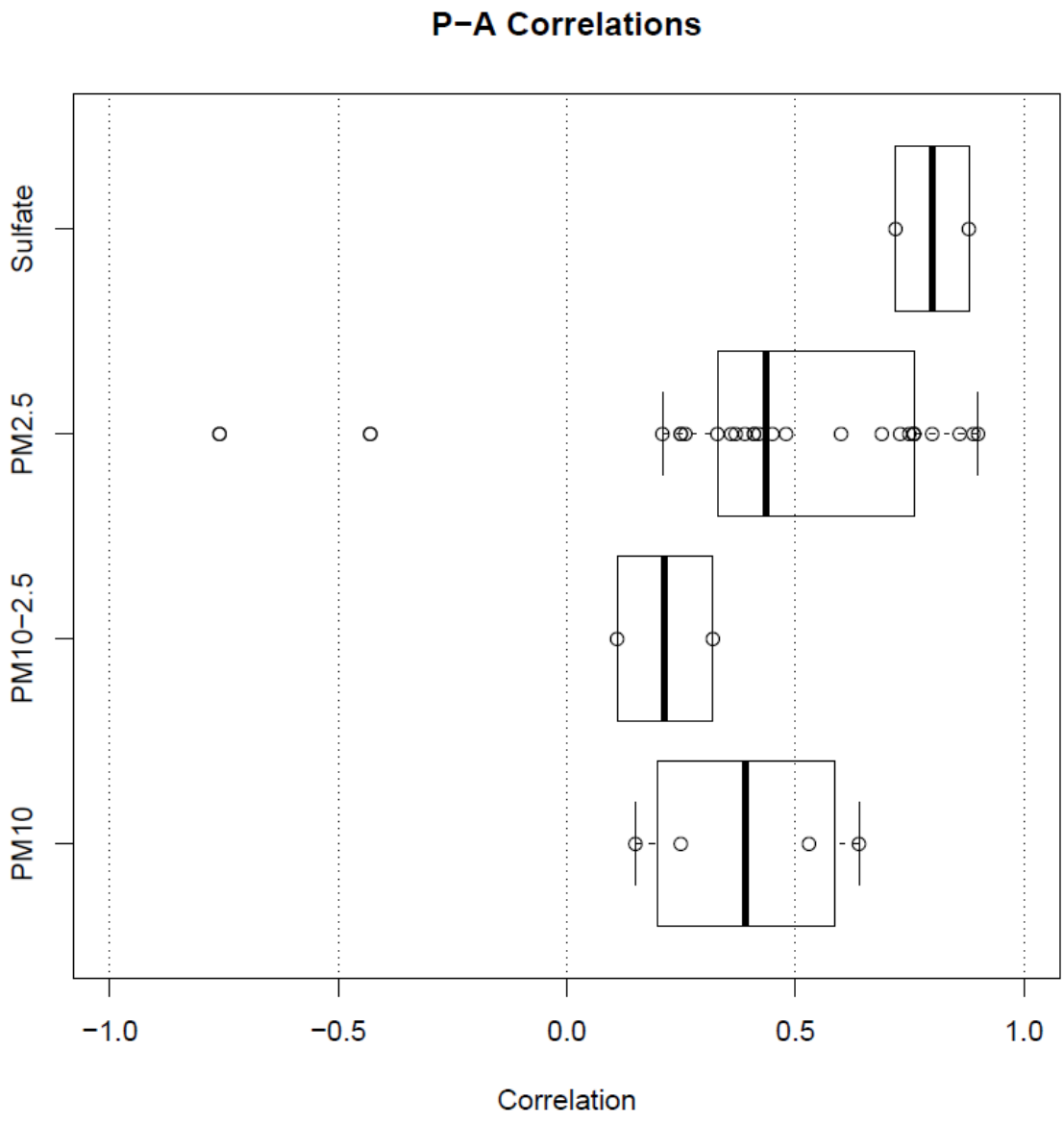
Recent studies reinforce previous conclusions that I/indoor-outdoor relationships are sensitive to particle size, with I/O typically decreasing in the $PM_{10-2.5}$ range. New studies add to the literature base for UFP, where I/O was found to decrease with decreasing particle size. UFP movement is more influenced by Brownian diffusion than are larger particles, which likely caused more UFP to diffuse to building surfaces instead of being transported indoors. Additional studies added to the characterization of indoor-outdoor relationships for different seasons and times of day. For most studies, I/O was higher during summer than winter and during daytime compared with nighttime.

3.4.1.3 Personal–Ambient Concentration Relationships

The new literature on personal-ambient relationships adds to findings from the 2009 PM ISA (U.S. EPA, 2009b), in which moderate correlations (0.3−0.7) were observed with median personal-ambient slope slightly higher than 0.5. The general understanding of these relationships is unchanged since the 2009 PM ISA. As with the previous section on indoor-outdoor relationships (Section 3.4.2), many of the studies published since the 2009 PM ISA that evaluated personal-ambient PM relationships were conducted outside the U.S., including studies in Europe, Mexico, South America, the Middle East, and Asia. Since PM levels, sources, and composition are likely to differ substantially in some areas from those typically encountered in the U.S., this section focuses on North American and European personal-ambient studies.

High correlations suggest that ambient concentrations are a good surrogate for personal exposure, while low correlations indicate exposure measurement error when using ambient concentration to represent personal exposure. Several studies, many of which were available at the time of the 2009 PM ISA (U.S. EPA, 2009b), have evaluated relationships between personal exposure and ambient PM concentrations in various U.S. cities, including: Baltimore, MD; Boston, MA; Chapel Hill, NC; Detroit, MI; and Steubenville, OH (Meng et al., 2012; Brown et al., 2009; Williams et al., 2008; Sarnat et al., 2006b; Koutrakis et al., 2005; Sarnat et al., 2005; Chang et al., 2000; Sarnat et al., 2000). These studies all evaluated 24-hour average exposures, except for Chang et al. (2000), which evaluated hourly exposures in a variety of microenvironments (e.g., indoor-home, indoor-other, outdoor-near-road, in-vehicle). Figure 3-4 shows personal-ambient correlations reported for Baltimore in Chang et al. (2000) and Sarnat et al. (2000) and New York City (Hsu et al., 2012). Both Baltimore studies evaluated $PM_{2.5}$, and Sarnat et al. (2000) reported personal-ambient correlations for PM_{10}, $PM_{10-2.5}$, and SO_4^{2-}. Hsu et al. (2012) also reported personal-ambient correlations for PM_{10}. Correlations ranged widely for $PM_{2.5}$, with a median of approximately 0.4 and an IQR of 0.3−0.7. PM_{10} correlations were similar to those for $PM_{2.5}$, while $PM_{10-2.5}$ correlations were somewhat lower, suggesting factors such as spatial variability and differential infiltration affect exposure to ambient $PM_{10-2.5}$. These results also suggest that PM_{10} was comprised primarily of $PM_{2.5}$ in these samples. Sulfate correlations were higher than those for $PM_{2.5}$. The recent findings of Hsu et al. (2012), in conjunction with older studies in the literature, indicate that a

greater portion of the variability in personal exposures is explained by variability in ambient PM for $PM_{2.5}$ and sulfate in $PM_{2.5}$, which tend to have lower spatial variability than $PM_{10-2.5}$ and UFP.

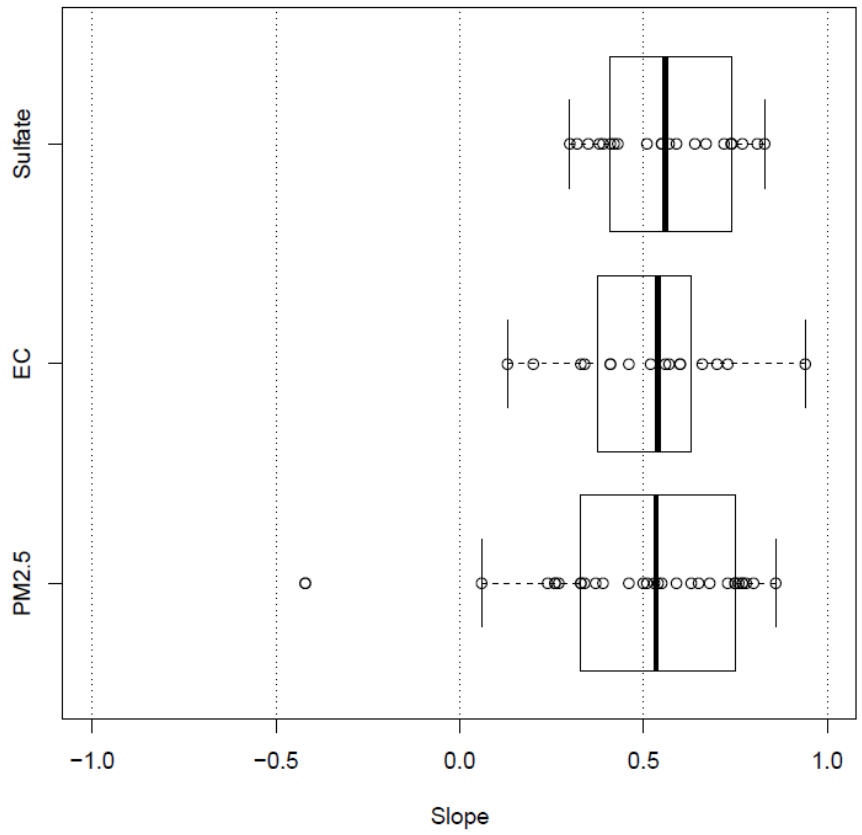


Source: Permission pending, Hsu et al. (2012); Chang et al. (2000); Sarnat et al. (2000).

Figure 3-4 Correlations between personal exposure and ambient PM concentration in Baltimore, MD.

Regressing personal exposure on ambient PM concentration yields a slope factor expressing the fraction of personal exposure from ambient PM. Figure 3-5 presents personal-ambient slopes (i.e., the ratio of total personal exposure to ambient concentration) from studies in the four cities listed previously (Meng et al., 2012; Brown et al., 2009; Sarnat et al., 2006b; Koutrakis et al., 2005; Sarnat et al., 2005). Several of these studies evaluated EC and SO_4^{2-} in addition to $PM_{2.5}$. Median slopes for $PM_{2.5}$, EC, and SO_4^{2-} were between 0.5 and 0.6. The wide variability in personal-ambient slopes is likely due in part to the study design, which evaluated personal exposure in different seasons and with different building ventilation conditions (e.g., closed vs. open windows). The variability may have also been attributed to variation in penetration and deposition for the components and houses. Ryan et al. (2015a) and Brokamp et al. (2015) analyzed concentration data from outdoor concentrations (outside residence) and total personal exposure samples for $PM_{2.5}$ mass and 24 $PM_{2.5}$ trace metals (Ag, Al, As, Ba, Br, Ca, Cl, Cr, Cu, Fe, K, Mn, Ni, Pb, S, Sb, Se, Si, Sn, Sr, Ti, V, Zn, Zr) from the RIOPA study of homes in Los Angeles, CA, Houston, TX, and Elizabeth, NJ. They presented correlation and outdoor-personal ratios (O/P) for each $PM_{2.5}$ component. Correlations of Spearman $R > 0.8$ were reported for S and V, while Spearman $R < 0.4$ was reported for Ag, Al, As, Ba, Ca, Cl, Cr, Cu, Fe, K, Mn, Ni, Sb, Si, Sr, Ti, Zn, Zr, and for $PM_{2.5}$ mass. Median O/P > 1 was observed for As, Br, Sb, Se, and V and O/P < 1 for $PM_{2.5}$ and the other components. The results for $PM_{2.5}$ and $PM_{2.5}$−S contrast those presented in Figure 3-5. Data were unavailable for $PM_{10-2.5}$ or UFP in these studies. These findings indicate that variability in the personal-ambient slope reflects differences in ventilation and other localized conditions for $PM_{2.5}$ mass concentration, which is not very sensitive to $PM_{2.5}$ composition.

New studies agree with the previously published literature on personal-ambient relationships. Studies have examined personal-ambient correlations for different PM size fractions and found that a greater portion of the variability in personal exposures is explained by variability in ambient PM for $PM_{2.5}$ and sulfate in $PM_{2.5}$, compared with $PM_{10-2.5}$, which tends to have greater spatial variability than $PM_{2.5}$. Median personal-ambient slopes are generally slightly greater than 0.5, and they likely reflect differences in residential ventilation, time-activity patterns (Section 3.4.2.1), and other localized conditions.



Source: Permission pending, Meng et al. (2012); Brown et al. (2009); Sarnat et al. (2006b); Koutrakis et al. (2005); Sarnat et al. (2005).

Figure 3-5 Slopes of the relationship between personal exposure and ambient PM concentration in four U.S. cities.

3.4.2 Factors Contributing to Error in Estimating Exposure to PM

This section builds upon discussions from the 2009 PM ISA (U.S. EPA, 2009b) about factors having the potential to cause error in exposure concentration estimates. Time-activity patterns, spatial variability, instrument error, and model accuracy and precision are discussed below, because these topics were frequently examined in exposure measurement error discussions. Summaries of each factor's discussion from the 2009 PM ISA are included in Section 3.4.2.1, Section 3.4.2.2, Section 3.4.2.3, and Section 3.4.2.4.

3.4.2.1 Time–Activity Patterns

The 2009 PM ISA (U.S. EPA, 2009b) reviewed time-activity behaviors among the population and how time spent in different locations varies among age groups. Recent additions have been made to time-activity databases, and technological advances in geographic positioning system (GPS) technologies have also expanded the information base regarding time-activity. Such new tools have enabled examination of factors that influence time-activity patterns and errors in those relationships.

Updated data are available from the Consolidated Human Activity Database (CHAD) to compare time-activity among different population strata for 25,431 individuals (Isaacs, 2014). Across the population, 75% of time is spent indoors at the place of residence; 5.5% is spent in transit; 16% indoors at work, school, or other locations; and 2.9% outdoors (Table 3-6). Substantially more time (82 and 83%) is spent indoors at home for children younger than 6 years and for adults older than 64 years, while teens ages 12−19 years and adults 20−64 years spent the least amount of time indoors at home (72 and 71%, respectively). Similarly, young children spent the least amount of time in transit (4.0%), while adults 20−64 years spent the most time in transit (6.9%). Adults 20−64 also spent the largest proportion of the day outdoors (3.4%), while older adults spent the least amount of time outdoors (2.2%). Young children ages 0−5 years and children ages 6−11 years spent less time outdoors than adults (2.4 and 3.0%, respectively). When comparing time-activity data across race (Table 3-7), Hispanic study participants spent slightly more time indoors at home than average (78%), while White study participants spent the most time outdoors (3.3%) compared with Asian (2.0%), Black (2.1%), and Hispanic (2.3%) participants. Males spent more time outdoors compared with females (3.6 vs. 2.2%) (Table 3-8), and adults 20−64 years with low and high education both spent less times indoors at home (74 and 70%, respectively), more time indoors at work/school/other (16 and 19%), and more time outdoors (3.7 and 3.5%) compared with the 20−64 year-old adult population (3.4%) (Table 3-9). It is possible that missing education data corresponded with lower time spent outdoors. It was most surprising to find that children spent less time outdoors than adults, while sex-specific differences in time-activity data were anticipated.

Recent studies have focused on the use of GPS technologies, such as in smartphones, to develop detailed time-activity pattern data. For example, Glasgow et al. (2014) analyzed the frequency of Android-based smartphones in recording positional data among a panel of study participants and found that on average 74% of the data were collected over intervals shorter than 5 min, which is a marked improvement over many time-activity studies using diaries.

Table 3-6 Total and age-stratified time activity data from the Consolidated Human Activity Database.

Location Type	All	0−5 yr	6−11 yr	12−19 yr	0−19 yr	20−64 yr	65+ yr
Indoor-residential	75.1%	82.0%	74.4%	71.6%	76.2%	71.4%	82.9%
Transit	5.53%	3.96%	4.29%	5.13%	4.42%	6.92%	5.14%
Indoor-work/school/other	15.5%	10.1%	16.7%	19.9%	15.3%	17.9%	8.71%
Outdoor	2.87%	2.35%	2.96%	2.53%	2.62%	3.39%	2.18%
Uncertain or missing	0.97%	1.59%	1.65%	0.85%	1.40%	0.48%	1.05%

Table 3-7 Total and race/ethnicity-stratified time activity data from the Consolidated Human Activity Database.

Location Type	All	Asian	Black	Hispanic	White
Indoor-residential	75.1%	75.3%	74.8%	78.4%	74.8%
Transit	5.53%	5.01%	5.25%	5.05%	5.54%
Indoor-work/school/other	15.5%	16.3%	16.6%	13.4%	15.0%
Outdoor	2.87%	2.02%	2.09%	2.34%	3.30%
Uncertain or missing	0.97%	1.42%	1.26%	0.84%	1.45%

Table 3-8 Total and sex-stratified time activity data from the Consolidated Human Activity Database.

Location Type	All	Female	Male
Indoor-residential	75.1%	76.6%	73.4%
Transit	5.53%	5.47%	5.60%
Indoor-work/school/other	15.5%	14.8%	16.4%
Outdoor	2.87%	2.21%	3.64%
Uncertain or missing	0.97%	0.92%	1.04%

Table 3-9 Total and education-stratified time activity data from the Consolidated Human Activity Database, among adults 20−64 years.

Location Type	All 20−64 yr	Low Education	High Education
Indoor-residential	71.4%	73.7%	70.0%
Transit	6.92%	6.42%	7.12%
Indoor-work/school/other	17.9%	16.0%	19.1%
Outdoor	3.39%	3.73%	3.52%
Uncertain or missing	0.48%	0.22%	0.27%

Positional errors are a concern for GIS and GPS-based technologies. Several studies found that median positional errors based on smartphones were less than 26 m (Ganguly et al., 2015; Lane et al., 2013; Wu et al., 2010). Glasgow et al. (2014) observed much larger errors, with an overall median positional accuracy of 342 m and a range from 98 to 1,169 m using an Android-based smartphone, while Wu et al. (2010) observed much smaller errors when comparing two smartphones with three other GPS technologies. To test the impact of the positional errors on concentration estimates used in exposure assessment studies, Ganguly et al. (2015) compared R-LINE modeled residential $PM_{2.5}$ concentrations when the positions were estimated with GIS or GPS over buffers of 0−100 m, 100−200 m, 200−500 m, and >500 m. Median concentration measurement errors were 5% or less for each buffer for annual average concentrations and 6% or less for 24-hour max concentrations. Average errors were 10% or less for each buffer for both annual average and 24-hour max concentrations.

Survey tools to assess time-activity may be subject to recall error among the subjects. Spalt et al. (2015) administered a survey to all participants in the Multi-Ethnic Study of Atherosclerosis (MESA) Air Study to ascertain information about time spent indoors and outdoors at home, at work/volunteer/school, in transit, or in other locations. A subset of the study population was asked to complete a time-activity diary as well. Correlation for indoor locations was Spearman $R = 0.63$ for home, Spearman $R = 0.73$ for work/volunteer/school, and Spearman $R = 0.20$ for other locations. Correlation for outdoor locations was much lower, with Spearman $R = 0.14$ at home, Spearman $R = 0.20$ for work/volunteer/school, and Spearman $R = 0.10$ for other locations. In transit, Spearman $R = 0.39$. These results suggest that study participants have better recall of the times spent inside their home or work/volunteer/school compared to other activities, because time spent at home or at work/volunteer/school tends to occur at routine times.

Excluding time-activity patterns from exposure studies may lead to bias and uncertainty in the exposure estimate. Nyhan et al. (2018) combined GPS records from 407,435 individuals in the metropolitan Boston, MA area with a hybrid model using land use regression and satellite data to predict $PM_{2.5}$ concentration on an hourly basis. They compared the time-activity-based model with one that used the daily average $PM_{2.5}$ concentration (also based on the hybrid LUR-satellite model) at location of resident for each participant and found that the residence-based exposure model produced predictions that were 9% lower than the model accounting for time-activity when averaging the results over a year. This suggests that omission of time-activity data may lead to underestimation of the exposure.

Residential mobility is one factor leading to error in estimating exposure for long-term exposure studies. Using a single address to represent exposure concentration over a period of several years may result in either under- or over-estimating exposure during the study period. For example, Brokamp et al. (2015) analyzed residential mobility for a cohort of children over the first seven years of life in Cincinnati, OH and found that 54% of the children changed residential address during that time, resulting in a 4.4% decrease in the cohort's average traffic-related air pollution exposure concentration (defined as BC estimates from an LUR model). They also noted that if the birth address is used for exposure estimation during the entire study period, exposure misclassification is increased for those that move earlier (due to more years at the incorrect address) or are more highly exposed (due to a greater likelihood of moving). An epidemiologic study of asthma incidence at age seven showed that not accounting for residential mobility resulted in bias toward the null.

Recognizing that the CHAD database observed people (across population subgroups) spending approximately 5.5% of their time in vehicles, several studies have measured UFP concentrations in and immediately outside vehicles to estimate infiltration. Hudda et al. (2012) observed that I/O was positively associated with increasing AER for vehicles tested in Los Angeles, CA and Sydney, Australia each with recirculating air and outside air intakes. I/O increased with increasing vehicle speed and age, with a maximum of approximately 0.75 under recirculating conditions and of approximately 0.9 under outside air intake. Bigazzi and Figliozzi (2012) estimated I/O when a vehicle in Portland, OR was operated with windows down, windows up with outside air intake, and windows up with recirculating air. Under those

conditions, I/O decreased from 0.85 to 0.53 to 0.1−0.17, respectively. Knibbs et al. (2010) tested I/O for five vehicles and four ventilation settings (outdoor air intake with lowest and second lowest fan speed, recirculation on with lowest fan speed, recirculation on with fan off). Older model vehicles (prior to 2000) had I/O of 0.89−1.04 for the outdoor air intake settings and 0.29−0.47 for the recirculation settings. Models built after 2000 had I/O of 0.66−1.04 for outdoor air intake settings and 0.08−0.68 for recirculation settings. Yamada et al. (2016) took measurements along four road segments and inside one tunnel in the greater Tokyo, Japan area for particles smaller than and larger than 50 nm and using open air or recirculating air. When fresh air entered the vehicle, I/O ranged from 0.5 to 0.6 for particles smaller than 50 nm and from 0.8 to 0.9 for particles larger than 50 nm. When the test automobile's ventilation was operated in recirculation mode, infiltration ranged from 0.1 to 0.2 for particles smaller than 50 nm and from 0.2 to 0.9 for particles larger than 50 nm. In a tunnel in the greater Salzburg, Austria area, Madl et al. (2015) measured vehicle ventilation filtration efficiency for UFP, which can be used to interpret I/O by subtracting reported filtration efficiency from 1. They observed I/O of approximately 0.3 when the vehicle's standard ventilation setting was used, which reduced to 0.1 when the vehicle was put into recirculation mode. In all, these studies show that large variability in I/O occurs with both outdoor air intake and recirculation settings, but I/O tends to be higher for outdoor air intake.

Exposure to PM, particularly UFP, has been found to be elevated during bicycling and walking near roadways (Buonanno et al., 2013b; Hudda et al., 2012; Berghmans et al., 2009; Boogaard et al., 2009; Briggs et al., 2008). A study in Minneapolis, MN used city-wide traffic flows and a LUR model for particulate matter (including NC, BC mass, and $PM_{2.5}$) to analyze the relationship between bicycling or walking and PM exposure concentrations in different parts of the city (Hankey et al., 2017). The authors found that areas classified as high activity and high exposure made up approximately one-tenth of the total grid cells, but accounted for 20−44% of active travel.

Updated time-activity data and tools for assessing time-activity data have improved the general understanding of time-activity data and related uncertainties in recent years. Children were surprisingly found to spend less time outdoors than adults, but White respondents did spend more time outdoors than their Asian, Black, and Hispanic counterparts. New technologies to assess study participant location, errors related to study participant recall, and residential mobility have been used to determine that location-based errors are within 6% for short-term and long-term exposure assessment, while omission of residential mobility can result in a bias in the exposure estimate, resulting in biasing the health effect estimate for a study of long-term $PM_{2.5}$ exposure.

3.4.2.2 Spatial Variability in Concentrations

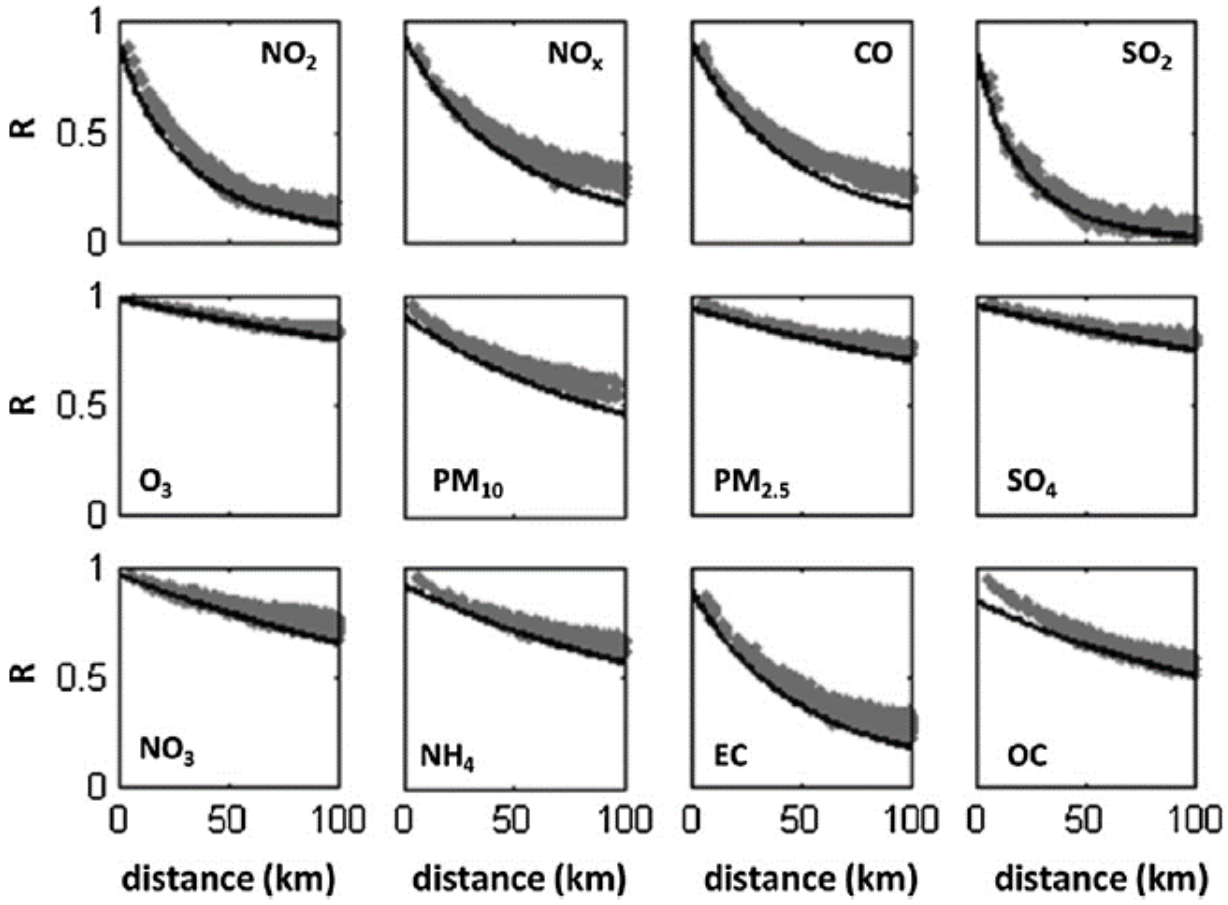
The 2009 PM ISA (U.S. EPA, 2009b) examined spatial relationships among $PM_{2.5}$ between AQS monitoring locations across neighborhood and urban scales. In general, this analysis suggested that correlations between monitors across space depended on the specific city's meteorology, topography, and

source mixture. For all cities studied, the between-monitor spatial correlations decreased with increasing distance between monitors. However, the correlation for $PM_{2.5}$ between Boston, MA monitor pairs was roughly Pearson $R = 0.8$ even when the monitors were 100 km apart. In contrast, correlation between $PM_{2.5}$ for Los Angeles monitor pairs was roughly Pearson $R = 0.2$ when the monitors were 100 km apart. The mountains and inversion patterns were thought to play a role in this comparatively low correlation. The 2009 PM ISA also investigated neighborhood scale monitor pair correlations among FRMs or FEMs in 15 CSAs or CBSAs and found that within 4 km, average correlation of Pearson $R = 0.93$ was maintained for a 4 km distance. At the time of the 2009 PM ISA, data were not available to study spatial variability in the concentration surface for $PM_{10–2.5}$ or UFP. Spatial distribution data for both UFP and $PM_{10–2.5}$ are still limited, especially for UFP. Data for UFP were available for two cities (Los Angeles, CA and Rochester, NY), and data from the Los Angeles study suggested that UFP had moderate spatial variability (coefficient of divergence [COD] between 0.2 and 0.6). It was thought that some background UFP reduced spatial variability, especially for particles larger than 40 nm (Section 2.5.1.2.4). Although some $PM_{10–2.5}$ data are available across the nation, micro-to-neighborhood scale data are not widely available at this size cut (Section 2.5.1.2.3). In cities where $PM_{10–2.5}$ measurements have been made in multiple locations, inter-monitor correlations were low. These limitations create uncertainty in characterizing spatial variability of exposure concentrations and its impact on interpreting results from epidemiologic studies, especially for long-term exposure to $PM_{10–2.5}$ and UFP.

Limitations in the use of ambient monitoring data to estimate exposure concentration arise when there is a lack of homogeneity and spatial autocorrelation of PM mass concentrations, which may occur for some size fractions and components (Baxter et al., 2013), causing the spatial range over which such estimates are used to vary widely. $PM_{10–2.5}$ and UFP concentration data tend to be more heterogeneous in space and hence more susceptible to spatial error (Section 2.5; Section 3.4.2.2). For large metropolitan areas, population exposure to primary anthropogenic components of PM (of any size fraction) may be substantially overestimated in terms of average concentration and temporal variation by the use of a fixed-site ambient monitor in close proximity to an industrial or energy generation source (Sarnat et al., 2015; Bell et al., 2011b). For example, traffic-related UFP and $PM_{2.5}$ components such as EC have elevated concentrations in close proximity to busy roadways (Zhu et al., 2009), potentially resulting in exposure misclassification (Ozkaynak et al., 2013; Bravo et al., 2012). Saturation sampling over longer time-scales may be used to ascertain spatial variation across an urban area, but at the expense of temporal resolution (Matte et al., 2013). Another limitation of using fixed-site ambient monitors to estimate exposure concentration is that ambient monitoring data can be incomplete due to missing data and sampling frequency limitations. Often missing data can be estimated using data from nearby monitors (e.g., by linear regression) or by temporal interpolation. Temporal interpolation can also be used for data analysis when the data are sampled with 1-in-3 or 1-in-6-day sampling frequencies (Junger and de Leon, 2015; Gomez-Carracedo et al., 2014; Junninen et al., 2004; Hopke et al., 2001), which is common for PM components. Interpolation schemes are used to capture hour-of-day and day-of-week trends. Estimates of mixing height using meteorological data and/or tracer component data are also used to improve the completeness of ambient monitor data.

Limited available $PM_{10-2.5}$ data for inter-site correlation and COD support previous statements that $PM_{10-2.5}$ tends to be spatially variable. Thornburg et al. (2009) measured correlation and COD in Detroit for personal multi-stage impactors measuring $PM_{10-2.5}$ and found Pearson $R = 0.28-0.63$ and COD = 0.17−0.41 during Summer and Pearson $R = 0.03-0.76$ and COD = 0.26−0.50 during Winter. Similarly, Lagudu et al. (2011) measured $PM_{10-2.5}$ using passive samplers and observed COD = 0.44−0.78 in the Spring and COD = 0.37−0.88 in the Fall. Neither the Thornburg et al. (2009) nor the Lagudu et al. (2011) studies included data for distances between specific monitors to ascertain if COD increased with increasing distance between samplers. This lack of data adds greater uncertainty to the characterization of $PM_{10-2.5}$ spatial variability.

Spatial variability of $PM_{2.5}$ components can vary among the components. Bell et al. (2011a) presented correlations for FRM or FEM pairs for seven $PM_{2.5}$ components (NH_4^+, EC, NO_3^-, OC, Si, Na^+, S) in a review paper. Bell et al. (2011a) observed that the bulk of the monitor-pair correlation is maintained relatively well (roughly Pearson $R = 0.8$) for NH_4^+, NO_3^-, and SO_4^{2-} (Figure 3-6). Other components had wider variability in correlations even when the monitor pairs were closer together, as was the case for EC, Si, and Na^+. OC correlations were more variable than for NH_4^+, NO_3^-, or SO_4^{2-} across monitor pair distances but not as variable as EC, Si, or Na^+. Dionisio et al. (2013) compared the coefficient of variation (CV = σ/μ) of six air pollutants' concentrations across space using a hybrid AERMOD-background model of concentrations in the Atlanta, GA metropolitan area. They observed the following ordinal relationship of the covariates' median CVs: NO_X (0.88) > CO (0.58) > EC (0.50) > $PM_{2.5}$ (0.13) > O_3 (0.07) > SO_4 (0.05) (see Figure 3-6). Likewise, Goldman et al. (2012) and Ivy et al. (2008) both used monitoring data from the Atlanta, GA metropolitan area to estimate spatial correlation functions, and they observed that the spatial correlograms for O_3, PM_{10}, $PM_{2.5}$, and the $PM_{2.5}$ components SO_4^{2-}, NO_3^-, NH_4^+, and OC were much less steep than for NO_2, NO_X, CO, SO_2, and EC. Hence, $PM_{2.5}$ was observed to be less spatially variable than copollutants frequently associated with traffic (NO_X, CO, EC) or industry (SO_2). Similarly, Goldman et al. (2012), Ivy et al. (2008) and Sajani et al. (2010) all observed less spatial variability of PM_{10} compared with NO_2 or NO_X. If PM_{10} were comprised primarily of $PM_{2.5}$, then these findings would be consistent with the Dionisio et al. (2013) results as well. These findings could reflect the influence of local sources and suggest that spatial variability of $PM_{2.5}$ components could have a large influence on monitor pair correlations for $PM_{2.5}$, with components with greater variation being influenced more by primary sources than components produced through secondary atmospheric chemistry.



Source: Permission pending Goldman et al. (2012).

Figure 3-6 Spatial correlation of $PM_{2.5}$ components for monitor pairs described in the review study.

It was known at the time of the 2009 PM ISA (U.S. EPA, 2009b) that spatial variability of $PM_{2.5}$ was lower than for $PM_{10–2.5}$ and UFP. Data to characterize $PM_{10–2.5}$ and UFP spatial concentration surfaces remain limited but generally support that comparison. More recent data for $PM_{2.5}$ components shows that components that are influenced by primary sources tend to be more spatially variable than components produced via atmospheric chemistry.

3.4.2.3 Instrument Accuracy and Precision

The influence of instrument error on health effect estimates from epidemiologic studies varies with study design. Inter-monitor comparison is often used to estimate instrument precision. Accuracy and

precision of ambient monitors is described in Section 2.5.4, and accuracy and precision for personal $PM_{2.5}$ monitors were described in the 2009 PM ISA (U.S. EPA, 2009b) and have not changed markedly since the last review.

More attention is given at present to $PM_{10–2.5}$, because those measurements were not as prevalent at the time of the 2009 PM ISA (U.S. EPA, 2009b). Errors associated with measurements of $PM_{10–2.5}$ are described in Section 2.4.2. Use of subtraction methods for estimating $PM_{10–2.5}$ concentration can lead to substantial errors. This is particularly true when the $PM_{10–2.5}$ is semivolatile. Clements et al. (2013) tested different methods for measuring PM_{10} and $PM_{2.5}$ and calculating $PM_{10–2.5}$ via subtraction methods and found that the nonvolatile PM endemic to Colorado were measured with less error by instruments that did not account for semivolatile losses. Biases in calculated $PM_{10–2.5}$ concentrations caused reductions in correlation coefficients across sites, leading to an incorrect picture of spatial variability in $PM_{10–2.5}$ concentration across the test area.

A number of studies have characterized errors associated with measuring UFP (Section 2.4.3). UFP concentrations are often referred to without specific reference to size distribution. Some studies report number count as UFP, while other studies use mobility methods to impose an upper particle size limit of 100 nm or 250 nm. CPCs typically have lower size detection limits of 10 nm (Liu and Kim, 1977), while mobility have lower size detection limits of 1 nm (Kangasluoma et al., 2015; Lehtipalo et al., 2014; Kuang et al., 2012; Jiang et al., 2011; Vanhanen et al., 2011; Iida et al., 2008). Hence, use of CPCs in an epidemiologic study of short or long-term exposure may lead to an underestimation of the UFP exposure concentration.

For epidemiologic studies of short-term exposure, Goldman et al. (2010) investigated instrument precision error at locations where ambient monitors were collocated. Correlations between collocated measurements of $PM_{2.5}$ mass and components (SO_4^{2-}, NO_3^-, NH_4^+, EC, OC) ranged from Pearson $R = 0.85$ for OC to Pearson $R = 0.97$ for $PM_{2.5}$ mass. Depending on specific conditions such as sampler type (e.g., passive vs. continuous), meteorological conditions, or presence of semivolatile PM, instrument errors may vary in total magnitude or direction so that error is not always positively correlated with concentration. Analysis of instrument error compared with measured and true (i.e., simulated) concentrations for the Goldman et al. (2010) study suggested that the error was not correlated with either measured or true concentrations. Hence, the instrument error was neither pure Berkson error nor pure classical error, but it probably retained Berkson-like and classical-like characteristics. If instrument error and concentration are positively correlated, then error in the exposure concentration estimates will be larger in locations where there are more prevalent or stronger primary sources or at times when PM emissions are higher for a given location. Moreover, if error is positively correlated with concentration, then it would be anticipated that the magnitude of the instrument error is largest at times of day when emissions are highest.

Instrumentation bias could be anticipated to influence exposure concentration estimates used in long-term PM exposure studies in some situations. For example, geostatistical or LUR models may

underestimate exposure concentration when the model is fit using data from samples that have experienced negative artifacts due to volatility. Ambient temperature and relative humidity would not be expected to vary greatly within a city. Because climate and ambient sources are more likely to differ among cities, instrumentation error occurring when warm temperatures exacerbate evaporation could have a larger influence on the comparison of exposure concentrations among cities.

3.4.2.4 Model Accuracy and Precision

Error in PM exposure model predictions leads to some error in the health effect estimates from epidemiologic studies in which they are used. However, the implications of the type of errors depends upon the application. In statistical models used in epidemiologic studies, spatial, temporal, or concentration biases and errors may align with the health data being used, leading to potential errors and increased uncertainties in the health effect estimates (NRC, 2007).

The performance of the exposure models in recreating exposure estimates can impact the ensuing health analyses. LOOCV is often used to assess the exposure concentration estimates (Section 3.3.2), particularly for LUR. One issue with LOOCV is that monitoring sites can be clustered, such that removing a monitor that is near other monitors does not "stress" the model, because the value from the nearby monitors will lead to an accurate replacement value. That issue, along with the majority of sites being clustered in urban areas, can lead to seemingly good performance metrics that are not indicative of how well the method can estimate exposure concentrations away from monitoring sites. Given that exposure models are developed, in part, to estimate levels away from observation locations it is informative to have approaches to evaluate how well the method can estimate exposures in such cases. One approach that has been developed is to remove multiple monitors that are spatially grouped such that they are not being influenced by nearby observations (Lv et al., 2016). A related issue arises in LUR modeling. If a hold-out technique uses 90% of the data to both build and train the model, a different set of independent variables may be chosen than those in the full model. Wang et al. (2014) argued that a preferable approach is to build the full model and retrain it with 90% of the data. Wang et al. (2015) found that the LUR model performance (R^2 ranged from about 0.3 to 0.9 for $PM_{2.5}$) was positively associated with the magnitude of the health effect estimate. Alexeeff et al. (2015) conducted a simulation study using high resolution fields developed from MAIAC satellite data as the "true" field, and developed simulated spatiotemporal fields by kriging and using LUR. R^2 of the kriging and LUR methods ranged from about 0.24 to 0.98. They linked poor performance (e.g., lower R^2) with bias in the health effect estimates. Goldman et al. (2011) and Goldman et al. (2010) also found in a simulation study that increased exposure measurement error led to negative bias in the health outcomes and increased uncertainty. These, and related studies, show the potential impact of the accuracy of the exposure concentration metrics on bias and uncertainty in the health effect estimates in an epidemiologic study.

A major issue in using concentration surfaces estimated by CTMs for epidemiologic analyses is that the errors in the model inputs [e.g., emissions, (Koo et al., 2015; Xu et al., 2015; Hao and Larkin, 2014; Larkin et al., 2014; Paulot et al., 2014; Urbanski et al., 2011; Zhang et al., 2010b), meteorology (Digar et al., 2011), and surface characteristics] and parameters (e.g., chemical reaction, thermodynamic, and turbulence descriptions) lead to output errors, including time- or location-varying biases (Hogrefe et al., 2015; Koo et al., 2015; Porter et al., 2015; Hogrefe et al., 2014; Rao et al., 2014; Appel et al., 2013; Appel et al., 2012; Simon et al., 2012; Napelenok et al., 2011; Civerolo et al., 2010; Foley et al., 2010; Zhang et al., 2010b; Swall and Foley, 2009). Meteorological models, which are typically used to provide inputs to air quality models, have similar issues with inputs and parameters, thus leading to uncertain output fields that also have errors and uncertainties. Arrandale et al. (2011) also noted that mean bias and correlation varied by region with distinct spatial patterns. Given the potential for such errors, understanding how well such models can reproduce PM (including size and components) concentration fields for exposure or exposure concentration modeling is important.

Errors can be large, particularly when considering individual PM components (e.g., OC) or size fractions (e.g., UFPs) (Koo et al., 2015; Stanier et al., 2014; Zhang et al., 2010b). In terms of model parameters, this is often due to a fundamental lack of understanding of the processes, for example knowledge of the chemical reactions and products involving organic compounds or nucleation (Donahue et al., 2013; Shiraiwa et al., 2013; Worton et al., 2013; Chen et al., 2011; Donahue et al., 2011; Hoyle et al., 2011; Pierce et al., 2011; Zhang et al., 2010a; Kulmala et al., 2009; Nieminen et al., 2009; Kroll and Seinfeld, 2008; Kuang et al., 2008; Kulmala and Kerminen, 2008). Koo et al. (2015) conducted an extensive evaluation of two CTMs (CMAQ and CAMx) for the same domain, and found that the models, overall, performed similarly for $PM_{2.5}$, but differences were found upon further investigation (e.g., performance for individual PM components, and how the errors varied based on region and time). The Koo et al. (2015) study demonstrated that the same model will perform differently, sometimes dramatically, depending upon domain and time period such that performance in one application is not definitive support that performance will be similar in a different application. The limited availability of sub-24-hour PM mass concentration and component data has inhibited the evaluation of CTMs for simulating the diurnal variation of PM. Koo et al. (2015) used diurnally varying $PM_{2.5}$ compositional information available from SEARCH (Hansen et al., 2006; Hansen et al., 2003) to further assess CMAQ and CAMx model performance and found that, in addition to a low bias in OC and ammonium, during the summer the models also simulated a drop during the daytime that was not found in the observations. This additional bias could impact studies that used temporally finer-scale $PM_{2.5}$ exposure concentration estimates.

Due to the various potential errors in using air quality models to develop exposure concentration fields, Marmur et al. (2006b) and Marmur et al. (2006a) concluded that the direct use of CTMs in epidemiologic studies of acute health endpoints would lead to attenuation in the observed outcomes. Spatially- and temporally-varying biases and errors would also lead to questions of their use in epidemiologic studies of long-term exposures as well if the fields are not modified (Bravo et al., 2012),

such as by blending with PM concentrations derived from satellite observations, as discussed in Section 3.3.3.

3.4.3 Costressor Relationships

To assess the independent effects of PM in an epidemiologic study of health effects, it is necessary to identify (Bateson et al., 2007): (1) which copollutants (e.g., NO_2, CO, BC) and additional exposures (e.g., noise, traffic levels) are potential confounders of the health effect-PM relationship so that their correlation with PM can be tested and, if needed, accounted for in the statistical model; (2) the time period over which correlations might exist so that potential confounders are considered appropriately for the time period relevant for the epidemiologic study design (e.g., pollutants or other factors that are correlated over the long term might not be important for a short-term exposure epidemiologic study); and (3) the spatial correlation structure across multiple pollutants, if the epidemiologic study design is for long-term exposure. Given that a covariate must be correlated with both the exposure and the health effect to be a confounder, the potential for confounding of PM-related health effects can vary by the health endpoint of interest.

For copollutants that do show high correlations, copollutant models may be appropriate to adjust the effect estimate for each pollutant for the potential confounding effects of another pollutant if each pollutant is associated with the health effect (Tolbert et al., 2007). If one copollutant is a surrogate for an etiologically linked pollutant, copollutant models may attribute the effect to the copollutant measured with less error, regardless of whether it is the etiologically linked pollutant. In copollutant models where PM is measured with more error than a copollutant, a differential effect occurs where the health effect estimate of PM exposure may be lower than the health effect estimate of the copollutant, even if PM is the true causal agent (Zeger et al., 2000), as discussed in the 2009 PM ISA (U.S. EPA, 2009b). If this occurs, the health effect related to PM exposure would be underestimated or potentially not detected. Positive correlation between PM and the copollutant and between the exposure measurement errors of PM and the copollutant can add more negative bias to the PM health effect estimate. Spatial variability of concentration differs among the particle size spectrum, and this may cause more exposure measurement error in $PM_{10-2.5}$ or UFP compared with $PM_{2.5}$ (Section 3.4.2.2). Hence, if $PM_{2.5}$ is measured with less error than copollutants, it is likely that the effect will be attributed to $PM_{2.5}$.

This section considers temporal copollutant correlations and how relationships among copollutants may change in space. Temporal copollutant correlations are computed from the time series of copollutant concentrations for two different collocated monitors. Temporal correlations are informative for epidemiologic studies of short-term PM exposure when the sampling interval is less than a month for each of the copollutants. Temporal correlations are informative for epidemiologic studies of long-term PM exposures when sampling intervals are months-to-years. Spatial relationships are evaluated by comparing within-pollutant variation across space for different pollutants. The following sections review

coexposures that can potentially confound the relationship between a health effect and PM exposure over different temporal and spatial resolutions.

3.4.3.1 Temporal Relationships among Ambient PM and Copollutant Exposures

AQS data presented in the 2009 PM ISA (U.S. EPA, 2009b) demonstrated most correlations between $PM_{2.5}$ and gaseous copollutants were typically between −0.2 and 0.8 with average and median values around 0.2 to 0.5. Correlations between $PM_{2.5}$ and $PM_{10–2.5}$ were observed in a similar range. Given limited data for $PM_{10–2.5}$ at the time when the 2009 PM ISA was written, correlations between $PM_{10–2.5}$ and gaseous copollutants were not presented.

To place the copollutant correlation discussion in the context of the epidemiologic studies, we present the correlation data for the epidemiologic studies in CHAPTER 5, CHAPTER 6, CHAPTER 7, CHAPTER 8, CHAPTER 9, CHAPTER 10, and CHAPTER 11 that reported correlations of $PM_{2.5}$, $PM_{10–2.5}$, or UFP with copollutants. Figure 3-7, Figure 3-10, and Figure 3-13 (for $PM_{2.5}$, $PM_{10–2.5}$, and UFP, respectively) plot study data for correlations with gaseous copollutants O_3, CO, SO_2, NO_2, and NO_X and with particulate copollutants. More data were available for $PM_{2.5}$ compared with $PM_{10–2.5}$ or UFP (as NC, based on the assumption that the majority of particles are smaller than 100 nm), and so Figure 3-7 is divided into four panels for all data combined, acute timescales within 1 hour, short-term timescales between 1 hour and 2 weeks (with most data obtained at a 24-hour timescale), and long-term timescales longer than 2 weeks. Only 24-hour data were available for $PM_{10–2.5}$ and UFP correlation data.

For acute and short-term timescales (within 1 hour and 2 weeks, respectively), median correlations of $PM_{2.5}$ with copollutants were ordered $CO > NO_2 > SO_2 > NO_X > O_3$ (Figure 3-7). Acute data were relatively sparse but produced median correlations that were lower than those for short-term. Because data were combined across studies, Figure 3-7 includes both Pearson and Spearman correlations. Short-term correlations for CO and NO_2 reached as high as $R = 0.9$, while roughly 20% of the short-term correlations between $PM_{2.5}$ and O_3 were negative. Correlation data between UFP and O_3 were limited to one study (Kearney et al., 2011), and three of four reported correlations were negative in contrast to the mostly positive correlations between $PM_{2.5}$ and O_3 (Figure 3-13). Data for short-term correlations of $PM_{2.5}$ with $PM_{10–2.5}$ and UFP were around $R = 0.5$, although data were also sparse for these comparisons. Median correlations of $PM_{10–2.5}$ and gases ranged between $R = 0.3$ and $R = 0.5$, although limited data were available for these comparisons. Correlations of $PM_{10–2.5}$ with CO and NO_2 were around $R = 0.5$, potentially indicating some commonality of sources, such as traffic emissions of CO and (indirectly) of NO_2 with $PM_{10–2.5}$ generated by brake dust (Section 2.4.2). For short-term correlations of UFP with copollutant gases and particles, median correlations were 0.5 for NO_2 and lower for everything else. It is possible that low correlations could be related to the short lifetime of UFP relative to other PM size fractions. However, because limited data for UFP correlations were available, few conclusions can be

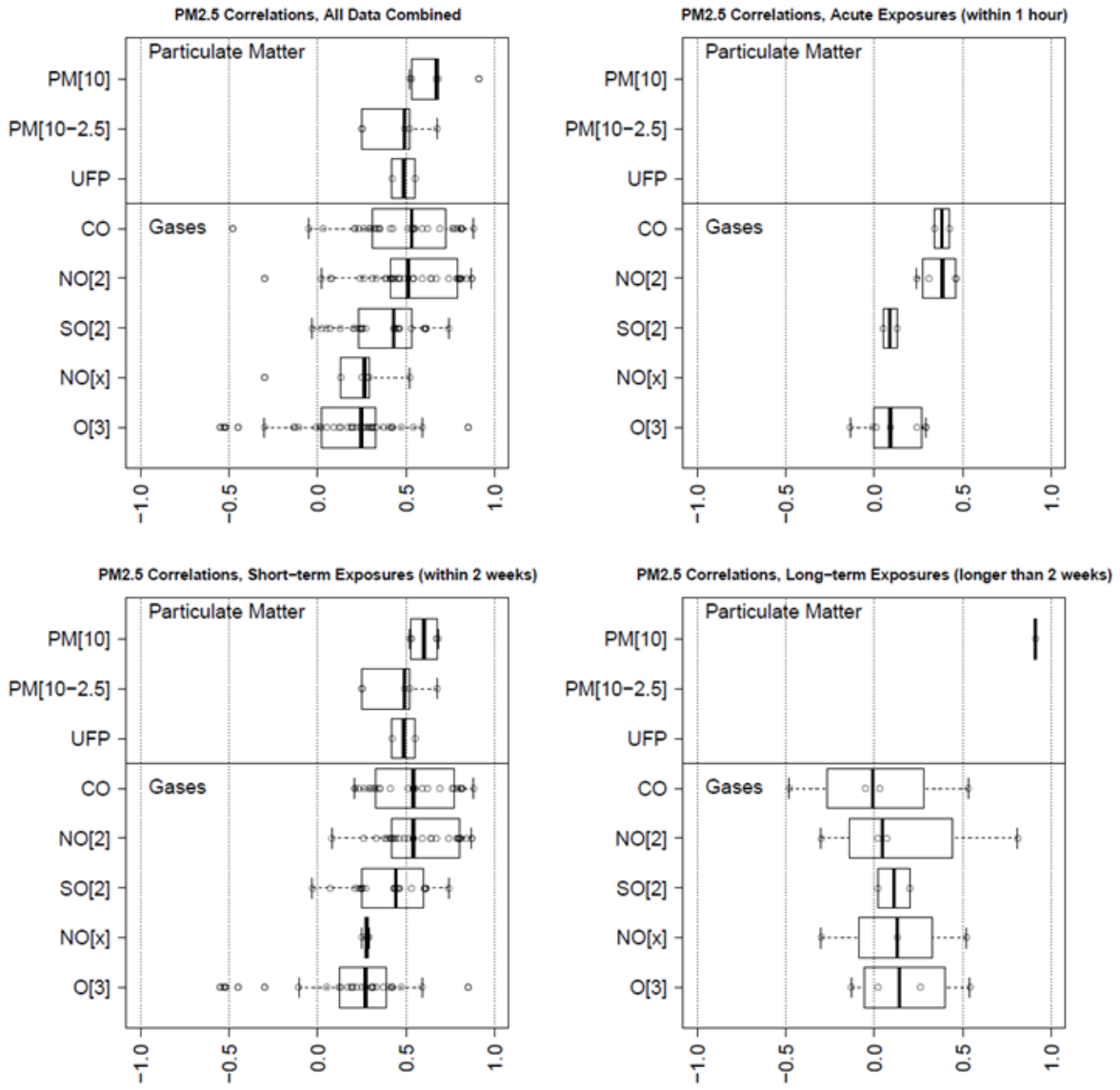
drawn. Because data were combined across studies, Figure 3-13 also includes both Pearson and Spearman correlations.

Median long-term correlations (i.e., longer than 2 weeks) between $PM_{2.5}$ and copollutants follow a pattern opposite to that for short-term correlations: $O_3 > NO_X > SO_2 > NO_2 > CO$ (Figure 3-7). Median correlations were between $R = 0$ and $R = 0.2$. Limited quantity of data existed for long-term correlations between $PM_{2.5}$ and copollutants and no data existed for long-term correlations of $PM_{2.5}$ with $PM_{10-2.5}$ or UFP. Moreover, overlapping 25th-to-75th percentile and 5th-to-95th percentile intervals reduce confidence in the comparison.

For comparison to the epidemiologic data, short-term (24-hour average) correlations of $PM_{2.5}$ and copollutants and of $PM_{10-2.5}$ and copollutants were studied using air quality data from collocated monitors reported within the U.S. EPA AQS repository system during 2013−2015. 438 sites met the 75% data completeness criteria presented in Section 2.5.1.1. Pearson correlations were used to evaluate temporal correlations among ambient $PM_{2.5}$ concentrations and NAAQS copollutant concentrations. Figure 3-8 displays the distribution of correlations between NAAQS copollutants and 24-hour $PM_{2.5}$ for annual data for 2013−2015, and Figure 3-9 displays the distribution of correlations broken down by season. For CO, SO_2, and NO_2, 1-hour daily max concentrations are used, while for O_3, 8-hour daily max concentrations are considered. Annual and seasonal copollutant correlation plots for 24-hour $PM_{10-2.5}$ are provided in Figure 3-11 and Figure 3-12.

Across seasons, 24-hour average $PM_{2.5}$ and $PM_{10-2.5}$ concentrations reported in the AQS consistently have the highest correlations with PM_{10} concentrations (median Pearson $R = 0.7−0.8$ for $PM_{2.5}$, median Pearson $R = 0.7−0.9$ for $PM_{10-2.5}$) (Figure 3-9, Figure 3-12). This could occur if $PM_{2.5}$ were a large contributor to PM_{10}, if $PM_{2.5}$ and $PM_{10-2.5}$ were of the same source, or if $PM_{2.5}$ and $PM_{10-2.5}$ were of different sources whose emissions were coordinated in time. Correlations between $PM_{2.5}$ concentrations and $PM_{10-2.5}$ concentrations are lower than either size fraction's correlation with PM_{10} across seasons (median Pearson $R = 0.2−0.5$), with lowest correlations in winter. This is consistent with observations from the epidemiology literature (Figure 3-7, Figure 3-10), although data for $PM_{10-2.5}$ correlations are limited. Figure 3-7 and Figure 3-10 do not distinguish between Pearson and Spearman correlations, because data are combined across studies. In the summer and spring, correlations of $PM_{2.5}$ with SO_2, NO_2, and CO are all roughly $R = 0.2$. In the fall and winter, however, correlations of $PM_{2.5}$ are ordered as $CO > NO_2 > SO_2$, consistent with correlations reported in the epidemiology literature (Figure 3-9). Higher correlations of CO and NO_2 with $PM_{2.5}$ may be indicative of combustion sources. Correlation of $PM_{2.5}$ and O_3 is highest during the summer (median Pearson $R \sim 0.45$) and is negative during the winter. High summer correlations could reflect photooxidation to produce simultaneously higher levels of O_3 and secondary PM (Section 2.3.2.3), (U.S. EPA, 2013). Median correlations of $PM_{10-2.5}$ with SO_2, NO_2, CO, and O_3 were all in the range of $R = 0.1−0.3$ across seasons. This may reflect the origin of $PM_{10-2.5}$ largely as dust rather than by combustion, other industrial processes, or

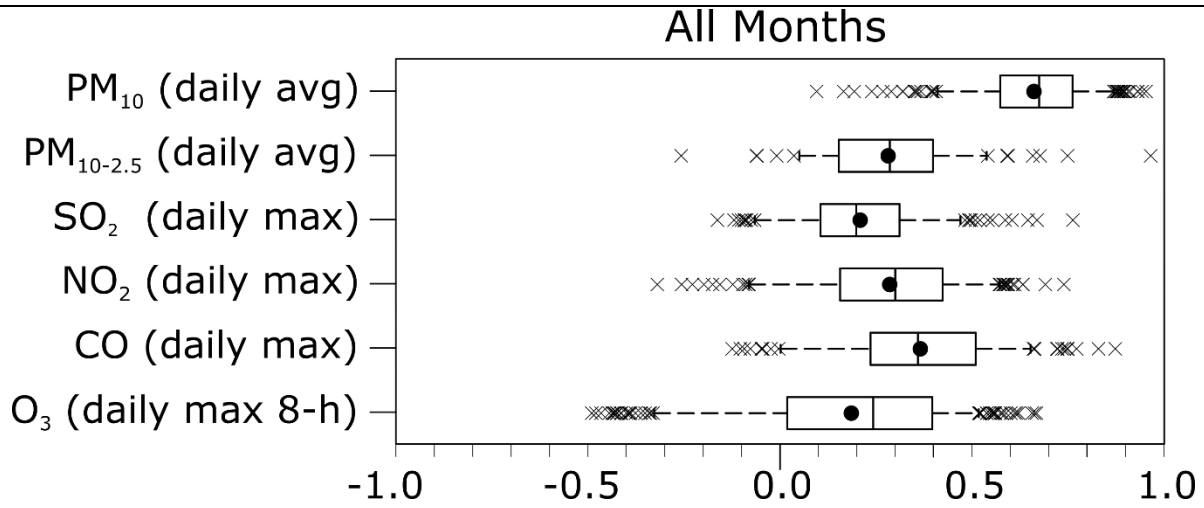
photochemistry. Correlation data from epidemiology studies (Figure 3-10) are higher for CO and NO_2, but only a limited number of studies reported those correlations.



Based on epidemiologic studies reporting correlations in CHAPTER 5, CHAPTER 6, CHAPTER 7, CHAPTER 8, CHAPTER 9, CHAPTER 10, and CHAPTER 11.

Source: Permission pending, References listed in Richmond-Bryant (2018).

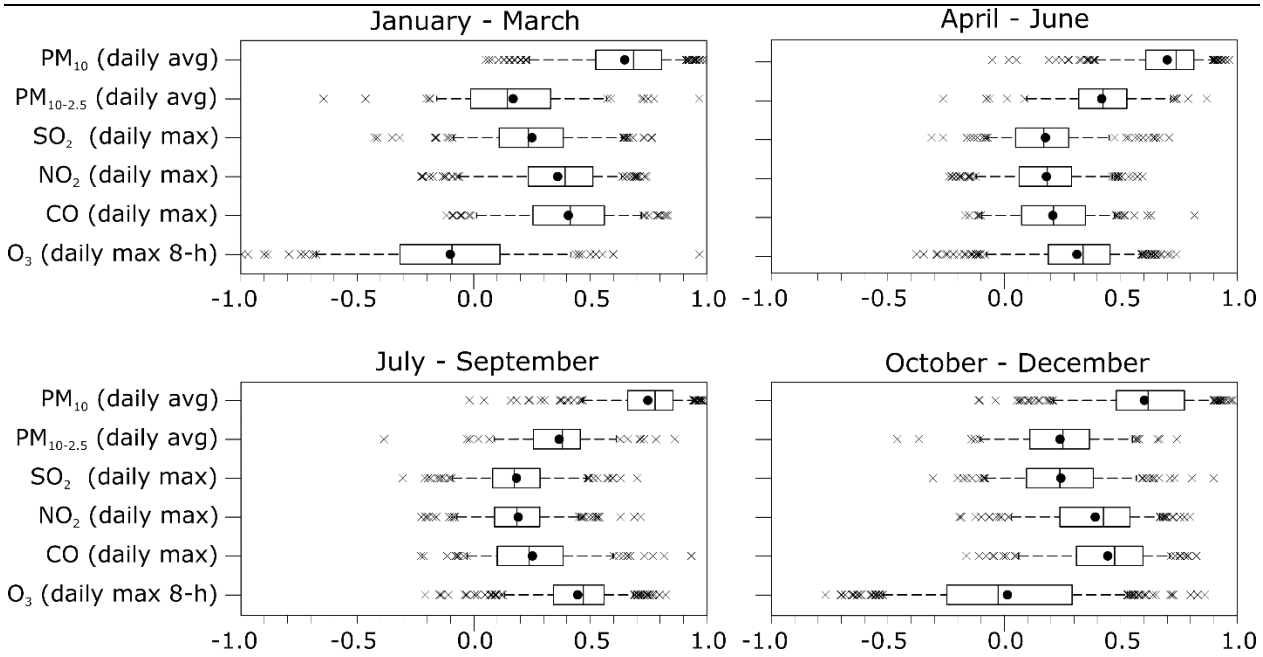
Figure 3-7 Correlations between $PM_{2.5}$ and copollutants for all data combined (top left), timescales within 1 hour (top right), short-term timescales within 2 weeks (bottom left), and long-term timescales greater than 2 weeks (bottom right).



CO = carbon monoxide; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than 2.5 µm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; S = sulfur.

Note: Shown are the median (line), mean (circle), and inner-quartile range (box), 5th and 95th percentile (whiskers) and extremes (x's).

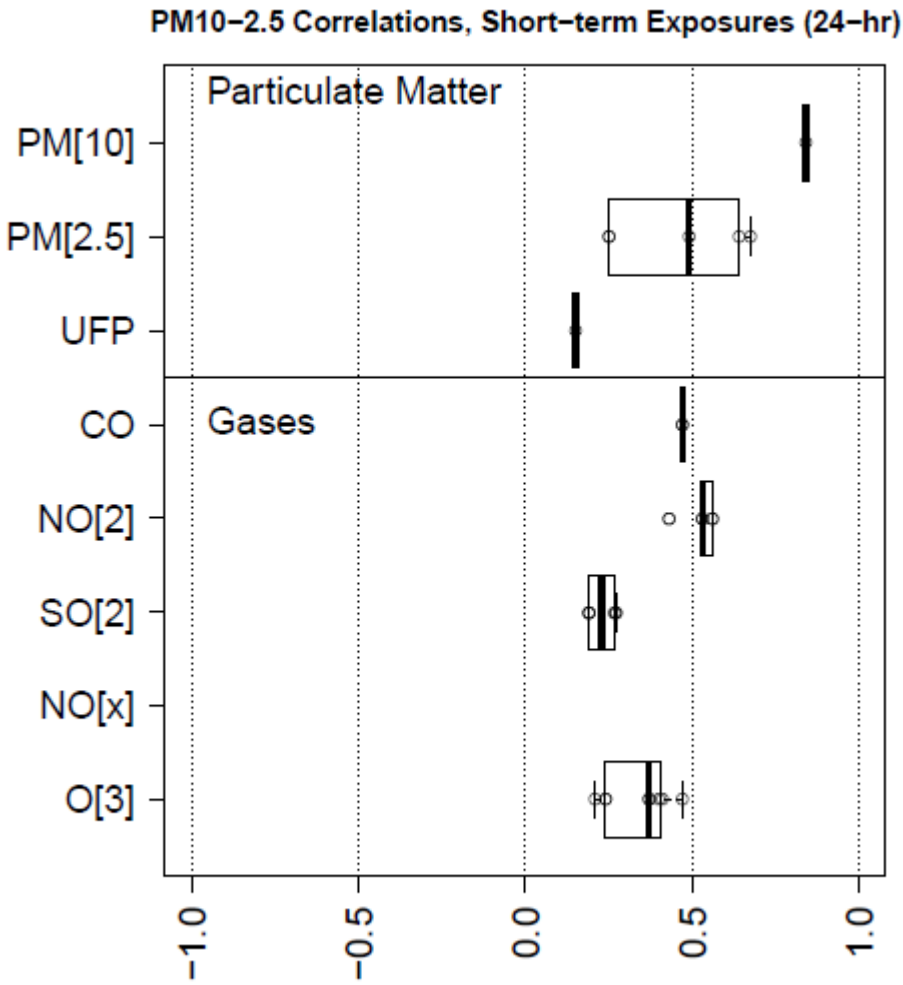
Figure 3-8 Distribution of Pearson correlation coefficients for annual 24-hour average concentration of $PM_{2.5}$ with collocated copollutants from the Air Quality System during 2013−2015.



CO = carbon monoxide; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than 2.5 µm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; S = sulfur.

Note: Shown are the median (line), mean (circle), and inner-quartile range (box), 5th and 95th percentile (whiskers) and extremes (x's).

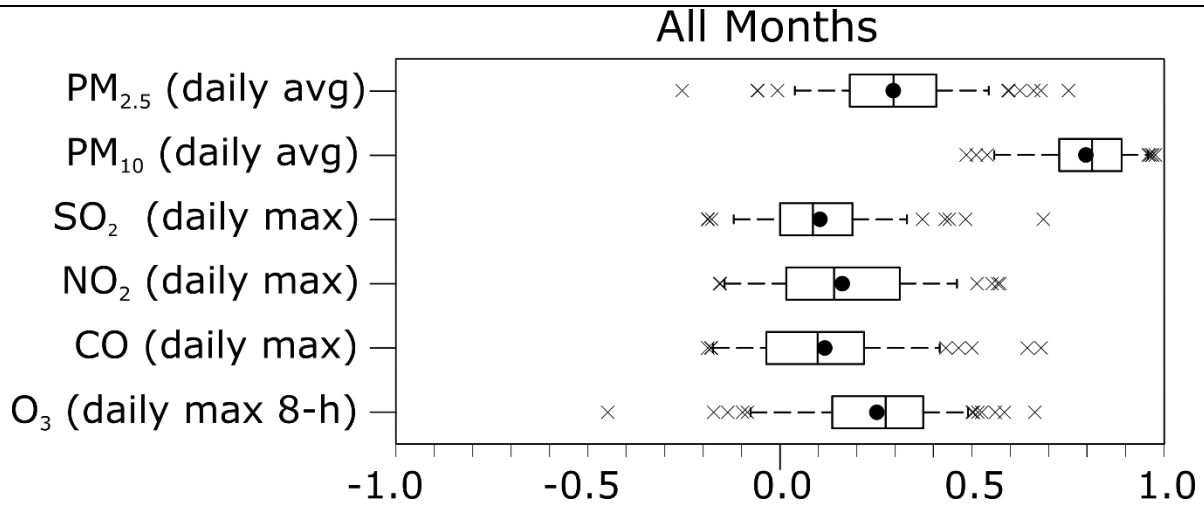
Figure 3-9 Distribution of Pearson correlation coefficients for comparison of seasonal 24-hour average concentration $PM_{2.5}$ with collocated copollutants from the Air Quality System during 2013−2015.



Note: Only 24-hour data were available for $PM_{10-2.5}$. Based on epidemiologic studies reporting correlations in CHAPTER 5, CHAPTER 6, CHAPTER 7, CHAPTER 8, CHAPTER 9, CHAPTER 10, and CHAPTER 11.

Source: Permission pending, (Chen et al. (2015); Cheng et al. (2015); Michikawa et al. (2015); Qiu et al. (2014); Raza et al. (2014); Alessandrini et al. (2013); Qiu et al. (2013); Rosenthal et al. (2013); Wichmann et al. (2013); Qiu et al. (2012); Atkinson et al. (2010)).

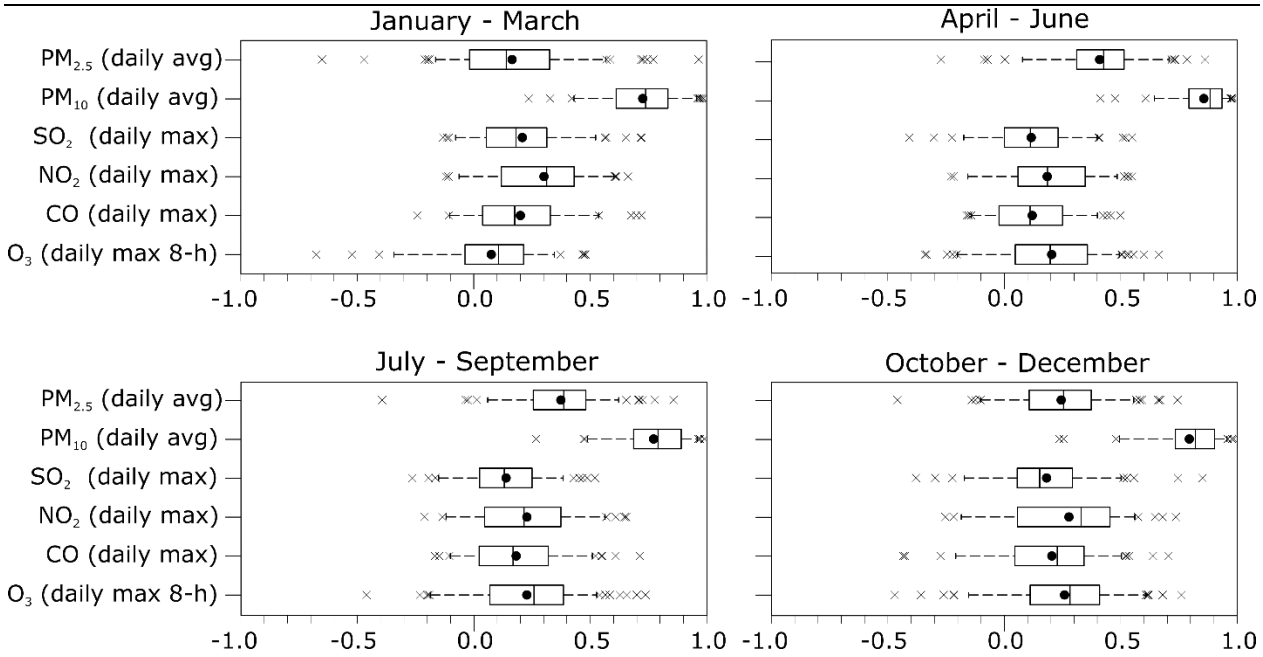
Figure 3-10 Pearson correlations between $PM_{10-2.5}$ and copollutants for short-term exposures.



CO = carbon monoxide; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than 2.5 µm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; S = sulfur.

Note: Shown are the median (line), mean (circle), and inner-quartile range (box), 5th and 95th percentile (whiskers) and extremes (x's).

Figure 3-11 Distribution of Pearson correlation coefficients for annual 24-hour average concentration of $PM_{10-2.5}$ with collocated copollutants from the Air Quality System during 2013−2015.

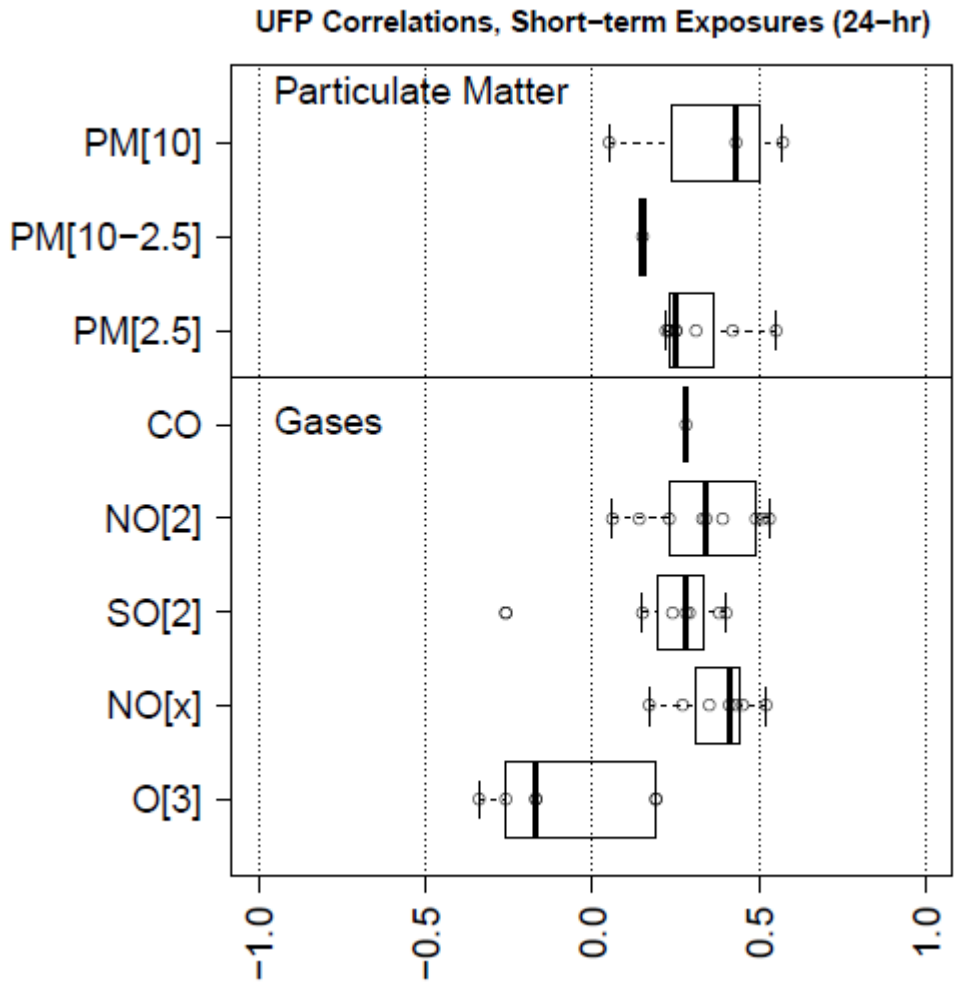


CO = carbon monoxide; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than 2.5 µm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; S = sulfur.

Note: Shown are the median (line), mean (circle), and inner-quartile range (box), 5th and 95th percentile (whiskers) and extremes (x's).

Figure 3-12 Distribution of Pearson correlation coefficients for comparison of seasonal 24-hour average concentration of $PM_{10-2.5}$ with collocated copollutants from the Air Quality System during 2013−2015.

Limited data were available from the peer-reviewed literature for correlations of UFP concentration with concentrations of other PM size fractions or of gases (Figure 3-13). Median Pearson correlations around $R = 0.5$ were reported for UFP with $PM_{2.5}$ and with NO_2 and NO_X. Without more data to identify copollutant relationships for UFP, it is difficult to interpret these data.



Note: Only 24-hour data were available. Based on epidemiologic studies reporting correlations in Chapters 5−11.
Source: Permission pending, Iskandar et al. (2012); Kearney et al. (2011); Leitte et al. (2011); Andersen et al. (2010); Atkinson et al. (2010); Belleudi et al. (2010).

Figure 3-13 Correlations between UFP and copollutants for short-term exposures.

3.4.3.2 Spatial Relationships among Ambient PM and Copollutant Exposures

When an epidemiologic study design relies on spatial contrasts to draw conclusions, such as for an epidemiologic study of long-term exposure, unmeasured spatial correlation between copollutants may lead to positive bias in the health effect estimate for each of the pollutants included in the model. Paciorek (2010) performed simulations and analyzed case study data (of the relationship between birth weight data and BC concentrations in eastern Massachusetts) to test the effect of spatial errors on health effect estimates in long-term exposure epidemiologic studies. In this study, Paciorek (2010) selected BC as a

PM component because it is spatially variable. He identified unmeasured spatial confounding as a key driver in biasing health effect estimates in a spatial regression. Paciorek (2010) maintained that bias can be reduced when variation in the exposure concentration metric occurs at a smaller spatial scale than that of the unmeasured confounder. The findings of Paciorek (2010) would be expected to be more significant for more spatially-variable $PM_{10-2.5}$, UFP, and BC than for $PM_{2.5}$, for which less spatial error would be anticipated.

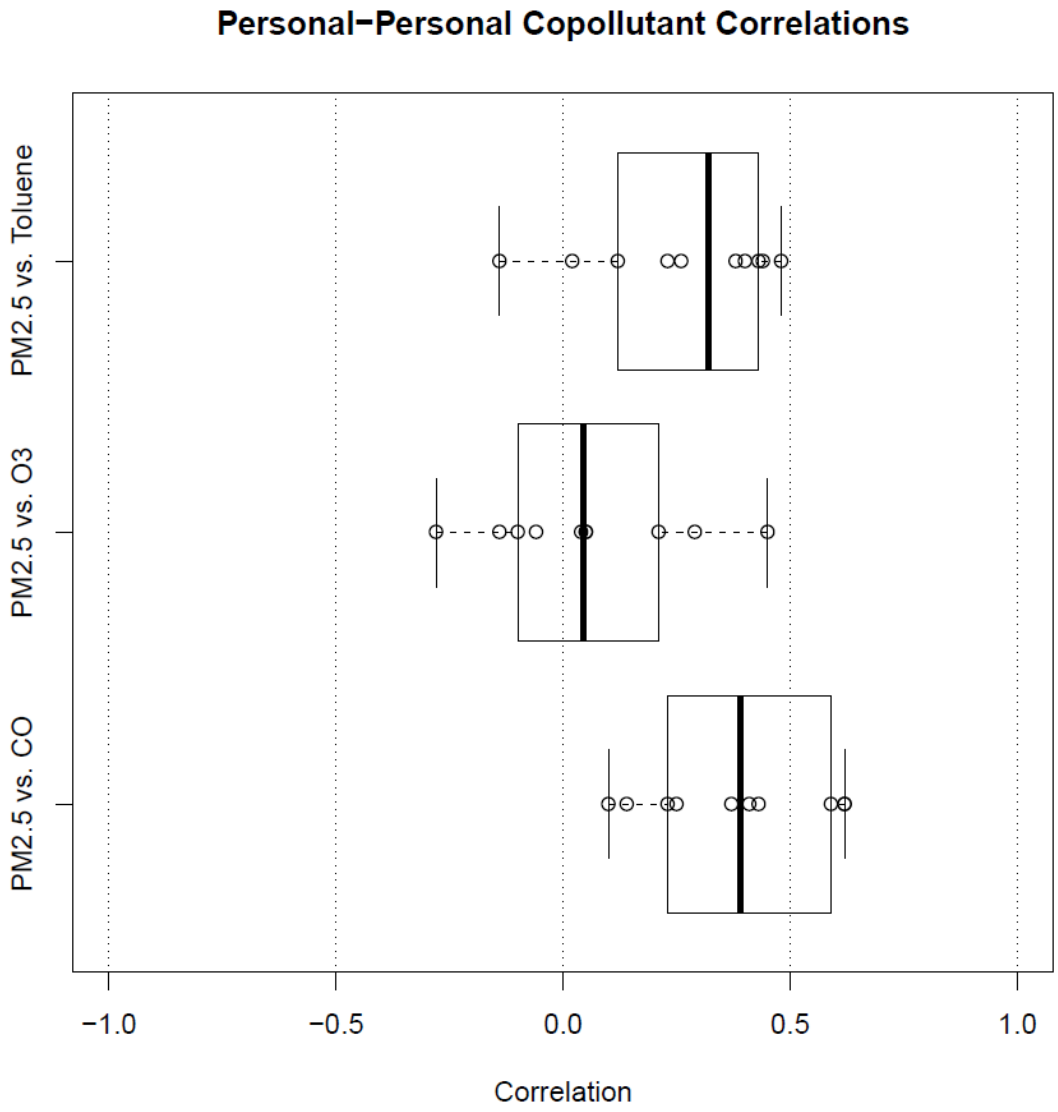
3.4.3.3 Personal and Indoor Relationships between PM and Copollutant Exposures

No new studies on relationships among personal and ambient copollutants had been performed since the 2009 PM ISA (U.S. EPA, 2009b). Those data are presented graphically in Figure 3-14, Figure 3-15, and Figure 3-16. Figure 3-14 displays copollutant correlations among personal exposures to $PM_{2.5}$, toluene, O_3, and CO. The data from Chang et al. (2000) were obtained in Baltimore, MD in the summer of 1998 and winter of 1999. Median correlations were 0.39 for the personal-personal relationship for $PM_{2.5}$ versus CO, 0.32 for $PM_{2.5}$ versus toluene, and 0.045 for $PM_{2.5}$ versus O_3. Correlations were highest when personal measurements were obtained outdoors away from the road during the summer for $PM_{2.5}$ versus O_3 and $PM_{2.5}$ versus CO during the summer and for $PM_{2.5}$ versus toluene during the winter. The higher correlations obtained away from the road may reflect the secondary nature of much of the measured $PM_{2.5}$.

Median personal-ambient slopes between $PM_{2.5}$ and gaseous copollutants are generally between 0 and 0.5, as shown in Figure 3-15. These data were obtained from Koutrakis et al. (2005), Sarnat et al. (2005), Sarnat et al. (2001), and Sarnat et al. (2006b) from Boston, MA, Baltimore, MD, and Steubenville, OH. Median relationships of personal $PM_{2.5}$ exposure with ambient gaseous copollutant concentrations were higher with more variability than those of personal SO_4^{2-} exposures with ambient gas concentrations, indicating that nonambient $PM_{2.5}$ exposure may have amplified these relationships and added uncertainty. Data were more limited for relationships between personal EC concentration and ambient gaseous copollutant concentrations, but these tended to be lower as well. Greater variability occurred in some cases for the relationships between personal exposure to gaseous copollutants and ambient concentrations of $PM_{2.5}$, EC, and SO_4^{2-}, perhaps as a result of limited amounts of data.

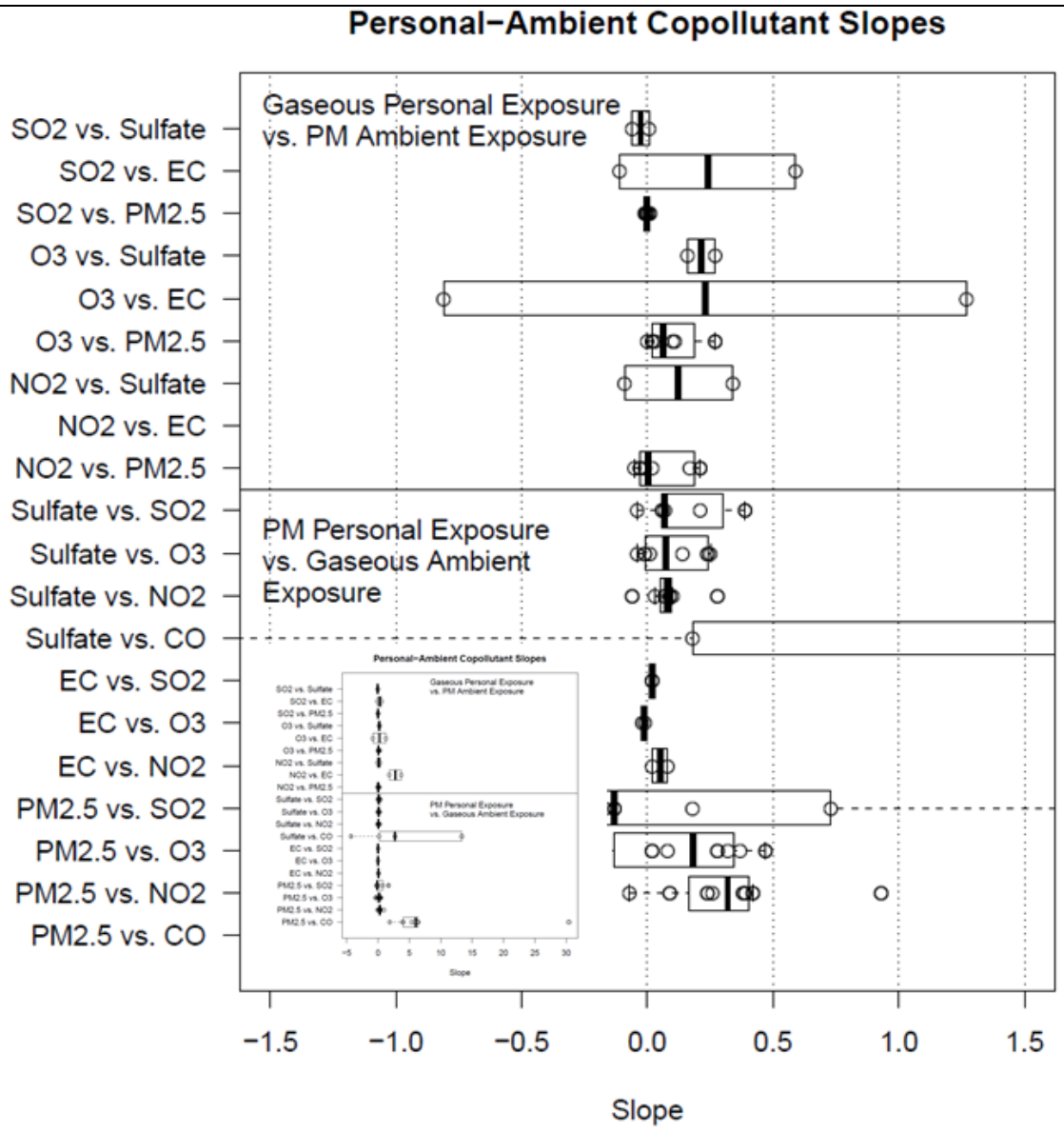
Median slopes for the relationship between personal exposure to PM or SO_4^{2-} with gaseous copollutants (NO_2, O_3, and SO_2) tended to be between 0 and 0.5 (Figure 3-16). The exception was the relationship between $PM_{2.5}$ and SO_2, which was negative but of similar magnitude. These data were obtained from Koutrakis et al. (2005), Sarnat et al. (2005), and Sarnat et al. (2001). A slight reduction in median slope along with smaller data intervals were observed when personal SO_4^{2-} exposure was used in lieu of personal $PM_{2.5}$ exposure, suggesting that the nonambient component of personal exposure may have influenced these relationships. Nonambient sources of O_3 and SO_2 are much less prevalent, so it is unlikely that they would have influenced their respective relationships. Although NO_2 does have indoor

(indirect) sources, variability in these relationships was lower than for the other gaseous copollutant exposures.



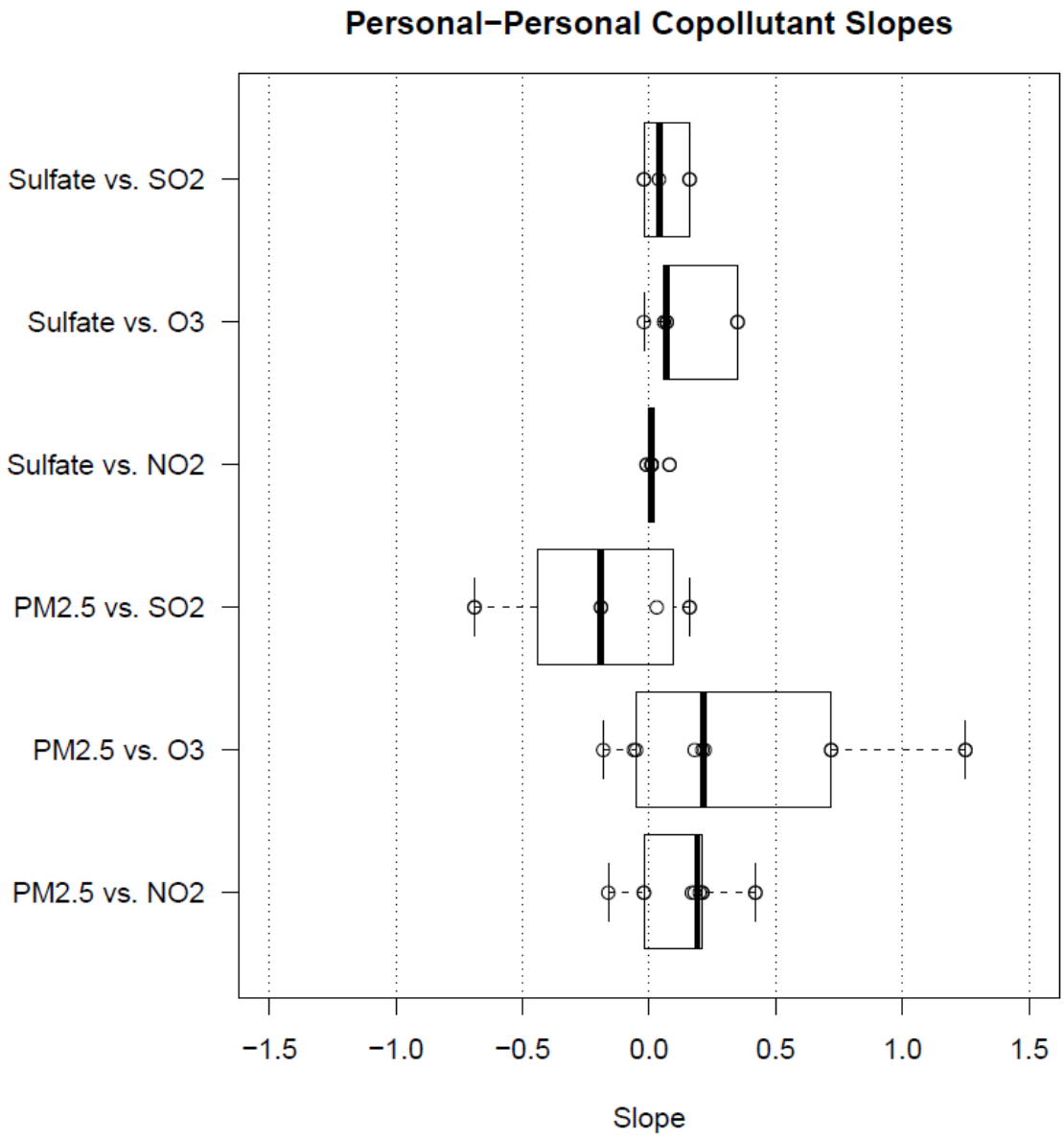
Source: Permission pending, (Chang et al., 2000).

Figure 3-14 Correlations between personal exposure to $PM_{2.5}$ mass and personal exposure to gases.



Note: Outliers for NO_2 vs. EC, SO_4^{2-} vs. CO, and $PM_{2.5}$ vs. CO are shown on the small inset figure.
Source: Permission pending, Sarnat et al. (2006b); Koutrakis et al. (2005); Sarnat et al. (2005); Sarnat et al. (2001).

Figure 3-15 Slopes for personal-ambient relationships. Top: Personal exposure to gaseous copollutants related to ambient exposure to $PM_{2.5}$ mass or EC or SO_4^{2-} components.



Source: Permission pending, Koutrakis et al. (2005); Sarnat et al. (2005); Sarnat et al. (2001).

Figure 3-16 Slopes for personal-personal relationships between $PM_{2.5}$ mass or SO_4^{2-} component and gaseous copollutants.

3.4.3.4 Traffic-related Noise

The 2009 PM ISA (U.S. EPA, 2009b) did not consider the relationship of PM with traffic-related noise levels. Recent evidence is inconsistent regarding the correlations of PM concentrations with traffic and noise levels (HEI, 2010). There are differences among the studies exploring the health effects of PM and noise regarding size cut of PM measured, road type, and surrounding features. Hence, the role of traffic and noise as confounders or independent variables in the relationship between health effects and PM exposure is unclear.

Several studies have examined the relationship of traffic-related noise with PM concentrations. Kheirbek et al. (2014) added noise level meters to the dense New York, NY monitoring project described in Ross et al. (2013) and observed that 1-week average noise level (measured as dB[A]), obtained at 60 locations during Fall 2012, correlated with Pearson $R = 0.45$ for $PM_{2.5}$ concentration and Pearson $R = 0.62$ for BC concentration. Boogaard et al. (2009) measured UFP, $PM_{2.5}$, and noise (measured as dB[A]) while bicycling on scripted 10- to 20-minute routes for ten cities in The Netherlands and found a median correlation of Pearson $R = 0.34$ across cities for UFP and noise while the median correlation was Pearson $R = 0.009$ for $PM_{2.5}$ and noise. Gan et al. (2012b) calculated the correlations among air pollutants and noise from road traffic and aircraft using 5-minute data from 103 sites in Vancouver, BC, Canada during 2003 (dates not stated). They observed lower correlations for $PM_{2.5}$ concentration with road traffic noise (Spearman $R = 0.14$) compared with that for BC (Spearman $R = 0.45$). However, correlations between $PM_{2.5}$ and aircraft noise were higher (Spearman $R = 0.31$) than for BC (Spearman $R = -0.07$). Over a 5-year average, Gan et al. (2012a) reported the correlation between $PM_{2.5}$ concentration and noise from road traffic to be Spearman $R = 0.14$. Reported correlation of 5-year average BC concentration with BC concentration had a Spearman $R = 0.44$. These findings are consistent with the short-term observations reported in Gan et al. (2012b).

Ross et al. (2011) also examined relationships of different frequency noises with $PM_{2.5}$ and EC concentrations using continuous monitors collecting 48,000 samples per second for six 24-hour periods in August 2009. Ross et al. (2011) measured the relationships between traffic level, noise, and concentrations of $PM_{2.5}$ and EC in New York, NY as part of the Ross et al. (2013) study. Unweighted noise of all frequencies was uncorrelated with $PM_{2.5}$ concentration (Spearman $R = 0.20$) but correlation increased for EC concentration (Spearman $R = 0.35$) for all times. Correlations were higher for medium frequency noise ($PM_{2.5}$: Spearman $R = 0.20$; EC: Spearman $R = 0.39$) compared with high frequency noise ($PM_{2.5}$: Spearman $R = 0.14$; EC: Spearman $R = 0.15$) but were similar for low frequency noise ($PM_{2.5}$: Spearman $R = 0.19$; EC: Spearman $R = 0.32$). Correlations between $PM_{2.5}$ and low frequency noise (Spearman $R = 0.3$) were higher during rush hour than at night for low frequency noise or for any time for medium and high frequency noise. At night, high frequency noise had a higher correlation with EC concentration (Spearman $R = 0.4$).

Distance to road has also been observed to influence the relationship between noise and PM concentration as a surrogate for exposure concentration. The Gan et al. (2012b) study described above

also reported Spearman correlations between 5-minute average. A-weighted equivalent noise (i.e., noise level that is adjusted to noise perception by the human ear) and concentrations of $PM_{2.5}$ and BC for buffers of 50 m and 150 m of a highway (defined as A1 and A2 roads) and a major road (defined as A1, A2, and A3 roads). Correlations for $PM_{2.5}$ and noise were Spearman $R = 0.02$ within 50 m of the highway, Spearman $R = 0.03$ within 150 m, and Spearman $R = 0.17$ when further than 150 m. For a major road, correlations for $PM_{2.5}$ and noise were Spearman $R = 0.24$ within 50 m, Spearman $R = 0.15$ within 150 m, and Spearman $R = 0.14$ when further than 150 m. Results for correlations between BC and noise were higher than for correlations between $PM_{2.5}$ and noise, and they were more consistent between highways (within 50 m: Spearman $R = 0.17$, within 150 m: Spearman $R = 0.38$, further than 150 m: Spearman $R = 0.41$) and major roads (within 50 m: Spearman $R = 0.26$, within 150 m: Spearman $R = 0.46$, further than 150 m: Spearman $R = 0.31$). Allen et al. (2009) studied the relationship between UFP concentration, and 5-minute average A-weighted equivalent noise for 105 locations in Chicago, IL and Riverside, CA using measurements taken in December 2006 and April 2007. After adjustment for regional unspecified air pollutant concentration gradients, correlation of UFP with noise was Pearson $R = 0.31$ for Chicago and Pearson $R = 0.41$ for Riverside. Correlation of noise with UFP concentrations was higher within a 100-m buffer of the road (Chicago: Pearson $R = 0.37$; Riverside: Pearson $R = 0.58$) compared with outside the buffer (Chicago: Pearson $R = 0.08$; Riverside: Pearson $R = 0.50$).

3.4.4 PM Composition and Exposure Assessment

Compositional differences in ambient PM and ambient PM that has infiltrated indoors were discussed briefly in the 2009 PM ISA (U.S. EPA, 2009b). Several studies cited in the 2009 PM ISA found that SO_4^{2-} comprised the largest proportion of ambient $PM_{2.5}$ exposure in studies from the eastern U.S., while a study in Denver found NO_3^- to be the largest contributor to $PM_{2.5}$. Studies of differential infiltration of $PM_{2.5}$ by BC or OC found that BC contributed more to indoor $PM_{2.5}$ compared with OC. 2013−2015 composition data across the U.S. shows that, while there is still more SO_4^{2-} in the east compared with the west, OC now is the most prevalent component of $PM_{2.5}$ in many areas across the country (Section 2.5.1.1.6).

This section provides new information on PM composition for $PM_{2.5}$, $PM_{10-2.5}$, and UFP from the peer-reviewed literature. Section 3.4.4.1 presents correlations between PM mass and composition from AQS and from the peer-reviewed literature. Section 3.4.4.2 is a new section of the ISA that presents data on studies of ROS exposure in the literature.

3.4.4.1 Composition

Select epidemiologic studies of the health effects of PM exposure have examined potential associations between health effects and exposure to PM components (CHAPTER 5, CHAPTER 6,

CHAPTER 7, CHAPTER 8, CHAPTER 9, CHAPTER 10, and CHAPTER 11). These studies compare the effect estimates for exposure to PM components with health effect estimates for exposure to total PM, measured as ambient mass concentration (MC), NC, or personal exposure concentration. This section presents relationships between concentrations of total PM with PM components.

Figure 3-17 displays correlations for 24-hour ambient $PM_{2.5}$ mass concentration with mass concentration for select components of $PM_{2.5}$ measured from the AQS during 2013−2015 on an annual basis, and Figure 3-18 displays the correlations on a seasonal basis. Median correlations with $PM_{2.5}$ were ordered as OC > SO_4^{2-} > EC > NO_3^- > Cl > Si, with correlations above Pearson $R = 0.5$ for OC, SO_4^{2-}, EC, and NO_3^-. Sulfate, NO_3^-, and OC are most commonly a product of chemical reactions of air pollutants in the atmosphere, and PM produced during atmospheric chemistry is often in the fine size range (Section 2.2). The median correlation of $PM_{2.5}$ with Cl and Si was approximately Pearson $R = 0.2$. On a seasonal basis, correlations between $PM_{2.5}$ and NO_3^- were lower during the spring and summer months, perhaps coinciding with less home heating fuel use during the summer. In the peer-reviewed literature (Figure 3-19), correlations of ambient $PM_{2.5}$ with ambient SO_4^{2-} and NO_3^-, used as exposure concentration surrogates, were similarly high (Ito et al., 2011; Ostro et al., 2010; Ostro et al., 2009), but much greater variability in correlations were observed for ambient OC and more so for EC or BC (which were combined for presentation purposes). Median correlations were around 0.5 for most trace metals, but higher correlations were observed for S, Zn, and V in New York (Ito et al., 2011) and Southern California (Ostro et al., 2010; Polidori et al., 2009). The higher correlations for S are likely explained by SO_4^{2-}. Ito et al. (2011) and Polidori et al. (2009) attributed elevated correlations with Zn and V to residential oil combustion.

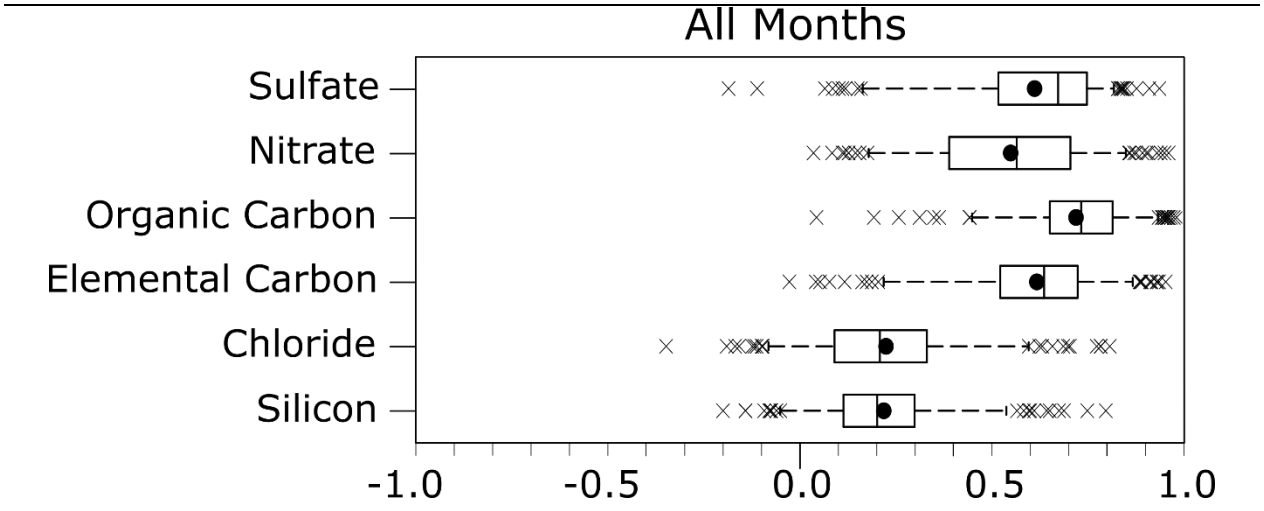


Figure 3-17 Distribution of Pearson correlation coefficients for annual 24-hour average $PM_{2.5}$ mass concentration with mass concentration of $PM_{2.5}$ components from the Air Quality System during 2013−2015.

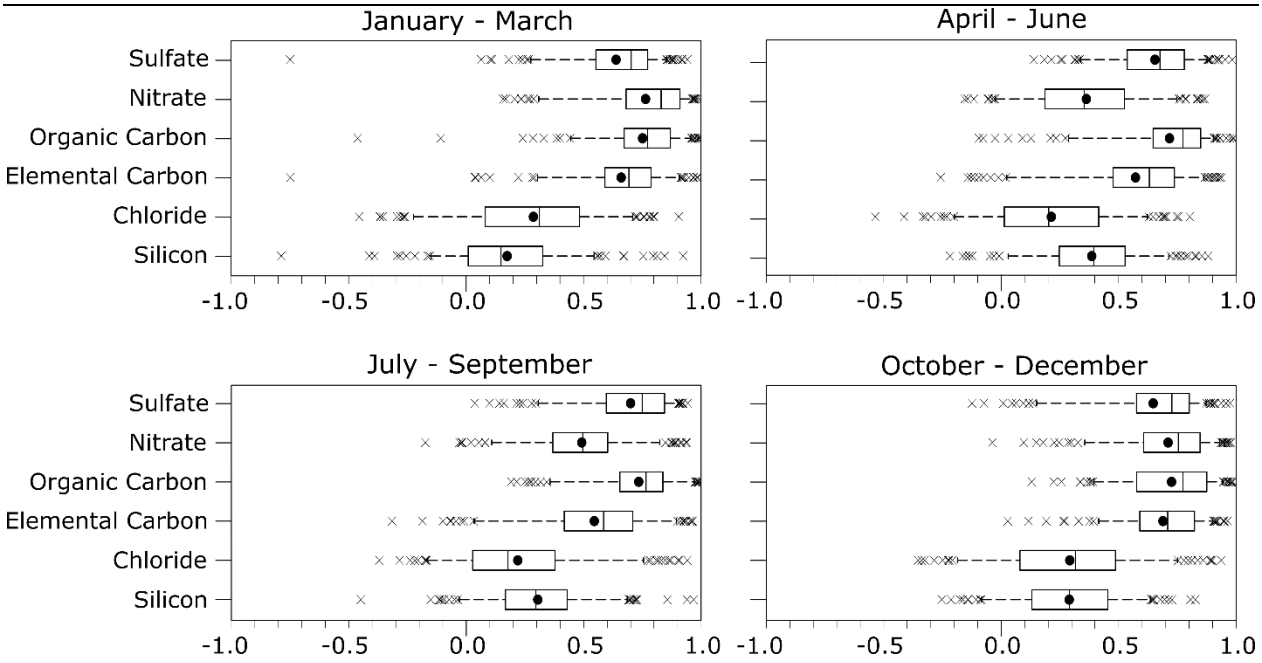
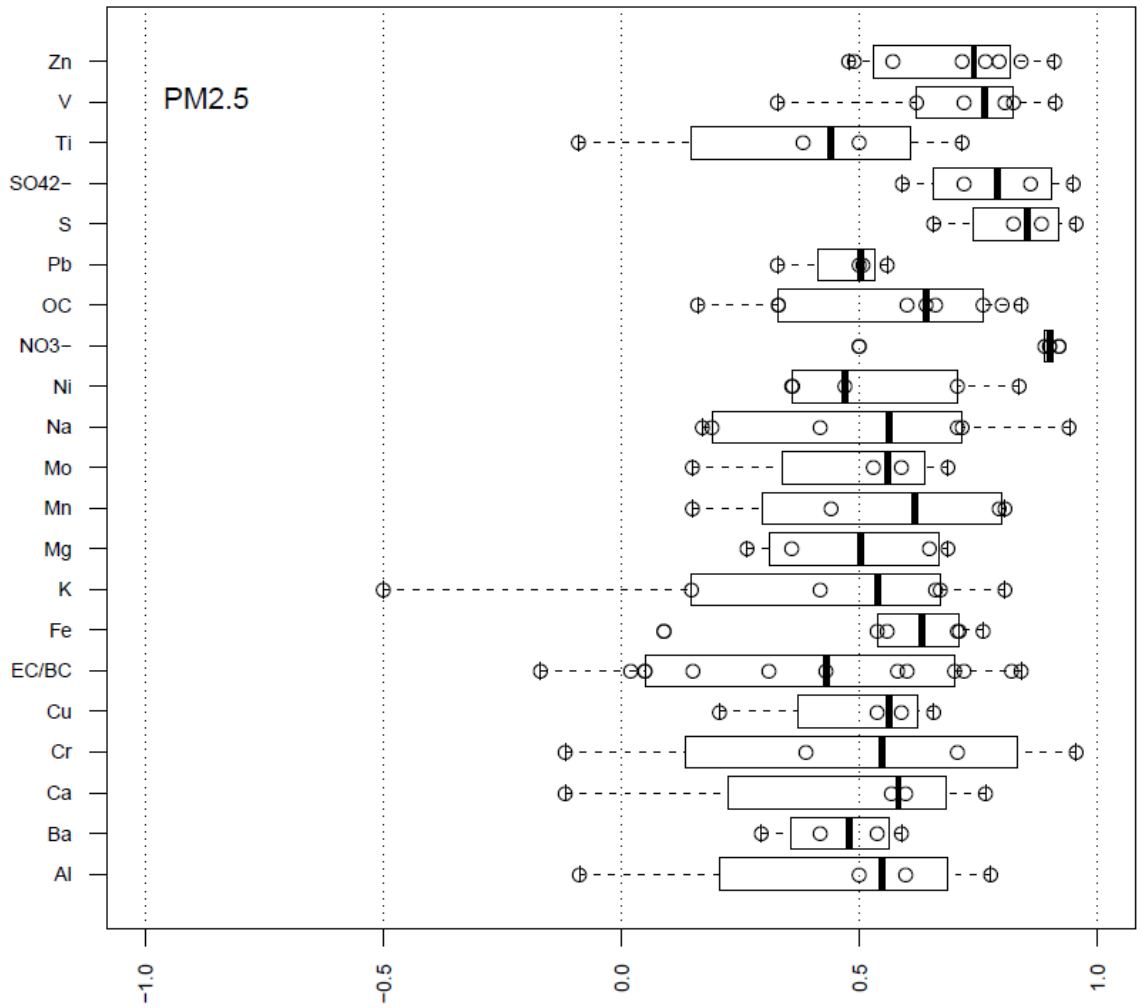


Figure 3-18 Distribution of Pearson correlation coefficients for comparison of seasonal 24-hour average total $PM_{2.5}$ mass with mass concentration of $PM_{2.5}$ components from the Air Quality System during 2013−2015.



Source: Permission pending, Polidori et al. (2009); Ito et al. (2011); Ostro et al. (2009); Raysoni et al. (2013); Zhang et al. (2016); Delfino et al. (2013); Delfino et al. (2010); Ostro et al. (2010).

Figure 3-19 Distribution of Pearson correlation coefficients for annual 24-hour average total $PM_{2.5}$ mass concentration with mass concentration of $PM_{2.5}$ components from the peer-reviewed literature during 2013−2015.

For SO_4^{2-}, OC, NO_3^-, and EC, site-specific correlations range from near Pearson $R = 1$ down to near Pearson $R = 0$ (Figure 3-17). This suggests spatial variability of the correlations between $PM_{2.5}$ and each component (Figure 3-20). Maps of Pearson correlations at AQS sites measuring $PM_{2.5}$ and components illustrate the level of variability for the four components. Correlations between $PM_{2.5}$ and SO_4^{2-} are highest in the northeastern and Midwestern portions of the U.S. Correlations between $PM_{2.5}$ and NO_3^- are highest in the West and markedly lower throughout the Southeast and Midwest. Correlations between $PM_{2.5}$ and EC appear highest in the West, possibly due to the influence of wildfire on $PM_{2.5}$ concentrations (Section 2.5.1.1.6).

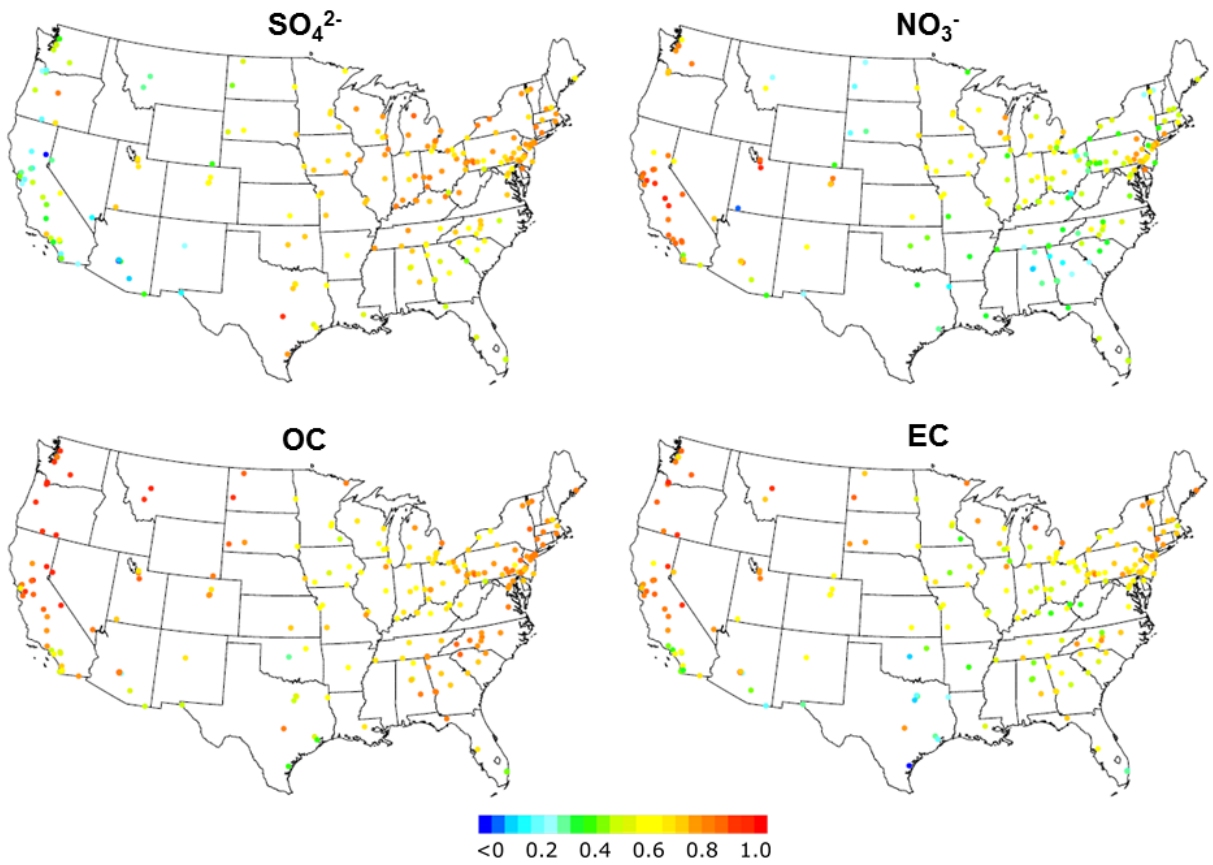


Figure 3-20 Maps illustrating national-scale variability of Pearson correlation coefficients for comparison of seasonal 24-hour average total $PM_{2.5}$ mass concentration with mass concentration of $PM_{2.5}$ components from the Air Quality System during 2013−2015.

Figure 3-21 displays annual correlations for 24-hour ambient $PM_{10-2.5}$ mass concentration with mass concentration for select components of $PM_{10-2.5}$ measured from the AQS during 2013−2015, and Figure 3-22 displays seasonal correlations. Median correlation of $PM_{10-2.5}$ mass concentration with Si was slightly lower than Pearson $R = 0.7$, while median correlations of $PM_{10-2.5}$ mass concentrations with the other $PM_{10-2.5}$ components were between Pearson $R = 0$ and Pearson $R = 0.3$. The difference between correlations for Si with those for the other components holds across seasons, with the highest correlation for Si and lowest correlations for all other components evident during the fall months (Figure 3-22). The higher correlation of $PM_{10-2.5}$ mass concentration and Si in $PM_{10-2.5}$ was likely due to the influence of dust, particularly in the Southwestern U.S. (Section 2.5). Figure 3-24 shows higher correlations in the Southwest, in support of this claim. Data for correlations between ambient $PM_{10-2.5}$ mass concentration and Si in $PM_{10-2.5}$ (for each of these studies, ambient $PM_{10-2.5}$ and components were measured by fixed-site monitors outside the location where personal samples were obtained, but no correlations were reported for personal samples) were not available in the literature for comparison (Raysoni et al., 2013; Delfino et al., 2010; Polidori et al., 2009), but median correlations for components reported were all less than Pearson $R = 0.5$ (Figure 3-23).

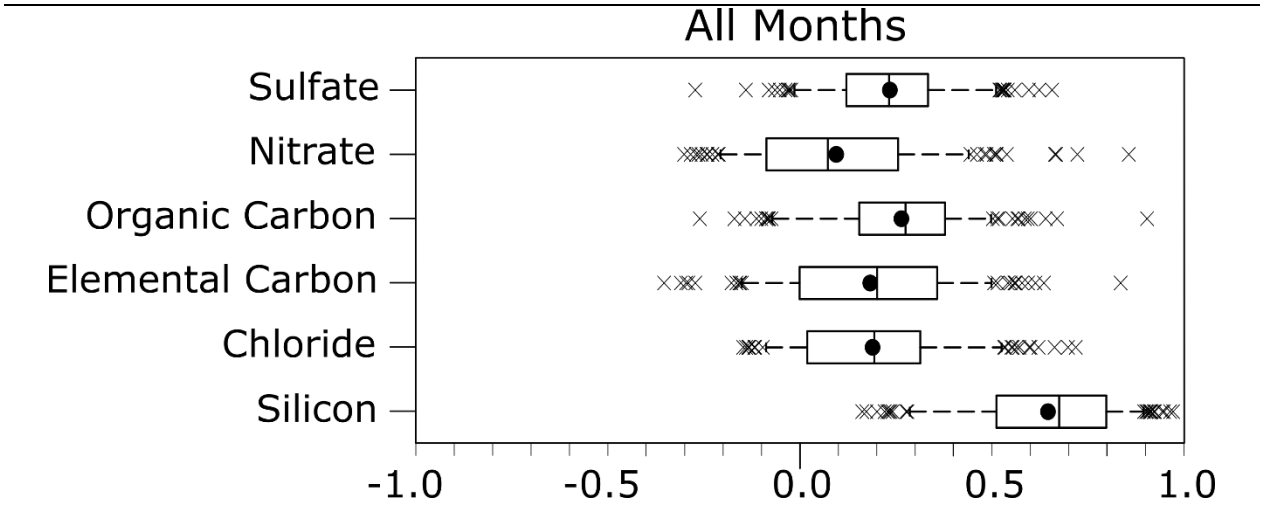


Figure 3-21 Distribution of Pearson correlation coefficients for annual 24-hour average total mass concentration of $PM_{10-2.5}$ with mass concentration of $PM_{10-2.5}$ components from the Air Quality System during 2013−2015.

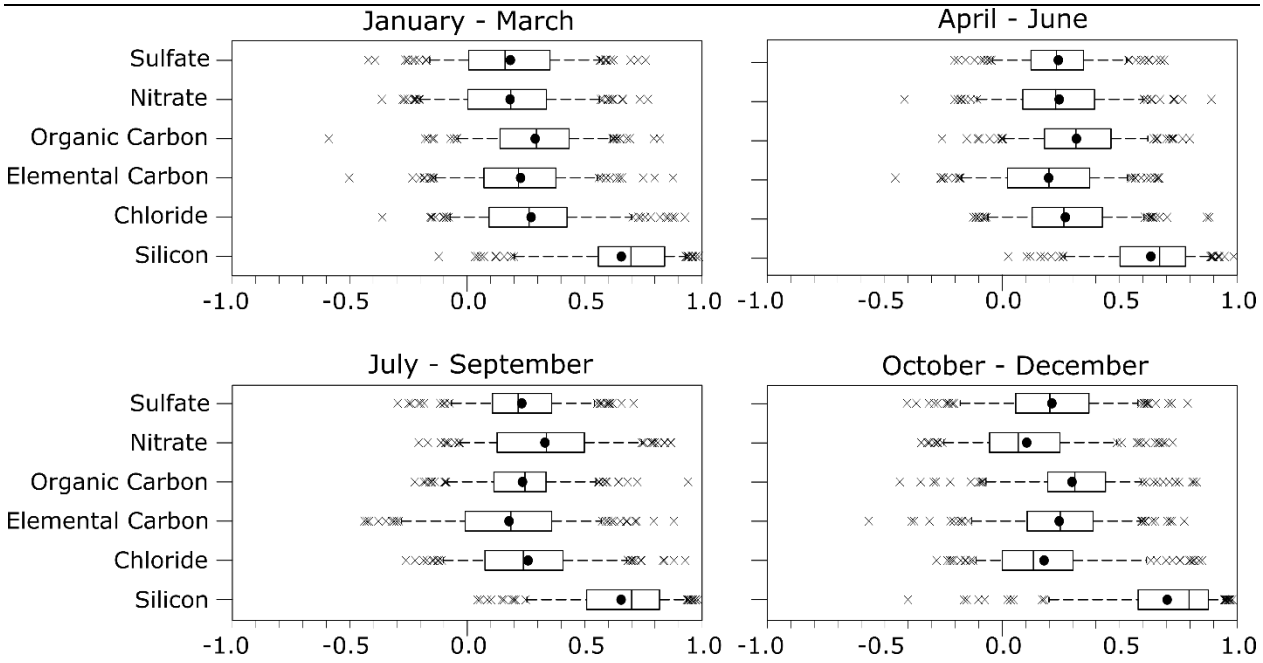
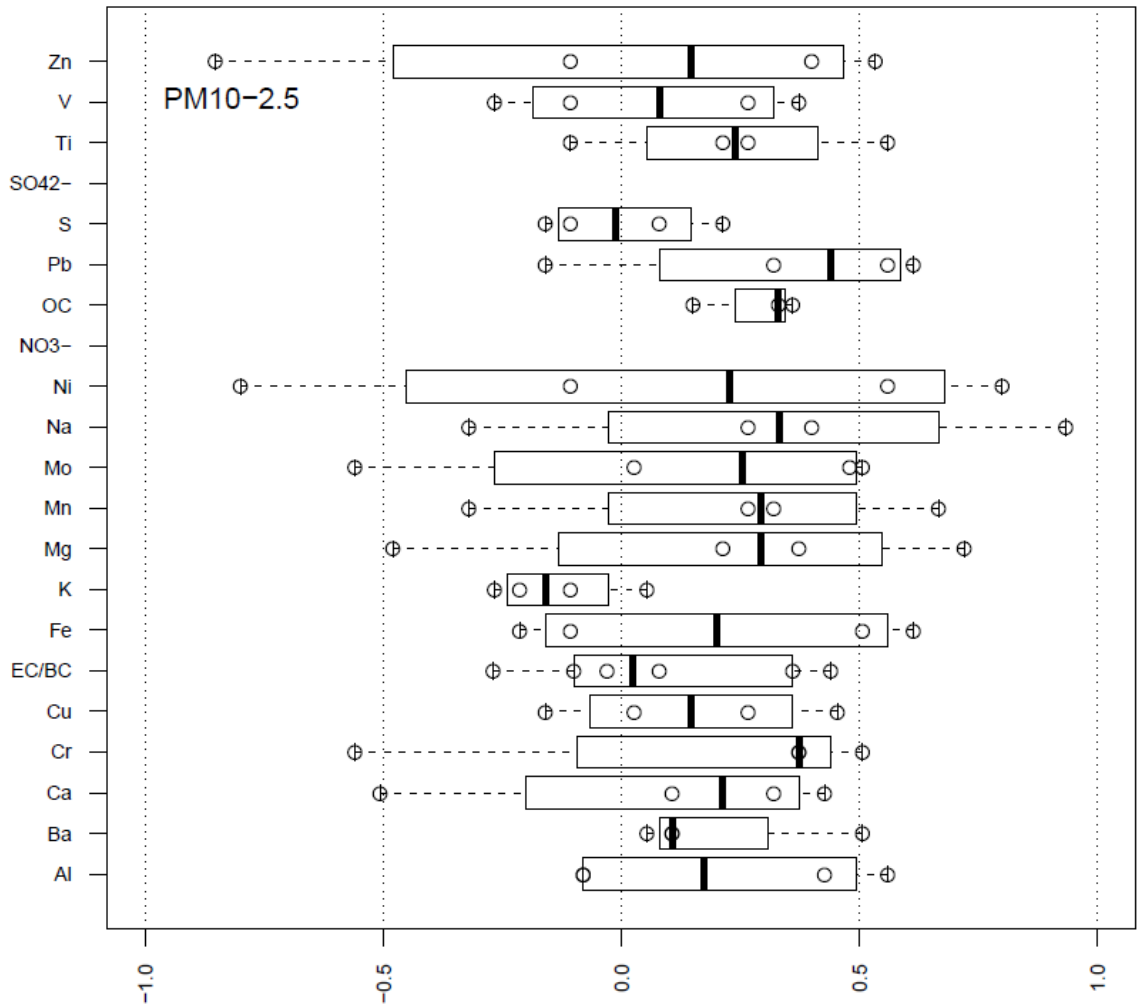


Figure 3-22 Distribution of Pearson correlation coefficients for comparison of seasonal 24-hour average total $PM_{10-2.5}$ mass concentration with mass concentration of $PM_{10-2.5}$ components from the Air Quality System during 2013−2015.



Source: Permission pending, Polidori et al. (2009); Raysoni et al. (2013); Delfino et al. (2010).

Figure 3-23 Distribution of Pearson correlation coefficients for annual 24-hour average total $PM_{10-2.5}$ mass concentration with mass concentration of $PM_{10-2.5}$ components from the peer-reviewed literature.

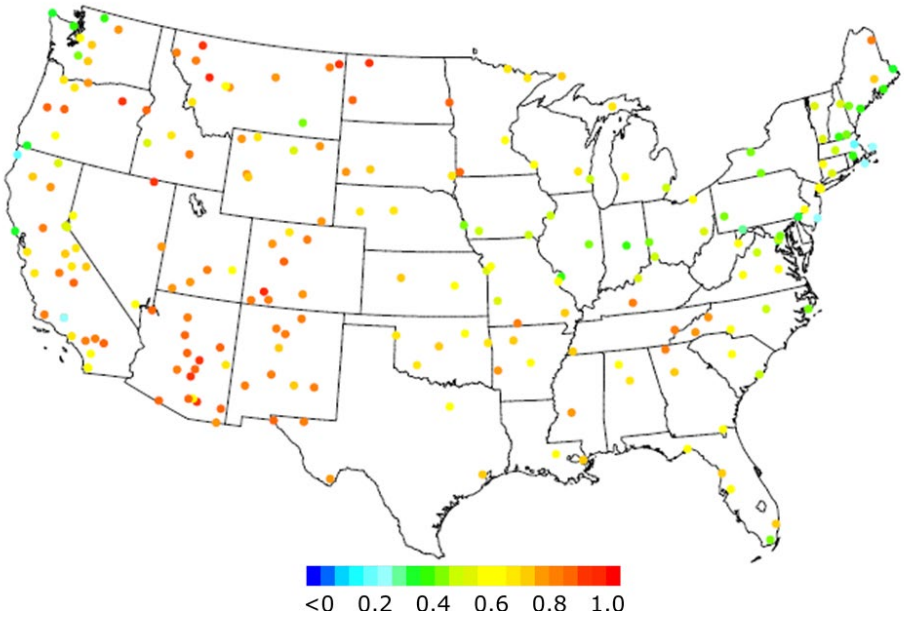
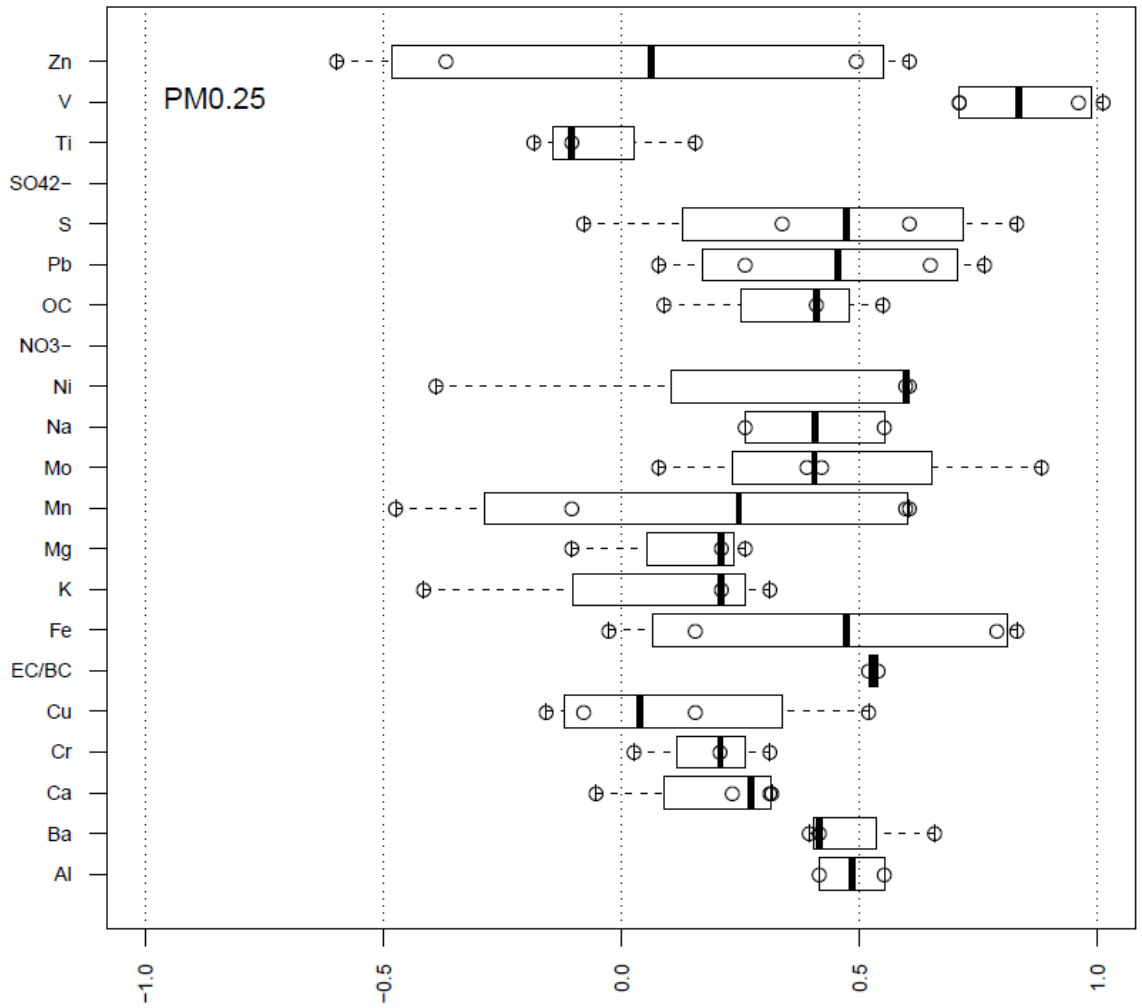


Figure 3-24 Map illustrating national-scale variability of Pearson correlation coefficients for comparison of seasonal 24-hour average total $PM_{10-2.5}$ mass concentration with mass concentration of Si in $PM_{10-2.5}$ from the Air Quality System during 2013−2015.

Exposure to UFP composition is informed by considering data for correlations of mass concentration for PM smaller than 250 nm ($PM_{0.25}$). These samples were measured using a cascade impactor, with concentrations of $PM_{0.25}$ components were calculated based on ambient fixed-site measurements for monitors placed outside retirement communities as surrogates for exposure concentration in Polidori et al. (2009) and Delfino et al. (2010), as shown in Figure 3-25. The highest median correlation was between $PM_{0.25}$ and V (Spearman $R = 0.8$), which tends to be present in heating oil and industrial waste (Polidori et al., 2009). Correlation between $PM_{0.25}$ and V was near Spearman $R = 1$ in the cool season and near Spearman $R = 0.7$ during the warm season, which is consistent with heating oil use. Medium correlations near Spearman $R = 0.5$ were reported for several components, including S (correlations with SO_4^{2-} were not reported at the $PM_{0.25}$ size cut), Pb, OC, Ni, Na, Mo, Fe, EC/BC, Ba, and Al. Both studies took place in 2005−2007, and ultra-low sulfur diesel fuel was phased in between 2006 and 2010. Moderate correlations for $PM_{0.25}$ with S, EC/BC, OC, and Ba could be related to traffic (Polidori et al., 2009).



Source: Permission pending, Polidori et al. (2009); Delfino et al. (2010).

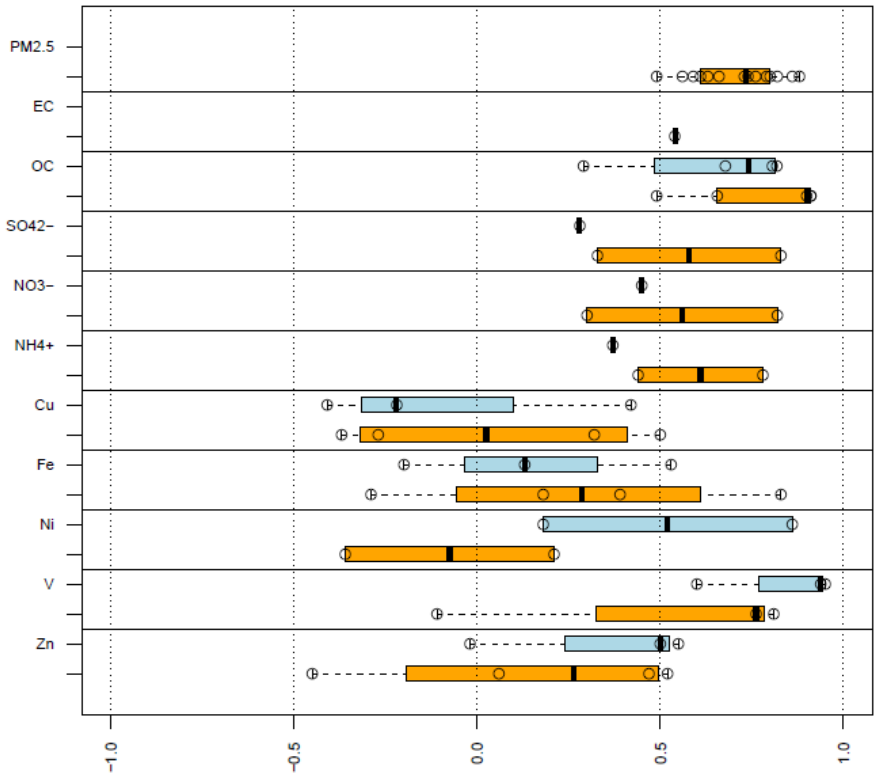
Figure 3-25 Distribution of Pearson correlation coefficients for annual 24-hour average total $PM_{0.25}$ mass concentration with mass concentration of $PM_{0.25}$ components from the peer-reviewed literature.

3.4.4.2 Reactive Oxygen Species

Recent exposure assessment studies inform biological plausibility discussions (Section 5.2.1, Section 5.3.1, Section 6.2.1, Section 6.3.1, and Section 10.2.1) because they measure oxidative potential

as a surrogate for oxidative stress. Oxidative stress and inflammation may be initiated by PM exposure, when a target site does not have enough antioxidant reserve to counteract the ROS. Oxidative stress can occur directly through redox reaction, or it can occur indirectly, where redox-inactive metals can form complexes with antioxidants so that the cell is then vulnerable to oxidation. The dithiothreitol (DTT) assay for measuring ROS inform PM's ability to cause oxidative stress directly [see Cho et al. (2005), Section 3.3.1.2]. Macrophage ROS assays [see Landreman et al. (2008), Section 3.3.1.2] provide a model of both direct and indirect oxidative stress, because both may occur in the model cell.

ROS activity for ambient PM is shown in Figure 3-26 through correlations of ROS macrophage and DTT assay results with mass concentration of $PM_{2.5}$, prevalent components (EC, OC, SO_4^{2-}, NO_3^-, and NH_4^+), and select trace metals (Cu, Fe, Ni, V, Zn) (Bates et al., 2015; Fang et al., 2015; Verma et al., 2009; Hu et al., 2008). Correlations between $PM_{2.5}$ mass concentration and DTT activity ranged from Pearson $R = 0.49$ to 0.88. No studies presented correlations between $PM_{2.5}$ mass and ROS activity based on the macrophage ROS assay, and limited data were available for the components presented. Most correlations were greater than 0.3 for EC, OC, SO_4^{2-}, NO_3^-, and NH_4^+. For trace metals, correlations ranged from positive to negative, where negative correlations imply that the ROS activity goes down with increasing concentration of the PM components or vice versa. In most cases, boxplots overlapped for the DTT and macrophage ROS assay, suggesting that both types of assay results covary similarly with measures of concentration for $PM_{2.5}$ components, despite the inability of DTT to capture indirect oxidation processes. These findings suggest that mass concentration of ambient $PM_{2.5}$ components may inform epidemiologic studies of oxidative stress and related effects. However, oxidative potential approaches are limited as a model of oxidative stress, because they do not reproduce the oxidative stress mechanisms. Moreover, macrophage ROS assay data are needed to correlate with ambient $PM_{2.5}$ mass concentration to consider if ambient $PM_{2.5}$ mass concentration is associated with direct and indirect ROS activity.



$PM_{2.5}$ = particulate matter with 50% aerodynamic diameter less than a nominal diameter of 2.5 μm; EC = elemental carbon; OC = organic carbon; SO_4^{2-} = sulfate; NO_3^- = nitrate; NH_4^+ = ammonium; Cu = copper; Fe = iron; Ni = nickel; V = vanadium; Zn = zinc.

Note: For each element, correlations obtained through the dithiothreitol assay are shown in orange at the bottom of each box and correlations obtained through the reactive oxygen species macrophage ROS assay are shown in light blue at the top of each box.

Source: Permission pending, Bates et al. (2015), Fang et al. (2015), Hu et al. (2008), Verma et al. (2009).

Figure 3-26 Pearson correlations of ambient air measures of oxidative potential with $PM_{2.5}$ mass and $PM_{2.5}$ components.

Personal exposure measurements were correlated to ROS activity for three studies of PM exposures in a school (Delfino et al., 2013) and retirement communities (Zhang et al., 2016; Delfino et al., 2010). In the school study, correlations ranged from Spearman $R = 0.77$ to 0.85 for the DTT assay's relationship to $PM_{2.5}$ mass, EC, OC, and water-soluble OC exposure concentrations. Similarly, correlations ranged from Spearman $R = 0.66$ to 0.86 for the same components for the macrophage ROS assay's relationship to $PM_{2.5}$ mass, EC, OC, and water-soluble OC exposure concentrations. The first retirement home study occurred between 2005 and 2007 and included Spearman correlations of macrophage ROS activity with $PM_{10–2.5}$, $PM_{2.5–0.25}$, and $PM_{0.25}$ mass exposure concentrations, along with

NC and components of EC, OC, BC, primary OC (POC), and secondary OC (SOC). Correlations of macrophage ROS activity with $PM_{10–2.5}$ and $PM_{2.5–0.25}$ were Spearman $R = 0.09$ and 0.07, respectively. Correlations of ROS activity with $PM_{0.25}$ mass exposure concentration (Spearman $R = 0.41$) and for NC (Spearman $R = 0.23$) were higher by comparison. EC, OC, BC, and POC had correlations of Spearman $R = 0.31$ to 0.40, while the correlation for SOC with ROS activity was 0.08.

Assays to measure ROS activity were recently evaluated for particles near the UFP size range. Zhang et al. (2016) correlated ROS activity of particulate matter smaller than 180 nm ($PM_{0.18}$) or of particulate matter between 180 and 250 nm ($PM_{0.25–0.18}$) with $PM_{2.5}$, BC, and components' exposure concentrations within the $PM_{0.18}$ and $PM_{0.25–0.18}$ size ranges. Correlation was Spearman $R = -0.17$ and 0.05, respectively for the DTT and macrophage ROS assays, for the correlation of $PM_{2.5}$ exposure concentration with ROS activity of $PM_{0.18}$. Correlation was Spearman $R = 0.20$ and 0.45 for the correlation of $PM_{2.5}$ exposure concentration with ROS activity of $PM_{0.25–0.18}$, so that ROS activity of $PM_{0.25–0.18}$ correlated more with $PM_{2.5}$ exposure concentration than did ROS activity of $PM_{0.18}$. Correlations among components of $PM_{0.18}$ exposure concentrations were higher for ROS activity of $PM_{0.18}$, but that pattern did not hold for ROS activity of $PM_{0.25–0.18}$. Additionally, larger differences were observed when correlations between exposure to mass concentration and ROS activity were measured by DTT (for DTT of $PM_{0.18}$, Spearman $R = 0.50$ to 0.86, and of $PM_{0.25–0.18}$, Spearman $R = 0.25$ to 0.62) than when they were measured by the macrophage ROS assay (for ROS of $PM_{0.18}$, Spearman $R = -0.02$ to 0.45, and of $PM_{0.25–0.18}$, Spearman $R = 0.09$ to 0.41). This may imply that for $PM_{0.25}$, mass exposure concentration of components may be associated with direct redox activity but not with indirect oxidation via antioxidant complexation. No correlations of $PM_{0.25–0.18}$ or $PM_{0.18}$ total mass exposure concentration were provided in the Zhang et al. (2016) study. However, the Delfino et al. (2010) study did provide correlation data for $PM_{0.25}$ and NC and found low-moderate correlations (Spearman $R = 0.41$ for $PM_{0.25}$ and Spearman $R = 0.23$ for NC), consistent with the correlations of the $PM_{0.18}$ and $PM_{0.25–0.18}$ components' mass exposure concentrations with the macrophage ROS assay results. Hence, multiple studies indicate that the macrophage ROS assay is a reliable indicator of oxidative potential.

3.4.5 Influence of Exposure Errors on Results from Epidemiologic Studies of Different Designs

Exposure measurement error, which refers to the biases and uncertainties associated with using concentration metrics as surrogates for the actual exposure of an individual or population (Section 3.2.1, Exposure Terminology), can be an important contributor to error in epidemiologic study results. Time-series studies assess the daily health status of a population of thousands or millions of people over the course of multiple years (i.e., thousands of days) across an urban area by estimating people's exposure using a short monitoring interval (hours to days). In these studies, the community-averaged concentration of an air pollutant measured at ambient monitors is typically used as a surrogate for individual or population ambient exposure. In addition, panel studies, which consist of a relatively small sample

(typically tens) of study participants followed over a period of days to months, have been used to examine the health effects associated with short-term exposure to ambient concentrations of air pollutants [e.g., Delfino et al. (1996)]. Panel studies may also apply a microenvironmental model to represent exposure to an air pollutant. A longitudinal cohort epidemiologic study, such as the American Cancer Society (ACS) cohort study, typically involves hundreds or thousands of subjects followed over several years or decades [e.g., Jerrett et al. (2009)]. Ambient concentrations are generally aggregated over time and by community as exposure surrogates.

Exposure error can bias epidemiologic associations between ambient pollutant concentrations and health outcomes and tends to widen confidence intervals around those estimates (Sheppard et al., 2005; Zeger et al., 2000). The importance of exposure error varies with study design and is dependent on the spatial and temporal aspects of the design. Other factors that could influence exposure estimates include topography of the natural and built environment, meteorology, instrument errors, use of ambient PM concentration as a surrogate for exposure to ambient PM, and the fact PM is one part of a complex mixture of pollutants. The following sections will consider various sources of error and how they affect the interpretation of results from epidemiologic studies of different designs.

3.4.5.1 Short-Term Exposure Studies

3.4.5.1.1 Time-Series Studies

As discussed in the 2009 PM ISA (U.S. EPA, 2009b), in most short-term exposure epidemiologic studies, the health effect endpoint is modeled as a function of ambient exposure, E_a, which is defined as the product of C_a and α, a term encompassing time-weighted averaging of microenvironmental exposures and infiltration of PM (Section 3.2.2, conceptual model). Time-series epidemiologic studies capturing the exposures and health outcomes of a large cohort frequently use the ambient concentration at a fixed-site monitor or an average of ambient concentrations across monitors as a surrogate for E_a in a statistical model (Strickland et al., 2011; Wilson et al., 2000). This is necessary due to the infeasibility of measuring personal exposures for studies involving thousands of participants. Moreover, for time-series epidemiology studies of short-term exposure, the temporal variability in concentration is of primary importance to relate to variability in the health effect estimate (Zeger et al., 2000). C_a can be an acceptable surrogate if the ambient monitor captures the temporal variability of the true air pollutant exposure. Spatial variability in PM concentrations across the study area could attenuate an epidemiologic health effect estimate if the exposures are not correlated in time with C_a when ambient monitoring is used to represent exposure in the statistical model. If exposure assessment methods that more accurately capture spatial variability in the concentration distribution over a study area are employed, then the confidence intervals around the health effect estimate may decrease.

In a time-series study of ED visits for cardiovascular disease, Goldman et al. (2011) simulated the effect of classical and Berkson errors due to spatiotemporal variability among ambient or outdoor (i.e., an ambient monitor situated outside the home) air pollutant concentrations over a large urban area. For 24-hour average $PM_{2.5}$, the relative risk (RR) per unit mass was negatively biased in the case of classical error (1.0094 compared to the base case of 1.0139) and negligibly positively biased in the case of Berkson error (1.0144). Negative bias means that the health effect estimate underestimates the true health effect. The 95% confidence interval range for RR per ppm of $PM_{2.5}$ was wider for Berkson error (0.0144) compared with classical error (0.0097). Similar results were obtained for $PM_{2.5}$ components (SO_4^{2-}, NO_3^-, NH_4^+, EC, and OC).

Recent studies have explored the effect of spatial exposure error on health effect estimates to test the appropriateness of using ambient monitoring for time-series studies. Goldman et al. (2010) simulated spatial exposure error based on a semivariogram function across monitor sites with and without temporal autocorrelation at 1- and 2-day lags to analyze the influence of spatiotemporal variability among ambient or outdoor concentrations over a large urban area on a time-series study of ED visits for cardiovascular disease. A random term was calculated through Monte Carlo simulations based on the data distribution from the semivariogram, which estimated the change in spatial variability in exposure with distance from the monitoring site. The average of the calculated random term was added to an ambient monitoring time series (considered in this study to be the base case) to estimate population exposure to $PM_{2.5}$ subject to spatial error. For the analysis with temporal autocorrelation considered, RR per ppm for 24-hour average $PM_{2.5}$ dropped slightly to 1.0126 (95% CI: 1.0113, 1.0139) when it was compared with the ambient monitor RR per ppm = 1.0139.[41] When temporal autocorrelation was not considered, RR per unit mass similarly dropped to 1.0123 for 24-hour average $PM_{2.5}$. The results of Goldman et al. (2010) suggest that spatial exposure error from use of ambient monitoring data results in biasing the health effect estimate towards the null to underestimate the true health effect, but the magnitude of the change in effect was small.

In another study analyzing the influence of spatiotemporal variability among ambient or outdoor concentrations over a large urban area on health effect estimates, Goldman et al. (2012) evaluated the effect of different types of spatial averaging on bias in the health effect risk ratio and the effect of correlation between measured and "true" ambient concentrations of $PM_{2.5}$ and PM_{10} and other air pollutant measures. Concentrations were simulated at alternate monitoring locations using the geostatistical approach described above (Goldman et al., 2010) for the 20 county Atlanta metropolitan area for comparison with measurements obtained directly from monitors at those sites. Geostatistical-simulated concentrations were considered by the authors to be "true" in this study, and other exposure assessment methods were assumed to have some error. Five different exposure assessment approaches were tested: (1) using a single fixed-site ambient monitor, (2) averaging the simulated

[41] Note that 95% CIs were not reported for the ambient monitor RR or for the cases where temporal autocorrelation was not considered.

exposure concentrations across all monitoring sites, (3) performing a population-weighted average across all monitoring sites, (4) performing an area-weighted average across all monitoring sites, and (5) population-weighted averaging of the geostatistical simulation (see Table 3-10). Goldman et al. (2012) observed that the exposure error was somewhat correlated with both the measured and "true" values, reflecting both Berkson and classical error components. For the single fixed-site ambient monitor, the exposure errors had a moderate positive correlation with the measured value. For the other exposure concentration estimation methods, the exposure errors were moderately negatively correlated with the "true" value, while having positive but lower magnitude correlation with the measured value. Additionally, the exposure bias, given by the ratio of the exposure error to the measured value, was higher in magnitude at the single fixed-site monitor than for the spatial averaging techniques for $PM_{2.5}$. Hence, compared with other exposure assessment methods, the health effect estimate would likely have greater bias towards the null (i.e., underestimation of the true health effect estimate) with reduced precision when a single fixed-site monitor is used to measure $PM_{2.5}$ concentration as a surrogate for exposure. However, exposure error is likely to cause some bias and imprecision for other exposure surrogate methods as well.

Table 3-10 The influence of exposure concentration metrics on error in health effect estimates.

Exposure Estimation Approach	Bias[(Z−Z*)/Z][a]	R^2(Z, Z*)[b]	*R*[(Z−Z*), Z*][c]	*R*[(Z−Z*), Z][c]
$PM_{2.5}$				
Fixed-site monitor	0.21	0.76	−0.10	0.41
Unweighted average	0.05	0.85	−0.28	0.14
Population-weighted average	0.05	0.84	−0.28	0.14
Area-weighted average	0.04	0.84	−0.29	0.13
Geostatistical model—population-weighted average	N/A	0.87	−0.38	0.00065

N/A = not applicable.

[a]Data provided by the authors for Figure 5 of Goldman et al. (2012).

[b]Data provided by the authors of Figure 4 of Goldman et al. (2012).

[c]Pearson correlation.

Note: Model errors were based on comparisons between measured data and simulated data at several monitoring sites. Errors were estimated for a single fixed-site ambient monitor, various monitor averages, and values computed from a geostatistical model. Z denotes the measured concentration, and Z* denotes the "true" concentration, considered here to be from the geostatistical model. Bias in the exposure concentration metric is given as the proportion of error between the measurement and true value to the measurement.

Source: Permission pending, Goldman et al. (2012).

In addition to the effect of the correlations and ratios themselves, spatial variation in their values across urban areas also impacts time-series epidemiologic results. The Goldman et al. (2010) and Goldman et al. (2012) findings suggest more Berkson error in the spatially resolved exposure concentration metrics compared with the fixed-site ambient monitor and more classical error for the fixed-site ambient monitor estimate compared with the other exposure assessment techniques. Hence, more bias would be anticipated for the health effect estimate calculated from the fixed-site ambient monitor, and more variability would be expected for the health effect estimate calculated with the more spatially resolved methods. Differences in the magnitude of exposure concentration estimates are not likely to cause substantial bias, but they tend more to widen confidence intervals and thus reduce the precision of the effect estimate (Zeger et al., 2000). The more spatially variable air pollutants studied in Goldman et al. (2012) also had more bias in the health effect estimates. This occurred across exposure assessment methods but was more pronounced for the fixed-site ambient monitoring data. Note that the Goldman et al. (2010), Goldman et al. (2011), and Goldman et al. (2012) studies were performed only in Atlanta, GA. These simulation studies are informative, but similar simulation studies in additional cities would aid generalization of these study results.

Dionisio et al. (2014) evaluated differences in $PM_{2.5}$ effect estimates derived from ambient monitors, an AERMOD air quality model to capture spatial variability, and a SHEDS personal exposure model incorporating infiltration and time-activity patterns for ZIP codes in Atlanta. They found that personal exposure model-based estimates were lower than ambient monitor and air quality model estimates, which were relatively similar to one another. The study also evaluated attenuation of health effect estimates in single-pollutant and copollutant models using a classical error attenuation factor relating the observed health effect estimate and health effect estimate that was designated by the authors to be "true". In single-pollutant models, using a fixed-site monitor reduced the size of the health effect estimate to about 80% of the effect estimate from the air quality model. The health effect estimate based on the fixed-site monitor was much more attenuated to approximately 25% of the health effect estimate when the personal exposure model was used for the exposure concentration estimate. The degree of attenuation was slightly greater in copollutant models with SO_4^{2-} and O_3, and slightly less in a copollutant model with NO_X. Due to the more regional nature of PM, little spatial variability in the health effect estimates and degree of attenuation was observed. The findings of this study also suggest that PM is not as susceptible to spatially varying exposure error as locally-emitted pollutants such as CO and NO_X.

To account for temporal variability in exposure, Dominici et al. (2004) used spline functions to control for the temporal trend in exposure concentration and outcome in time-series studies. Szpiro et al. (2014) compared a version of this method with an approach to pre-adjust the exposure to account for the time trend, without need to account for the trend in the outcome, to reduce bias in the effect estimate. This method is particularly applicable for repeated-measure cohort studies, since it takes advantage of the additional exposure data available from more frequent pollutant measurements compared to the infrequent outcome and covariate measures.

Section 3.4.2.4 also describes the influence of instrument accuracy and precision on the relationship between ambient PM concentrations and personal exposure to ambient PM. Exposure measurement error related to instrument precision has a smaller effect on health effect estimates in time-series studies compared with error related to spatial gradients in the concentration because instrument precision would not be expected to modify the ability of the instruments to respond to changes in concentration over time. Goldman et al. (2010) investigated the influence of instrument error on health effect estimates in a time-series epidemiology study by studying differences in exposure concentration estimates and health effect estimates obtained using collocated monitors. In this study, a random error term based on observations from collocated monitors was added to an ambient monitor's time series to simulate population estimates for ambient air concentrations subject to instrument precision error in 1,000 Monte Carlo simulations. Virtually no change in the risk ratio was observed for 24-hour average $PM_{2.5}$; the RR per ppm with simulated instrument precision error was 1.0138 compared with RR per ppm = 1.0139 for the ambient monitor. The amount of bias in the health effect estimate related to instrument precision was very small.

As described in the 2009 PM ISA (U.S. EPA, 2009b), nonambient sources of PM include indoor combustion, cooking, cleaning, and other activities. However, such exposure is unlikely to be temporally correlated with ambient PM exposure (Wilson and Suh, 1997), and therefore would not affect epidemiologic associations between ambient PM and a health effect in a time-series study. In simulations of a nonreactive pollutant, Sheppard et al. (2005) concluded that nonambient exposure does not influence the health outcome effect estimate if ambient and nonambient concentrations are independent. Because personal exposure to ambient PM is some fraction of the ambient concentration, it should be noted that effect estimates calculated based on personal exposure rather than ambient concentration will be positively biased in proportion to the ratio of ambient concentration to ambient exposure, and daily fluctuations in this ratio can widen the confidence intervals in the ambient concentration effect estimate. Uncorrelated nonambient exposure will not bias the effect estimate but may also widen the confidence intervals (Sheppard et al., 2005; Wilson and Suh, 1997).

3.4.5.1.2 Panel Studies

Panel or small-scale cohort studies involving dozens of individuals may use more individualized concentration measurements, such as personal exposures, residential fixed-site indoor or outdoor measurements, or concentration data from local study-specific monitors. Modeled concentrations are not typically used as exposure surrogates in panel epidemiologic studies. Probabilistic, distribution-based approaches are not designed to estimate exposures for specific individuals, such as might be needed for panel epidemiologic studies. Another main disadvantage of the modeling approach is that the results of modeling exposure assessment must be compared to an independent set of measured exposure levels (Klepeis, 1999). In addition, resource-intensive development of evaluated and representative model inputs

is required, such as human activity patterns, distributions of air exchange rate, and deposition rate. Therefore, modeled exposures have been used much less frequently in panel epidemiologic studies.

Panel studies using hourly or other subdaily measurements are used to evaluate subclinical health effects, such as biomarkers of inflammation [e.g., Dubowsky et al. (2006)]. Sensitivity to averaging time may be tested by fitting models with various averaging times to identify the time period most associated with effects. However, temporal variations in exposure and covariates (e.g., temperature, other pollutants) can lead to temporal variability in exposure measurement error. Malloy et al. (2010) proposed a wavelet approach to add time-varying data into the statistical model used in an epidemiologic study. Simulations adding exposure measurement error to an hourly $PM_{2.5}$ data set indicated that the fine-scale wavelets describing shorter-frequency variation captured most of the exposure error, with little error accounted for by the coarse wavelets. The standard moving average approach of fitting models with successively longer averaging times showed the greatest exposure error at shorter averaging times (less than 20−60 hours), while the effect of simulated error was similar across averaging times wavelet approach showed similar error over averaging times of 10 hours or greater. This suggests that the wavelet approach may be better able to identify associations with health effects over short averaging times (e.g., 24 hours or less).

To evaluate the effect of small-scale intraurban spatial variability on health effect estimates, Sarnat et al. (2012) considered the influence of local exposure concentration metrics on respiratory effect estimates for a panel of school children. This study was conducted along the U.S.-Mexico border in El Paso, TX and Ciudad Juarez, Mexico, and 48-hour average concentrations measured from fixed-site ambient monitors, monitors outside the children's schools, and monitors inside the children's schools were all used as surrogates for PM exposure concentration. For $PM_{2.5}$, slightly higher health effect estimates were observed for indoor monitors compared with outdoor and fixed-site ambient monitors (2.7, 2.3, and 2.4%, respectively), although confidence intervals overlapped. $PM_{10–2.5}$ had a higher health effect estimate for indoor than outdoor monitors (2.8 vs. 2.0%), again with overlapping confidence intervals. No fixed-site ambient $PM_{10–2.5}$ data were available. For both $PM_{2.5}$ and $PM_{10–2.5}$, multivariate models with both indoor and outdoor concentration only showed associations for indoor concentration. This effect was more pronounced for $PM_{10–2.5}$, which exhibits greater urban spatial variability than $PM_{2.5}$. The authors suggested that exposure measurement error could result in biasing the health effect estimate toward the null to underestimate the health effect, given the finding of higher health effect estimate for the outdoor $PM_{2.5}$ monitor compared with the outdoor $PM_{10–2.5}$ monitor.

3.4.5.2 Long-Term Exposure Cohort Studies

For cohort epidemiologic studies of long-term human exposure to PM, where the difference in the magnitude of the concentration is of most interest, if C_a is used as a surrogate for E_a, then α can be considered to encompass the exposure measurement error related to uncertainties in the time-activity data and infiltration. Spatial variability in PM concentrations across the study area could lead to bias in the

health effect estimate if C_a is not representative of E_a. This could occur if the study participants are clustered in a location where their PM exposure is higher or lower than the exposure estimated at a modeled or measurement site. There is limited information regarding whether C_a is a biased exposure surrogate in the near-road environment for epidemiologic studies of long-term exposure.

Choice of exposure surrogate can influence error in the health effect estimate. For example, Baxter et al. (2010) calculated bias and RMSE for health effect estimates based on different exposure estimation methods including evaluated regression models, distance from a major road, and an indoor exposure model that accounts for factors such as seasonality in infiltration of ambient $PM_{2.5}$ and EC. The simulated indoor concentrations produced unbiased health effect estimates, while the other exposure surrogates typically (but not always) biased the health effect estimate towards the null to underestimate the true health effect and inflated the RMSE relative to that of the indoor model. Distance surrogates had much larger biases and RMSE compared with models containing $PM_{2.5}$ or EC concentration measures. Kioumourtzoglou et al. (2014) developed linear mixed effects models to calibrate exposure surrogates (fixed-site ambient monitor and monitor outside a residence) against what was considered by the authors to be "true" personal exposure to ambient $PM_{2.5}$, estimated by multiplying the fixed-site ambient $PM_{2.5}$ measurement by the ratio of personal to ambient SO_4^{2-}. The calibration coefficients indicated that the fixed-site ambient monitor only captured 31% of the "true" personal exposure to ambient $PM_{2.5}$, and the outdoor monitor captured 54% of the "true" personal exposure to ambient $PM_{2.5}$. Hence, in both cases, the exposure surrogate was lower than the sulfate-derived personal exposure.

Researchers have recently compared the choice of ground-based or satellite-based estimation methods on epidemiologic effect estimates. Jerrett et al. (2016) compared several residential exposure concentration estimation methods using ground-based data (i.e., monitor, meteorological, land use, or spatial information) or satellite data for a large subset of the ACS cohort (668,629 individuals). The authors found that although the various methods yielded similar median $PM_{2.5}$ exposure concentration estimates (approximately 12 $\mu g/m^3$), effect estimates for circulatory mortality during 1982−2004 were much lower for the satellite methods than the ground-based methods. Of the seven methods tested, the highest effect estimate was produced by a ground-data-only two-stage model consisting of LUR followed by a BME kriging model of the residuals; this method also had the best model fit. This model produced a relative risk (95% CI) of 1.14 (1.11−1.17) per 10 $\mu g/m^3$ $PM_{2.5}$, while the lowest relative risk was observed with one of the two satellite-only methods (RR = 1.02, 95% CI = 1.00−1.04). Jerrett et al. (2016) calculated the Akaike Information Criterion (AIC) to assess model fit and found a negative association between HR and AIC ($R^2 = 0.94$), which suggests that use of the satellite method alone produced an attenuated effect estimate. The LUR-BME method estimated exposure concentrations on a 30 × 30 m (0.03 × 0.03 km) grid, while this satellite-only method provided estimates on a 1 × 1 km grid. The results of the Jerrett et al. (2016) study suggest that exposure estimation methods incorporating locally available ground data may introduce less exposure error than remote sensing methods alone, but that satellite methods have the capability to identify associations when ground data are lacking.

Spatial resolution of the exposure concentration estimates has been evaluated to examine the influence of spatial exposure error in cohort studies. For example, Alexeeff et al. (2015) fit kriging and LUR models based on 100 or 500 monitoring sites [derived from a satellite downscaling approach described in Kloog et al. (2014) and Section 3.3.3] and estimated bias and uncertainty for each exposure concentration model used to compute health effect estimates for linear and logistic health effect simulations. For the LUR models, which had the highest model R^2 (71 to 84%) compared with the satellite-downscaling estimates, the effect estimates were biased away from the null to overestimate the health effect estimate in all cases. Bias in the linear models was reduced from 4−5% for LUR fit with 100 monitors to 1% for the LUR fit with 500 monitors, and confidence interval coverage increased from 48 to 68%. Bias in the logistic models was reduced from 3−4% for LUR fit with 100 monitors to 2% for LUR fit with 500 monitors, and confidence interval coverage increased from 91 to 94%. The kriging models had much lower model R^2 (24−44%). One kriging model fit to long-term average monitor data also produced bias away from the null to overestimate the health effect estimate that reduced with number of monitors, but with larger magnitude biases. The other produced bias mostly towards the null to underestimate the health effect estimate, with magnitude of bias increasing with increased number of monitors.

Gryparis et al. (2009) noted that smoothing of the true exposure concentration surface can cause Berkson error in the effect estimate. Gryparis et al. (2009) simulated three spatial surfaces of increasing variability and then tested five types of exposure concentration modeling approaches: plug-in exposure concentration estimation where the "true" exposure concentrations (as designated by the authors) are predicted by a smoothing model; plug-in exposure concentration estimation with variance correction; regression calibration using hold-out predictions, covariates, and observations; and two types of Bayesian surface models (full Bayesian and two-stage Bayesian approaches) fitting a joint model for the health and exposure concentration data. Simulation results produced negative biases to underestimate the health effect for the plug-in exposure concentration estimation methods with and without variance correction, and those biases became larger in magnitude with increasing spatial variability (for the plug-in method with variance correction, simulation results produced −57% bias for the smoothest surface and −419% bias in the most spatially variable surface). Likewise, the mean squared error (MSE) increased and confidence interval coverage decreased with increasing variability of the "true" exposure concentration surface. Biases and MSEs were much smaller in magnitude for the regression calibration and Bayesian exposure concentration assignment methods, and those biases were positive and so overestimated the health effect (maximum bias was 23% for the two-stage Bayes method for the most spatially variable exposure concentration surface). MSE for the regression calibration and Bayesian methods also increased with increasing variability of the "true" exposure concentration surface. Regression methods have also been applied to correct ambient monitor data or spatial modeling estimates of $PM_{2.5}$ exposure based on indoor SO_4^{2-} to ambient $PM_{2.5}$ ratios in studies all-cause mortality (Hart et al., 2015a) and lung cancer (Hart et al., 2015b). In each study, the health effect estimate was lower when no exposure error correction method was applied. This implies that the smoother, non-corrected method introduced error into the exposure estimate that resulted in negative bias to underestimate the health effect.

The greater spatial characterization of $PM_{2.5}$ exposure concentration estimates from a combined satellite-LUR method with 50 m resolution developed by Kloog et al. (2011) resulted in higher mortality effect estimates compared with cohort studies using city-wide concentrations for the entire population based on a 10 km resolution grid (Kloog et al., 2013). This is consistent with a reanalysis of the ACS cohort conducted by Willis et al. (2003), which found that a subset analysis including only individuals living in a county with a sulfate monitor yielded an all-cause mortality effect estimate twice that for the entire cohort (1.5 vs. 1.25). The Kloog et al. (2013) study also found an effect of monitor distance, with a higher effect estimate for the population living within 20 km of a monitor than for those living farther away. This spatial influence on epidemiologic effect estimates is consistent with the null bias resulting from classical error.

The influence of spatial exposure error on health effect estimates varies with the study parameters, such as exposure model selection and location. Wu et al. (2011) compared health effect estimates for birth outcomes from four hospitals in Los Angeles and Orange Counties, CA given $PM_{2.5}$ concentrations as estimated using nearest monitors and the CALINE4 dispersion model. For preeclampsia, crude and adjusted odds ratios were consistently lower when the nearest monitor was used to estimate exposure concentration instead of the more spatially resolved dispersion model. Differences in the odds ratio for the two exposure concentration estimation methods were larger for Los Angeles County compared with Orange County. For Los Angeles County, the odds ratios were also below one when the nearest monitor was used, in contrast with Orange County, where the odds ratios were both above one. However, for preterm (<37 weeks gestation) and very preterm births (<30 weeks gestation), odds ratios were lower for the nearest monitor exposure concentration estimation method compared with the dispersion model in Los Angeles, but in Orange County, the opposite was observed. These findings indicate that higher spatial resolution may improve estimation of health effects.

Exposure error in studies of long-term exposure has the potential to be larger for $PM_{2.5}$ components than for $PM_{2.5}$ mass concentration, since the spatial variability of $PM_{2.5}$ components tends to be greater than for $PM_{2.5}$ mass concentration (Sun et al., 2013). Within components, the reported concentrations were also sensitive to the methods of measurement, with nearest monitor typically producing greater relative variability (measured as IQR/median) compared with IDW and city-wide average concentrations, respectively. Sun et al. (2013) compared statistical models of cardiovascular disease biomarkers associated with long-term exposure to $PM_{2.5}$ mass, EC, OC, Si, and S concentration using the nearest monitor, IDW, and city-wide average metrics. In general, effect estimates with city-wide averages tended to be lower in magnitude compared with the nearest monitor or IDW approaches for both the $PM_{2.5}$ mass and component metrics for one biomarker (CIMT) and for another biomarker (CAC) only for the Si component. Using finer-scale concentration estimates to approach the same problem, Kim et al. (2014) observed CIMT effects for Si but not EC. Little bias with $PM_{2.5}$ mass or S (as an indicator of SO_4^{2-}) concentration suggests that the less spatially variable metrics are less subject to bias related to exposure measurement error.

When a spatial concentration model, such as LUR or a spatiotemporal model, is used to develop a set of exposure concentration estimates for input into a long-term exposure epidemiologic study, minimizing error in the exposure or exposure concentration estimate does not always minimize error in the health effect estimate (i.e., β). Szpiro et al. (2011a) used simulation studies to evaluate the bias and uncertainty of the health effect estimate obtained when using correctly specified and misspecified exposure concentration models. The correct exposure concentration model was a spatiotemporal model with three geographic covariates while the misspecified model included only two of these three geographic covariates. In practice, covariates in spatiotemporal models may include variables such as population within a given buffer, proximity to industrial sources or highways, or building density. Szpiro et al. (2011a) did not explicitly state what the covariates were; as a statistical simulation study, the objective was to explore the impact of removing from the model a geographic covariate that may influence the exposure concentration. They estimated the exposure concentration model parameters using monitor data and predicted exposure concentrations at subject locations. They studied two conditions: where the variation in the third covariate was identical in the monitor and subject data versus where it was much smaller in the monitor data than in the subject data. Szpiro et al. (2011a) showed that prediction accuracy of the exposure concentration estimate was always higher for the correctly specified model compared with the misspecified model. The health effect estimate had better properties (lower RMSE) for the correct model when the third covariate had identical variability in the monitor and subject data. However, when the third covariate was much less variable in the monitor data, then the health effect estimate had better properties for the misspecified model. The results of Szpiro et al. (2011a) demonstrate one situation where use of a more accurately defined exposure concentration metric does not improve the health effect estimate.

Another simulation study evaluating the influence of exposure estimation methods on bias in health effect estimates considered the joint effect of exposure measurement error and confounding (Cefalu and Dominici, 2014). Exposure measurement error due to spatial variability in ambient concentrations or land use variables is often accounted for by exposure prediction models, such as LUR. Health effect models then may adjust for some of these same covariates as a means of reducing confounding of the effect estimate. Cefalu and Dominici (2014) demonstrated that if covariates are included in the exposure prediction model, but not the health effect model, the magnitude of bias in the health effect estimate is always increased relative to the simulated "true" exposure (as designated by the authors). The bias may be in either direction, depending on which covariates are omitted. To eliminate this bias, all potential confounders included in the health model must be included in the exposure prediction model, unless they are uncorrelated with exposure. Their simulation compared models with increasing numbers of covariates, and they found that in some situations the bias increased despite an increase in R^2, a similar result to the Szpiro et al. (2011a) study in which an improved exposure concentration metric did not improve the health effect estimate. One difficulty in applying these results to interpret epidemiologic study results is the uncertainty regarding the proper set of confounders to be included in the exposure and health models. While the Szpiro et al. (2011a) and Cefalu and Dominici (2014) simulations were for a generic air pollutant, they are relevant to spatially variable $PM_{10-2.5}$ or UFP.

Preferential sampling may occur when the exposure concentration model is fit to a set of spatial data, and exposures at other locations in the domain are not well represented. Sheppard et al. (2012) performed a series of simulations to study successively greater spatial correlations between monitors and study participants using kriging and nearest monitor to estimate $PM_{2.5}$ exposure concentration. Bias between the health effect estimate of the "true" exposure concentration (as designated by the authors) was compared with that derived from the kriged or nearest monitor exposure concentration estimates. Sheppard et al. (2012) found that bias decreased as spatial correlation between the "true" exposure concentration and the modeled exposure concentration increased. Both the kriging and nearest monitor exposure concentration models caused the coverage of the 95% confidence interval to be underestimated, but the underestimation was greater for nearest monitor. Furthermore, underestimation of the confidence interval became smaller with increasing spatial dependence of the "true" and modeled exposure concentrations. These results suggest that correlation between the "true" and modeled exposure reduces bias in the health effect estimate and reduces underestimation of variability in the health effect estimate. Lee et al. (2015) simulated several scenarios in which spatial variability explained successively larger portions of the exposure concentration variability to test for the effect of preferential sampling. Lee et al. (2015) also compared geospatial models of $PM_{2.5}$ components EC and S fit with the national network (urban and rural), CSN (urban), and IMPROVE (rural) networks and found large differences in the modeled exposure concentration surface. These results support the point that the nature of the monitors is important in deriving the surface. In general, Lee et al. (2015) found that the more preferential sampling occurred, the larger the relative bias and standard error of the effect estimate. In practice, studies of LUR have shown that fitting a model in one city and then applying it to another city can lead to large errors (U.S. EPA, 2016). The results of Lee et al. (2015) would imply that this practice would add error to the effect estimate.

Error correction is a relatively new approach to estimate the correct the classical-like standard error of exposure estimates and potentially to correct for bias in the exposure estimates used in statistical models for longitudinal cohort studies (Szpiro et al., 2011b). Szpiro and Paciorek (2013) and Bergen and Szpiro (2015) established that two conditions must hold for the health effect estimate to be predicted correctly: the exposure concentration estimates from monitors must come from the same underlying distribution as the true exposure concentrations, and the health effect model adjusts for confounding in the population. Szpiro and Paciorek (2013) performed several simulations to investigate what happens when these conditions are violated. In one set of simulations, the distribution of the exposure concentration was varied. When the assigned exposure concentration measurements were set to be uniform across space, the health effect estimate was biased away from the null (i.e., overestimated the health effect) with different standard error compared with the case when the exposure subjects were collocated with the study participants. When the model was misspecified, the health effect estimate was biased towards the null (i.e., underestimated the health effect) with different standard errors compared with the correctly specified model. Bias correction and bootstrap calculation of the standard errors improved the model prediction, even when the "true" model (as designated by the authors) contained several degrees of freedom. Spiegelman (2013) noted that the new measurement error correction methods developed by Szpiro and

Paciorek (2013) are a version of regression calibration. Bergen et al. (2013) applied error correction to models of long-term exposure to $PM_{2.5}$ components (EC, OC, Si, and S). They found that exposure errors in the EC and OC models were almost pure Berkson errors, so that the bootstrap calculation of the standard errors did not improve the estimates. Si and S were influenced by Berkson-like error, and bootstrap simulation of the standard errors was used for error correction. Absence of notable bias supports the observation of negligible classical-like error in the Si and S exposure concentration estimates.

In the case of long-term exposure cohort studies, nonambient contributions to the total personal exposure measurements would be expected to widen the confidence interval around the health effect estimates by adding noise to the exposure signal. Also, addition of any non-negative nonambient component to the personal exposure measurement would result in an underestimate of exposure to ambient PM, because the average total personal PM exposure would have to be either equal to or greater than the average personal exposure to ambient PM. This exposure error could bias the health effect estimate towards the null to underestimate the true health effect.

3.5 Summary

The exposure assessment chapter in the 2009 PM ISA (U.S. EPA, 2009b) synthesized a plethora of new research on PM, most of which focused on $PM_{2.5}$. The exposure assessment chapter in the 2009 PM ISA found that $PM_{10–2.5}$ tended to be more spatially variable than $PM_{2.5}$ at microscale, neighborhood scale, and urban scale, because $PM_{10–2.5}$ was more sensitive to local sources and loss processes, such as gravitational setting. UFP was also noted to be more spatially variable due to growth processes, but fewer data were available. Secondary production of $PM_{2.5}$ was noted to contribute to the relatively lower heterogeneity in its spatial concentration distribution. Similarly, infiltration was found to vary with particle size fraction, with the greatest infiltration factors occurring for $PM_{2.5}$ and infiltration decreasing with increasing particle size, due to surface impaction of $PM_{10–2.5}$ during the infiltration process. Source apportionment studies for SO_4^{2-}, as a marker of ambient $PM_{2.5}$, were presented as a method for distinguishing personal exposure to ambient $PM_{2.5}$ from total $PM_{2.5}$ exposure. Other components, such as EC and OC, were found not useful for apportionment of ambient $PM_{2.5}$ exposure, given their indoor sources. Spatial variability in PM concentration was noted to add uncertainty to exposure estimates.

Errors and uncertainties in the exposure assessment methods can add bias and uncertainty to health effect estimates from epidemiologic studies on the health effects of PM exposure. With regard to use of exposure surrogates in epidemiologic studies, the 2009 PM ISA (U.S. EPA, 2009b) noted that separating total PM exposure into ambient and nonambient components reduces uncertainty in health effects estimates. The 2009 PM ISA also noted that time-series studies of short-term $PM_{2.5}$ exposure generally use concentration data from fixed-site monitors as surrogates for exposure concentration, based on the assumption that temporal variability is captured at the monitor. Panel studies utilizing personal $PM_{2.5}$ exposure measurements found associations between short-term ambient $PM_{2.5}$ exposure and health

effects, and those findings were strengthened by focusing on the ambient component of exposure. It was noted that long-term $PM_{2.5}$ exposure studies produced health effects estimates that were most accurate when the PM concentration distribution does not vary substantially in space. Findings from the recent literature build from these results.

Fixed-site monitoring is still frequently utilized for exposure concentration surrogates for $PM_{2.5}$ (Section 3.3.1.1). Fixed-site monitoring data for $PM_{10-2.5}$ must be used with more caution. Generally, dichotomous samplers produce the most reliable measurements of $PM_{10-2.5}$ for use in exposure studies. Collocated PM_{10} and $PM_{2.5}$ monitors used to calculate $PM_{10-2.5}$ concentration by difference can have higher errors and uncertainties due to differences in flow rates for the two instruments, while differences between PM_{10} and $PM_{2.5}$ taken over a county or city to estimate $PM_{10-2.5}$ concentration has higher errors and uncertainties. CPCs are most commonly used to measure UFP. Some portion of the UFP size distribution may be omitted when using CPCs, since they do not typically measure particles smaller than 10 nm.

Substantial advances to exposure modeling have been made in recent years (Section 3.3.2). Spatial interpolation methods, LUR, dispersion models, and CTMs were already commonly used to estimate $PM_{2.5}$ exposure concentration. Improvements in modeling the OC component of $PM_{2.5}$ have improved the accuracy of CTMs in recent years. Additionally, hybrid approaches drawing input from CTMs, satellite observations of AOD, surface measurements of PM concentration, and land use variables data have been combined into spatiotemporal models. Microenvironmental exposure models have also been applied with input concentrations from these methods for comparison in epidemiology studies. The majority of studies using these methods are applied to model $PM_{2.5}$. These methods are employed less frequently to estimate $PM_{10-2.5}$ and UFP exposure concentration, related in part to less availability of input data. Epidemiologic study design influences selection of exposure concentration estimation methods.

Copollutant confounding of the PM health effect estimate may occur if exposure to the copollutants and their relationships to the health effect of interest are both correlated with PM exposure (Section 3.4.3). Median correlations of 24-hour ambient $PM_{2.5}$ with concentrations of ambient CO, NO_2, and O_3 during 2013−2015 were as high as Pearson $R = 0.5$, and upper correlations reached near 1. Copollutant correlation varied with season (highest for O_3 in summer and for CO and NO_2 in winter). Median correlations of 24-hour ambient $PM_{10-2.5}$ concentrations during the same time period were as high as Pearson $R = 0.4$, and upper correlations typically below Pearson $R = 0.7$−0.8. Median correlations between $PM_{2.5}$ and $PM_{10-2.5}$ range between 0.2 and 0.5, with higher values in summer and fall. Correlation data for UFP were very limited, but they indicate correlations as high as Pearson $R = 0.5$ for NO_2 and NO_X, which are also traffic-related pollutants. Moderate-to-strong correlations may introduce a greater degree of confounding into epidemiologic study results, depending on the relationship between the copollutants and the health effect of interest.

Ambient PM data from fixed-site monitors continue to be commonly used in health studies as a surrogate for PM exposure concentration (Section 3.3.1.1). Advantages to using fixed-site monitoring

data are that they provide a long-term record of concentration trends and they undergo rigorous quality assurance if FRMs or FEMs are used. The concentration profile of $PM_{2.5}$ tends to be less variable across the urban or neighborhood scale compared with $PM_{10–2.5}$ or UFP. Therefore, ambient $PM_{2.5}$ concentrations estimated at fixed-site monitors often provide a reasonable representation of exposure concentrations throughout the study area (Section 3.4.2.2). However, the higher degree of spatial variability in ambient $PM_{10–2.5}$ and UFP across an urban area may not be captured by a fixed-site monitor. Uncharacterized variability in a time-series of exposure concentrations across space, resulting from use of fixed-site monitoring data, in a time-series study of $PM_{10–2.5}$ or UFP exposure may attenuate health effect estimates, so that the health effect estimate underestimates the true health effect (Section 3.4.5.1). Bias may occur in either direction for long-term exposure studies, depending on whether the fixed-site monitor is over- or underestimating ambient $PM_{10–2.5}$ or UFP exposure concentration for the population of interest (Section 3.4.5.2). In all study types, use of fixed-site monitoring ambient $PM_{10–2.5}$ or UFP concentrations in lieu of the true exposure is expected to widen confidence intervals beyond what would be obtained if the true exposure were used. Personal monitors directly measure PM exposure, but they produce a relatively limited data set, making them most suitable for panel epidemiologic studies (Section 3.4.5.1.2). Without accompanying time-activity data, ambient PM exposure cannot be distinguished from personal PM exposure in personal monitoring studies (Section 3.4.2.1).

When spatial variability of exposure concentration surfaces is not accurately modeled, the health effect estimate tends to be biased towards the null with decreased probability that the confidence intervals contain the true health effect. Bias towards the null means that the health effect estimate is underestimating the true health effect. This is particularly true when the actual spatial variability is much higher than what is represented by the model (Section 3.4.5.2). Hybrid models typically have good cross-validation, especially for $PM_{2.5}$, and have the potential to reduce exposure measurement error and resulting bias and uncertainty in health effect estimates produced by epidemiologic models of long-term exposure to PM, even for spatially-varying size fractions and components. Bias correction and bootstrap calculation of standard errors have also been shown to improve health effect estimate prediction from spatiotemporal models when the exposure estimates have a classical-like error structure. When the exposure estimates have a Berkson-like error structure, health effect estimates would only be expected to improve when model covariates are chosen so that the statistical distribution of the modeled exposure concentrations is close to the distribution of the true exposure concentrations.

In summary, exposure error tends to produce underestimation of health effects in epidemiologic studies of PM exposure, although bias in either direction can occur. New developments in PM exposure assessment, including hybrid spatiotemporal models that incorporate satellite observations of AOD, land use variables, surface monitoring data from FRMs, and/or CTMs, have led to improvements in spatial resolution of the $PM_{2.5}$ concentration surface. These advancements have reduced bias and uncertainty in health effects estimates. However, high correlations with some gaseous copollutants necessitate evaluation of the impact of confounding on health effects estimates, using two-pollutant models to ascertain robustness of epidemiologic study results. $PM_{10–2.5}$ and UFP concentrations are typically more

spatially variable than $PM_{2.5}$ concentrations, and concentration data for those size fractions are less frequently available as model input or for use in validating hybrid models. As a result, there is typically less uncertainty in health effect estimates derived from both monitored and modeled exposure estimates for $PM_{2.5}$ compared with $PM_{10-2.5}$ and UFP.

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CHAPTER 4 DOSIMETRY OF PARTICULATE MATTER

Overall Conclusions regarding the Dosimetry of Particulate Matter (PM)

- Our basic understanding of the mechanisms of particle deposition and clearance has not changed since the last PM ISA (U.S. EPA, 2009). However, comparisons of deposition across species have improved. Evidence in this review also better quantifies the fraction of inhaled particles reaching the lungs and particle translocation from the respiratory tract.
- Evidence included in this review shows a smaller fraction of inhaled air enters though the nose of children relative to adults. This, in combination with lower nasal particle deposition efficiency in children compared to adults, results in a greater fraction of inhaled PM reaching and potentially depositing in the lungs of children relative to adults.
- New dosimetric information shows that PM_{10} overestimates the size of particles likely to enter the human lung. New dosimetric information that improves interspecies extrapolations, quantifies the fraction of inhaled PM entering the lungs of humans and rodents.
- New information, altering a conclusion in the last PM ISA, shows that particle translocation from the olfactory mucosa via axons to the olfactory bulb may be important in humans.
- New data show translocation of gold nanoparticles from the human lung into circulation. Of deposited particles, a small fraction (0.05%) eliminated via urine is quantitively similar between humans and rodents. New rodent data show that the fraction (≤0.2% for particles 5−200 nm) of nanoparticle translocation from the lungs is particle size dependent and that gastrointestinal tract absorption of particles is a minor route into circulation.

4.1 Introduction

Particle dosimetry refers to the characterization of deposition, translocation, clearance, and retention of particles and their components within the respiratory tract and extrapulmonary tissues. This chapter summarizes basic concepts presented in dosimetry chapters of more recent PM AQCDs (U.S. EPA, 2004, 1996) and the PM ISA (U.S. EPA, 2009), and updates the state of the science based upon new literature appearing since publication of these PM assessments. Although the basic understanding of the mechanisms governing deposition and clearance of inhaled particles has not changed, there is significant additional information on the role of certain biological determinants such as sex, age, and lung disease on deposition and clearance.

Relative to the last PM ISA (U.S. EPA, 2009), extra emphasis is placed on differences between children and adults. In general, children breathe less through the nose and have less deposition in the extrathoracic airways than adults. This leads to a relatively higher concentration of PM reaching the lower airways of children than adults. Much of the literature described in this chapter supporting differences in route of breath as a function of age and sex comes from older literature that was not included in prior reviews. Additionally, substantially more particle translocation data have become available on the extent of inhaled material is detected in organs. Some studies have evaluated whether translocation is due to direct air-blood barrier translocation from the lung versus gastrointestinal uptake of particles or solubilization with subsequent movement to organs. There are also limited data on transplacental

movement of particles. Although only a small portion of insoluble particles translocate to extrapulmonary organs, their translocation can be rapid (<1 hour) and is size dependent. Translocation of particles depositing on the olfactory epithelium to the olfactory bulb is also now recognized as a potentially important route of movement to the brain for insoluble particles (<200 nm) or soluble components of any sized particle in humans as well as rodents.

The dose from inhaled particles deposited and retained in the respiratory tract is governed by a number of factors. These include exposure concentration and duration, activity and breathing conditions (e.g., nasal vs. oronasal and minute ventilation), and particle properties (e.g., particle size, hygroscopicity, and solubility in airway fluids and cellular components). The basic characteristics of particles as they relate to deposition and retention, as well as anatomical and physiological factors influencing particle deposition and retention, were discussed in depth in CHAPTER 10 of 1996 PM AQCD and updated in CHAPTER 6 of the 2004 PM AQCD. Species differences between humans and rats in particle exposures, deposition patterns, and pulmonary retention were also reviewed by Brown et al. (2005). New to this review, similarities in particle deposition among several species are provided. Other than a brief overview in this introductory section, the disposition (i.e., deposition, absorption, distribution, metabolism, and elimination) of fibers and unique nano-objects (e.g., hollow spheres, rods, fibers, tubes) is not reviewed herein (see Section P.3.1). Substantial exposures to fibers and unique nano-objects generally occur in the occupational settings rather than the ambient environment.

The deposition by interception of micro-sized fibers was briefly discussed in the 1996 and 2004 PM AQCD, but fiber retention in the respiratory tract was not addressed. Airborne fibers (length/diameter ratio ≥3), can exceed 150 μm in length and appear to be relatively stable in air. This is because their aerodynamic size is determined predominantly by their diameter, not their length. Fibers longer than 10 μm can deposit by interception and when aligned with the direction of airflow may penetrate deep into the respiratory tract. Once deposited, macrophage mediated clearance is the primary mechanism of removing micro-sized particles from the pulmonary region. The length of fibers can, however, affect their phagocytosis and clearance. For example, fibers of >17 μm in length are too long to be fully engulfed by rat alveolar macrophages and can protrude from macrophages (i.e., macrophage frustration) (Zeidler-Erdely et al., 2006). The ability of fibers, particularly small ones (<5 μm length and <0.25 μm diameter), to translocate from the lungs to the parietal pleura, liver, and kidney is reviewed by Miserocchi et al. (2008). Further discussion of the fiber disposition in the respiratory tract is beyond the scope of this chapter.

The term “ultrafine particle” has traditionally been used by the aerosol research and inhalation toxicology communities to describe airborne particles or other laboratory generated aerosols used in toxicological studies that are ≤100 nm in size (based on physical size, diffusivity, or electrical mobility). Generally consistent with the definition of an ultrafine particle (UFP), the International Organization for Standardization (ISO) define a nanoparticle as an object with all three external dimensions in the nanoscale, i.e., from approximately 1 to 100 nm (ISO, 2008). The ISO also defined a nano-object as a

material with one or more external dimensions in the nanoscale. The terms, nanoparticle and UFP, have been used rather synonymously in the toxicological literature. Within this chapter the usage of UFP or nanoparticle is restricted to particles have physical diameter or mobility diameter (the size of a sphere having the same diffusivity or movement in an electrical field as the particle of interest) less than or equal 100 nm, whereas other chapters may extend the definition to <0.30 µm (Section P.3.1 and Section 2.4.3.1).

4.1.1 Size Characterization of Inhaled Particles

Particle size is a major determinant of the fraction of inhaled particles depositing in and cleared from various regions of the respiratory tract. The distribution of particle sizes in an aerosol is typically described by the lognormal distribution (i.e., the situation in which the logarithms of particle diameter are distributed normally). The geometric mean is the median of the distribution, and the variability around the median is the geometric standard deviation (GSD or σ_g).

The particle size associated with any percentile of the distribution, d_i, is given by:

$$d_i = d_{50\%}\,\sigma_g^{z(P)}$$

Equation 4-1

where: z(P) is the normal standard deviate for a given probability. In most cases, the aerosols to which people are naturally exposed are polydisperse. By contrast, most experimental studies of particle deposition and clearance in the lung use monodisperse particles (GSD <1.15). Ambient aerosols may also be composed of multiple size modes, each mode should be described by its specific median diameter and GSD.

Aerosol size distributions may be measured and described in various ways. When a distribution is described by counting particles, the median is called the count median diameter (CMD). On the other hand, the median of a distribution based on particle mass in an aerosol is the mass median diameter (MMD). Impaction and sedimentation of particles in the respiratory tract depend on a particle's aerodynamic diameter (d_{ae}), which is the size of a sphere of unit density that has the same terminal settling velocity as the particle of interest. The size distribution is frequently described in terms of d_{ae} as the mass median aerodynamic diameter (MMAD), which is the median of the distribution of mass with respect to aerodynamic equivalent diameter. Alternative descriptions should be used for particles with actual physical sizes below ≈0.5 µm because, for those sized particles, aerodynamic properties become less important and diffusion becomes ever more important. For these smaller particles, their physical diameter or CMD are typically used since diffusivity is not a function of particle density. For small irregular shaped particles and aggregates, the diameter of a spherical particle that has the same diffusion coefficient in air as the particle in question is appropriate, i.e., a thermodynamic diameter. Unless stated otherwise, all particle diameters in the text of this chapter that are ≥0.5 µm are aerodynamic diameters.

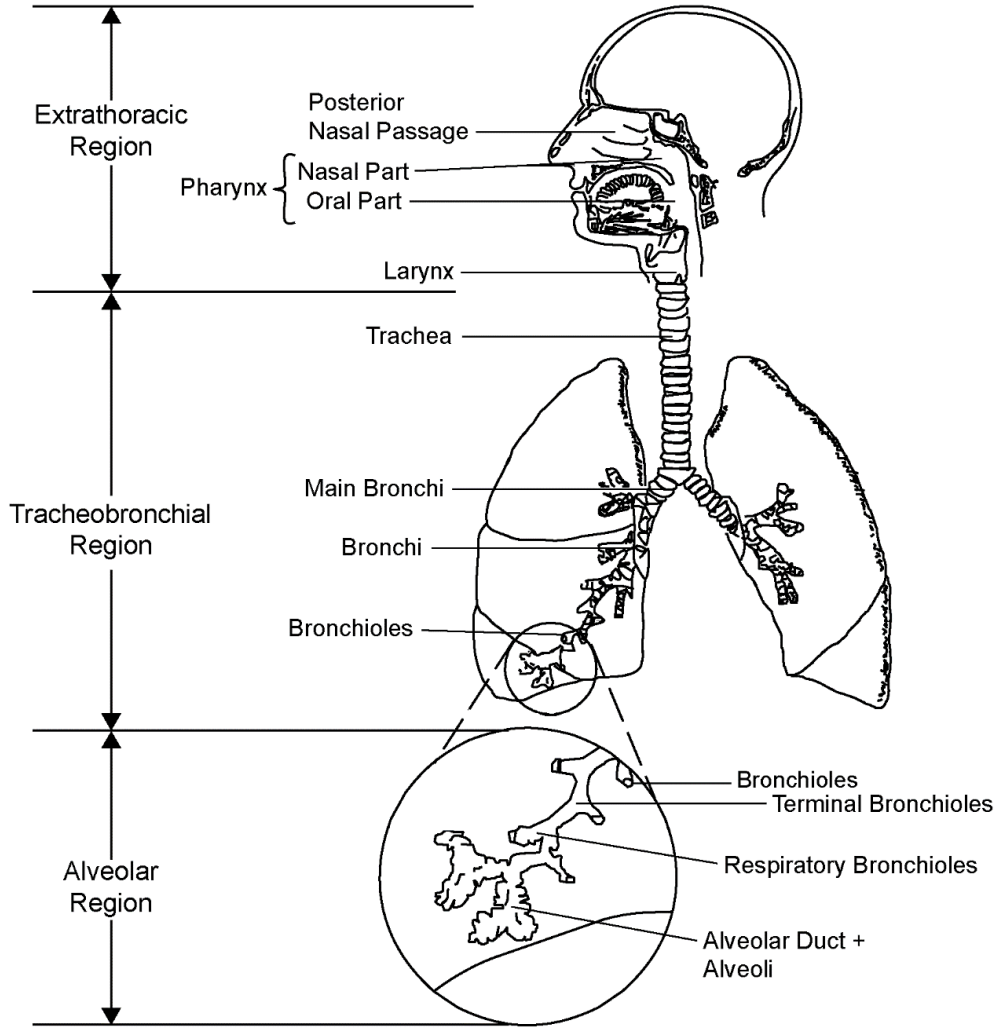
All particle diameters ≤0.1 µm are a thermodynamic diameter. A few studies provide UFP deposition data and continue to monitor deposition to diameters of 0.2 to 0.3 µm. Those larger 0.2 to 0.3 µm particles should be assumed to be thermodynamic diameters. Within this chapter, plots of predicted particle deposition with particles between 0.1 and 0.5 µm were simulated assuming unit density spheres so that the physical, thermodynamic, and aerodynamic diameters are the same.

A number of papers have become available that assess the deposition and translocation of very small nanoparticles below 10 nm in diameter (see Section 4.3.3). Calculation of particle surface area for micron sized particles have are general calculated as πd^2. Specific surface area (i.e., normalized to particle mass) is $6/(\rho d)$, where ρ is particle density. However, when particle diameter is below 10 nm, this means of estimating surface area become imprecise. Below 10 nm, it becomes necessary to consider the angularity of the surface in particles consisting of a small number of atoms (Janz et al., 2010). It is also interesting to consider the number of atoms in some of the newer nanoparticle literature. For instance, considering gold nanoparticles, a 1.2 nm particles contain 35 gold atoms, a 1.4 nm particle has 55 gold atoms, and a 1.8 nm particle has 150 gold atoms (Pan et al., 2007).

4.1.2 Structure and Function of the Respiratory Tract

4.1.2.1 Anatomy

The basic structure of the human respiratory tract is illustrated in Figure 4-1. In the literature, the terms extrathoracic (ET) region and upper airways or upper respiratory tract are used synonymously. The terms lower airways and lower respiratory tract are used to refer to the thoracic airways, i.e., the combination of the tracheobronchial (TB) region which is the conducting airways and the alveolar region which is the functional part or parenchyma of the lung. A review of interspecies similarities and differences in the structure and function of the respiratory tract is provided by Phalen et al. (2008). Although the structure varies, the illustrated anatomic regions are common to all mammalian species with the exception of the respiratory bronchioles. Respiratory bronchioles, the transition region between ciliated and fully alveolated airways (i.e., alveolar ducts and sacs), are found in humans, dogs, ferrets, cats, goats, and monkeys (Phalen et al., 2008; Phalen and Oldham, 1983). Respiratory bronchioles are absent in rats and mice and abbreviated in hamsters, guinea pigs, rabbits, oxen, sheep, and pigs (Phalen et al., 2008; Phalen and Oldham, 1983). The branching structure of the ciliated bronchi and bronchioles also differs between species from being a rather symmetric and dichotomous branching network of airways in humans to a more monopodial branching network in other mammals including monkeys.



Source: Permission pending, Based on ICRP (1994) and U.S. EPA (1996).

Figure 4-1. Diagrammatic representation of human respiratory tract regions.

The development of the lung is not complete at birth. Prior to the work of Dunnill (1962), there were two competing opinions as to whether the lung was: (1) fully developed at birth and simply increased in volume by increasing dimensions of the airways and alveoli or (2) increased in volume by the creation of new units (alveoli and alveolar sacs) within the distal lung. Based on postmortem morphometric analysis of 20 lungs from 10 children, Dunnill (1962) concluded there was continued creation of new alveolar sacs and alveoli from birth to 8 years of age. This conclusion, in part, was based on the observation that the number of alveoli in the 8-year-old child was close to that observed in an adult male. After about 8 years of age, the continued increase in lung volume was presumed due to increased airway and alveolar dimensions. In a larger study 36 boys and 20 girls ranging from 6 weeks to 14 years of age, Thurlbeck (1982) concluded that the creation of new alveoli continued until at least 2 years of age,

but that there is considerable variability in the number of alveoli among individuals and a considerably larger number of alveoli than observed by Dunnill (1962). This variability and larger number of alveoli lead Thurlbeck (1982) to question whether the lungs of 8 year old child in the Dunnill (1962) study would have continued to grow with creation of additional alveoli. Although it was clear from these studies that new alveoli were created in humans postnatally, it was unclear when this process ceased.

Recent work shows postnatal creation of alveoli into young adulthood occurs in multiple mammalian species. The prenatal and postnatal creation of alveoli is synonymously termed alveogenesis, alveologenesis, and alveolarization in the literature (Bourbon et al., 2005). Lewin and Hurtt (2017) review six stages of lung development (i.e., embryonic, pseudoglandular, canlicular, saccular, alveolar, and microvascular maturation) across several mammalian species as well as some aspects of immune function development and some causes of impaired lung development. Here, a few points related to the structural development of the lung are noted based largely on Lewin and Hurtt (2017). The canlicular stage is completed about 25 gestational weeks in humans and is marked by the completion of tracheobronchial airways branching structure. Alveolar cells become identifiable during the saccular stage at about 24 weeks in human fetus and about 19 days in rat fetus. Subsequently, terminal bronchioles end in sac-like structures. Rats and mice are born at this stage of respiratory development, whereas alveolarization begins prenatally with 10−20% of adult alveoli found at birth in humans, rabbits, and sheep. Rapid alveolarization occurs during the first 3 weeks of life in rats and first 2−3 years in humans (Herring et al., 2014). Following the period of rapid alveolarization there is evidence for a more gradual increase that may occur to until young adulthood for multiple species including rodents, dogs, monkeys, and humans (Lewin and Hurtt, 2017; Herring et al., 2014; Narayanan et al., 2012; Hyde et al., 2007). This is consistent with the period of increasing in lung volume in humans with age (and height) until around 18 years of age in females and 20 years of age in males (Hankinson et al., 1999).

4.1.2.2 Breathing Rates

Some general species information relevant to particle dosimetry (e.g., breathing parameters and respiratory surface areas) is provided in Table 4-1. The data in this table are for gross comparison among resting adults since specific strains are not individually characterized nor are changes with animal age characterized. Additional data for rats on respiratory tract volumes and breathing rates as a function of animal weight are available from Miller et al. (2014). Across species, ventilation rates increase with increases in activity. Within species, there are also differences among strains in breathing patterns and rates. Furthermore, stress due to experimental protocols may alter breathing patterns differentially among species. In rats, Mauderly and Kritchevsky (1979) reported restraint to cause increased breathing frequency (f) and decreased tidal volume (V_T), while minimally affecting overall minute ventilation. In mice, Mendez et al. (2010) reported restrained animals to have approximately 2.4 times the minute ventilation of unrestrained animals (27 and 64 mL/min, respectively). Most of this increase in minute ventilation came from a doubling of f from 145 min^{-1} to 290 min^{-1}. However, in a study of four mouse

strains, DeLorme and Moss (2002) consistently observed decreased breathing frequency and minute ventilation in restrained mice (f, 335 min^{-1}; minute ventilation, 70 mL/min) relative to unrestrained mice (f, 520 min^{-1}; minute ventilation, 120 mL/min). These findings are consistent with Alessandrini et al. (2008), who reported a breathing frequency of 500 min^{-1} and minute ventilation of 106 mL/min in unrestrained mice. Thus, even within one species there can be large differences in breathing conditions between studies. Breathing patterns and minute ventilation must both be considered to accurately assess particle deposition fractions and dose rates.

Table 4-1. Typical respiratory parameters and body weights among animals and humans.

Species	Breathing Frequency min^{-1}	Tidal Volume mL	Minute Ventilation mL/min	Functional Residual Capacity mL	Alveolar surface Area m^2	Body Weight kg
Mouse (restrained)	290[a]	0.22[a]	64[a]	0.5[e]	0.05[f]	0.02[f]
Mouse (unrestrained)	145[a]	0.19[a]	27[a]	0.5[e]	0.05[f]	0.02[f]
Rat	102[b]	2.1[b]	214[b]	3.5[e]	0.4[f]	0.4[f]
Dog	22[c]	175[c]	3,600[c]	500[c]	52[f]	16[f]
Human (male)	12[d]	625[d]	7,500[d]	3,300[d]	140[d]	73[d]
Human (female)	12[d]	444[d]	5,330[d]	2,700[d]	100[g]	60[d]

[a]Mendez et al. (2010).
[b]de Winter-Sorkina and Cassee (2002).
[c]Mauderly (1979).
[d]ICRP (1994).
[e]Takezawa et al. (1980), anesthetized animals.
[f]Stone et al. (1992).
[g]Alveolar surface area of male scaled by ratio of total lung capacity, i.e., 4.97 ÷ 6.98.

Table 4-1 shows considerable variation among species in adults. The effect of activity on ventilation rates is discussed in Section 4.2.4.1 in relation to the effect of activity in adults on particle deposition. Minute ventilation changes with age and growth [for humans see U.S. EPA (2011)]. Breathing patterns of humans are well recognized to change with increasing age, i.e., V_T increase and respiratory rates decrease (Tobin et al., 1983a; Tabachnik et al., 1981). Some guidance for humans with regard to changing breathing patterns with age and activity are provided by ICRP (1994). Recent data show median f decreases linearly from 44 min^{-1} in infants to 30 min^{-1} at 2 years of age and linearly from 22 min^{-1} at 6 years to 15.5 min^{-1} at 18 years (Fleming et al., 2011). Allometric scaling can be used to adjust breathing

patterns of immature animals as a function body weight (BW, kg). Breathing frequency (min^{-1}) from Piccione et al. (2005) is $82*BW^{-0.287}$ and aligns well with breathing frequency for rats, but for mice provides a value between that of restrained and unrestrained animals. Minute ventilation (L/min) from Bide et al. (2000) is $0.499*BW^{0.809}$ and aligns well with minute ventilation for rats, but for mice provides a value lower than that of unrestrained animals. Allometric predictions for mice can be scaled (observed ÷ predicted value) to match those of adults in Table 4-1 and tidal volume may be estimated as minute ventilation divided by breathing frequency.

The ICRP indicated a 3-month-old infant might be expected to breathe with a minute ventilation of 1.5 L/min (V_T, 39 mL; *f*, 38 min^{-1}) at rest/sleep and 3.2 L/min (V_T, 66 mL; *f*, 48 min^{-1}) during light activity/exercise. Some more recent data suggest higher respiratory rates for 3-month-olds with a median *f* of 42 min^{-1} with 10th to 90th percentiles of 34 and 56 min^{-1}, respectively (Fleming et al., 2011). For their in vitro investigation of nasal versus oral particle penetration into the lower respiratory tract, Amirav et al. (2014) used minute ventilations of 2.0 and 3.2 L/min (50 and 80 mL V_T at 40 min^{-1}) for 5month-olds as well as for 14-month-olds and minute ventilations of 2.4 and 3.6 L/min (80 and 120 mL V_T at 30 min^{-1}) for 20-month-olds based on the recent literature. Normalized to body mass, median daily ventilation rates (m^3/kg-day) decrease over the course of life (Brochu et al., 2011). This decrease in ventilation relative to body mass is rapid and nearly linear from infancy through early adulthood. Relative to normal-weight male and female adults (25−45 years of age; 0.271 m^3/kg-day), ventilation rates normalized to body mass are increased 1.5 times in normal-weight children (7−10 years of age; 0.402 m^3/kg-day) and doubled in normal-weight infants (0.22−0.5 years of age; 0.538 m^3/kg-day).

4.1.2.3 Epithelial Lining Fluid

The site of particle deposition within the respiratory tract has implications related to lung retention and surface dose of particles as well as potential systemic distribution of particles or solubilized components. There are progressive changes in airway anatomy with distal progression into the lower respiratory tract. In the bronchi there is a thick liquid lining and mucociliary clearance rapidly moves deposited particles toward the mouth. In general, in the bronchi, only highly soluble materials moving from the air into the liquid layer will have systemic access via the blood. With distal progression, the protective liquid lining diminishes and mucus clearance rates slow. Soluble compounds and some poorly soluble UFPs may potentially cross the air-liquid interface to enter the tissues and the blood, especially in the alveolar region.

The epithelial lining fluid (ELF) over most of the tracheobronchial region may generally be described as consisting of two layers: an upper mucus layer and a periciliary layer, which surrounds the cilia (Button et al., 2012; Widdicombe, 2002; Widdicombe and Widdicombe, 1995; Van As, 1977). The length of motile human cilia is about 7 µm in the distal nasal airways, trachea, and bronchi and around 5 µm in the bronchioles (Yaghi et al., 2012; Song et al., 2009; Clary-Meinesz et al., 1997; Widdicombe

and Widdicombe, 1995). In the healthy lung, the thickness of the periciliary layer is roughly the length of the cilia (Song et al., 2009; Widdicombe and Widdicombe, 1995). This periciliary layer forms a continuous liquid lining over the tracheobronchial airways; whereas the upper mucus layer is discontinuous and diminishes or is absent in smaller bronchioles (Widdicombe, 2002; Van As, 1977). The periciliary layer may be the only ELF layer (i.e., there is little to no overlaying mucus) in the ciliated airways of infants and healthy adults who are unaffected by pathology related to disease, infection, or other stimuli (Bhaskar et al., 1985).

The ELF covering the alveolar surface is considerably thinner than the periciliary layer found in the tracheobronchial region. The alveolar ELF consists of two layers: an upper surfactant layer and a subphase fluid (Ng et al., 2004). Bastacky et al. (1995) conducted a low temperature scanning electron microscopy analysis of rapidly frozen samples (9 animals; 9,339 measurements) of rat lungs inflated to approximately 80% total lung capacity. The alveolar ELF was found to be continuous, but of varied depth. Three distinct ELF areas were described: (1) a thin layer (0.1 μm median depth, GSD ~ 2.16; GSDs were calculated from 25th, 50th, and 75th percentiles of the distributions) over relatively flat areas and comprising 80% of the alveolar surface, (2) a slightly thinner layer (0.08 μm, GSD ~ 1.79) over protruding features and accounting for 10% of the surface, and (3) a thick layer (0.66 μm, GSD ~ 2.18) occurring at alveolar junctions and accounting for 10% of the surface. Based on these distributions of thicknesses, 10% of the alveolar region is covered by an ELF layer of 0.04 μm or less. Presuming that these depths would also occur in humans at 80% total lung capacity and assuming isotropic expansion and contraction, depths should be expected to be 20−40% greater during normal tidal breathing (rest and light exercise) when the lung is inflated to between 50−60% total lung capacity averaged across the respiratory cycle. During tidal breathing, a median ELF depth of 0.12−0.14 μm would be expected over 80% of the alveolar surface with 10% of the alveolar surface having a median depth of around 0.05 μm or less. Considering the entire distribution of depths during tidal breathing, about 30, 60, and 90% of the alveolar surface would be estimated to have a lining layer thickness of less than or equal to 0.1, 0.2, and 0.5 μm, respectively.

4.1.3 Route of Breathing

As humans, we breathe oronasally, i.e., through both our nose and mouth. In general, we breathe through our nose when at rest and increasingly through the mouth with increasing activity level. Few people breathe solely through their mouth. In contrast to humans, rodents are obligate nose breathers. Brown et al. (2013) found that the penetration of particles greater than 1 μm into the lower respiratory tract of humans was more affected by route of breathing than age, sex, activity level, or breathing pattern (i.e., V_T and f). This section describes how route of breathing, also referred to as "respiratory mode" or "breathing habit" in the literature, is affected by age, sex, activity level, and upper respiratory tract anomalies. Based on literature that is decades old but that has not been included in prior PM ISA or

AQCDs, this section will show that children breathe more though the mouth than adults and that across all ages, males breathe more through their mouth than females.

One of the more commonly referenced studies in dosimetric papers is Niinimaa et al. (1981). This paper is referenced in all prior PM reviews back to 1982 PM AQCD (U.S. EPA, 1982) as the primary data source on route of breathing. Niinimaa et al. (1981) examined route of breathing in a group of healthy individuals (15−35 years of age; 14 M, 21.6 ± 3.8 years; 16 F, 22.9 ± 5.4 years) recruited via advertisements posted on the University of Toronto campus. The investigators found that most individuals, 87% (26 of 30) in the study, breathed through their nose until an activity level was reached where they switched to oronasal breathing. Thirteen percent (4 of 30) of the subjects, however, were oronasal breathers even at rest. These two subject groups (i.e., the 87 and 13% of subjects) are commonly referred to in the literature [e.g., ICRP (1994)] as "normal augmenters" and "mouth breathers," respectively. More recently, Bennett et al. (2003) reported a more gradual increase in oronasal breathing with males (n = 11; 22 ± 4 years) tending to have a greater oral contribution than females (n = 11; 22 ± 2 years) at rest (87 vs. 100% nasal, respectively) and during exercise (45 vs. 63% nasal at 60% maximum workload, respectively).

Consistent with this trend for women to have a greater nasal contribution (Bennett et al., 2003), in a large study of children (63 M, 57 F; 4−19 years), Leiberman et al. (1990) reported a statistically greater nasal fraction during inspiration in girls relative to boys (77 and 62%, respectively; $p = 0.03$) and a marginally significant difference during expiration (78 and 66%, respectively; $p = 0.052$). Another large study (88 M, 109 F; 5−73 years) also reported females as having a significantly greater fraction of nasal breathing than males (Vig and Zajac, 1993). This effect was largest in children (5−12 years) with an inspiratory nasal fraction of 66% in males and 86% in females during resting breathing. This study also reported that the partitioning between the nose and mouth was almost identical between inspiration and expiration. In children and adults, sex explains some interindividual variability in route of breathing with females breathing more through the nose than males.

A few studies have attempted to measure oronasal breathing in children as compared to adults (Bennett et al., 2008; Becquemin et al., 1999; James et al., 1997; Vig and Zajac, 1993). James et al. (1997) found that children (n = 10; 7−16 years) displayed more variability than older age groups (n = 27; 17−72 years) with respect to their oronasal pattern of breathing with exercise. Becquemin et al. (1999) found that children (n = 10; 8−16 years) tended to display more oral breathing both at rest and during exercise than adults (n = 10; 27−56 years). The highest oral fractions were also found in the youngest children. Similarly, Bennett et al. (2008) reported children (n = 12; 6−10 years) tended to have a greater oral contribution than adults (n = 11; 18−27 years) at rest (68 vs. 88% nasal, respectively) and during exercise (47 vs. 59% nasal at 40% maximum workload, respectively). Vig and Zajac (1993) reported a statistically significant effect of age on route of breathing which was most apparent in males with the fraction of nasal breathing increasing from 67% in children (5−12-year-olds) to 82% in teens (13−19-year-olds), and 86% in adults (20−73 years). Females had a nasal fraction of 86% in children and

teens and 93% in adults. Based on these studies, the nasal fraction appears to increase with age until adulthood.

Several large studies have reported an inverse correlation ($r = -0.3$ to -0.6) between nasal resistance and nasal breathing fraction (Vig and Zajac, 1993; Leiberman et al., 1990; Leiter and Baker, 1989). However, neither pharmaceutical constriction nor dilation of the nasal passages affected the nasal fraction (Leiberman et al., 1990; Leiter and Baker, 1989). Nasal resistance decreases with age and is lower in females than males (Vig and Zajac, 1993; Becquemin et al., 1991). These differences in nasal resistance may account for larger nasal fractions in adults than children and females than males. Smaller studies (n = 37) have not found a significant correlation between nasal resistance and nasal fraction but have noted that those having high resistance breathe less through the nose (James et al., 1997). Bennett et al. (2003) reported a tendency for lower nasal resistance in African-American blacks (5 M,6 F; 22 ± 4 years) relative to Caucasians (6 M, 5 F; 22 ± 3 years). The nasal fraction in blacks tended to be greater at rest and 40% maximum workload and achieved statistical significance relative to Caucasians at 20 and 60% maximum workload. Leiter and Baker (1989) reported that of the 15 mouth-breathing children as identified by a dentist, pediatrician, or otolaryngologist in their study, the three having greatest nasal resistance breathed 100% through the mouth. These investigators also reported that the nasal fraction was negatively correlated ($p \leq 0.004$) with nasal resistance during both inspiration and expiration. However, the correlation appears driven by the three individuals with 100% mouth breathing. In a study of 102 children (evenly divided by sex) aged 6 to 14 years, Warren et al. (1990) reported that both nasal cross-sectional area and the fraction of nasal breath both increased with age, but did not report the association between these parameters or assess the effect of sex. The average nasal breathing fraction increased linearly from about 47% at 6 years of age to 86% at 14 years of age. Overall, breathing habit appears related to nasal resistance, which may explain some of the effects of age and sex on breathing habit.

Diseases affecting nasal resistance may also affect breathing route. Chadha et al. (1987) found that the majority (11 of 12) of patients with asthma or allergic rhinitis breathe oronasally even at rest. James et al. (1997) also reported the subjects (n = 37; 7−72 years) having hay fever, sinus disease, or recent upper respiratory tract symptoms tended to the have a greater oral contribution relative to those absent upper respiratory tract symptoms. James et al. (1997) additionally observed that two subjects (5.4%) breathed solely through the mouth but provided no other characteristics of these individuals. Greater oral breathing may occur due to upper respiratory tract infection and inflammation.

Some studies of children suggest obesity also affects breathing habit. Using MRI, Schwab et al. (2015) examined anatomic risk factors of obstructive sleep apnea in children (n = 49 obese with sleep apnea, 38 obese control, 50 lean controls; 11−16 years of age). In obese children with sleep apnea, adenoid size was increased relative to both obese and lean controls not having sleep apnea. The size of the adenoid was also increased in male obese controls (n = 24) relative to male lean controls (n = 35), whereas adenoid size was similar between female obese controls (n = 14) and female lean controls

(n = 15). Both nasopharyngeal cross-sectional area and minimum area were similar between lean and obese controls, but decreased in obese children with obstructive sleep apnea. In a longitudinal study of children (n = 47 F, 35 M) assessed annually from 9 to 13 years of age, Crouse et al. (1999) found nasal cross-section was minimal at 10 years of age. The authors speculated this may be due to prepubertal enlargement of the adenoids. In a 5 year longitudinal study of children (n = 17 M, 9 F) following adenoidectomy, Kerr et al. (1989) reported a change in mode of breathing from oral to nasal. These studies suggest the obese children, especially boys, may have increased oral breathing relative to normal weight children.

In summary, breathing habit is affected by age, sex, nasal resistance, and possibly obesity. Numerous studies show children to inhale a larger fraction of air through their mouth than adults. Across all ages, males also inhale a larger fraction of air through their mouth than females. Other factors that increase nasal resistance such as allergies or acute upper respiratory infections can also increase the fraction of oral breathing. Obesity, especially in boys, may also contribute to increased nasal resistance and an increased oral fraction of breathing relative to normal weight children.

4.1.4 Ventilation Distribution

Ventilation distribution refers to how an inhaled breath becomes divided in the lung. Ventilation distribution affects the partitioning or mass transport of inhaled aerosols between lung regions and the residence time within these regions. The effects of ventilation distribution on particle deposition are discussed in Section 4.2.4.6. In large mammals such as humans, there is a gravity induced gradient which causes the volume of alveoli in dependent lung regions (i.e., the lowest areas in the lungs) to be smaller than those in nondependent lung regions. During normal tidal breathing, dependent regions may have somewhat increased ventilation relative to nondependent regions. As a breath is distributed, so too may be associated airborne particles. Some experimental data are available on the association between regional deposition of ultrafine, fine, and coarse particles and regional ventilation in the healthy and diseased lung. Ventilatory inhomogeneity due to obstructive disease generally exceeds normal gravity induced gradients.

The distribution of ventilation has been studied in a number of animal species. There is a pronounced gravitation gradient in the ventilation distribution of standing horses with the dependent (ventral) regions receiving more of each breath than the nondependent (dorsal) regions (Amis et al., 1984). In standing Shetland ponies, late-term pregnancy has been reported to increase ventilation to the nondependent regions possibly due to intra-abdominal pressure on the dependent (ventral) regions (Schramel et al., 2012). In contrast to horses, data out to 20 days postpartum showed equal ventral-dorsal ventilation in these ponies. In the supine position, dogs and sloths show increased ventilation of the dependent (dorsal) regions relative to the nondependent (ventral) regions (Hoffman and Ritman, 1985). However, in the prone position there is essentially uniform ventral-dorsal ventilation in both the dogs and sloths. Thus, the position in which rats are exposed may influence the regional delivery and deposition of

inhaled aerosols. In rats, the nondependent region of the lung has been reported to be better ventilated, whether positioned supine, prone, or on either side (Dunster et al., 2012; Rooney et al., 2009). In humans, ventilation patterns are affected by both body position and lung inflation.

Milic-Emili et al. (1966) showed apical (nondependent) to basal (dependent) differences in pleural pressure can affect ventilation distribution in healthy individuals. In upright humans, the apical lung receives the majority of an inhaled air at low lung volumes (less than 20% vital capacity). Above this volume, the vertical proportioning of ventilation is relatively constant across a breath with basal regions (dependent part) having somewhat increased ventilation relative to apical regions (Milic-Emili et al., 1966). The effect of gravity is shifted by changes in body position. For instance, while lying on the left side, aerosols inhaled at low lung volumes will be preferentially transported into and deposited in the right lung (Bennett et al., 2002). In upright individuals at high lung volumes (70% or more of total lung capacity), particles are transported preferentially into and deposit in the left lung (Bennett et al., 2002). A more uniform left-right distribution of particle deposition is observed for inhalations closer to functional residual capacity (FRC). Left-right asymmetry in particle deposition at high lung volumes is primarily due to differences in ventilation between the lungs (Möller et al., 2009). The effect of gravity-induced gradients on ventilation and left-right asymmetry in upright individuals described here for healthy individuals, however, are small relative to the ventilatory heterogeneity caused by obstructive lung disease (Suga et al., 1995).

4.1.5 Particle Inhalability

In order to potentially become deposited in the respiratory tract, particles must first be inhaled. The inspirable particulate mass fraction of an aerosol is that fraction of the ambient airborne particles that can enter the uppermost respiratory tract compartment, the head (Soderholm, 1985). The American Conference of Governmental Industrial Hygienists (ACGIH) and the International Commission on Radiological Protection (ICRP) have established inhalability criteria for humans (ACGIH, 2005; ICRP, 1994). These criteria are indifferent to route of breathing and assume random orientation with respect to wind direction. They are based on experimental inhalability data for $d_{ae} \leq 100$ µm at wind speeds of between 1 and 8 m/s. For the ACGIH criterion, inhalability is 97% for 1 µm particles, 87% for 5 µm, 77% for 10 µm, and plateaus at 50% for particles above ~40 µm. The ICRP criterion, which also plateaus at 50% for very large d_{ae}, does not become of real importance until 5 µm where inhalability is 97%. Dai et al. (2006) reported slightly lower nasal particle inhalability in humans during moderate exercise than rest (e.g., 89.2 vs. 98.1% for 13 µm particles, respectively). Nasal particle inhalability is similar between an adult and 7-year old child (Hsu and Swift, 1999). Inhalability into the mouth from calm air in humans also becomes important for d_{ae} >10 µm (Anthony and Flynn, 2006; Brown, 2005). Unlike the inhalability from high wind speeds which plateaus at 50% for d_{ae} greater than ~40 µm, particle inhalability from calm air continues to decrease toward zero with increasing d_{ae} and is affected by route of breathing.

Inhalability data in laboratory animals, such as rats, are only available for breathing from relatively calm air (velocity ≤ 0.3 m/s). For nasal breathing, inhalability becomes an important consideration for particles larger than 1 µm in rodents and 10 µm in humans (Ménache et al., 1995). The inhalability of particles of 2.5, 5, and 10 µm is 80, 65, and 44% in rats, respectively, whereas it only decreases to 96% for an d_{ae} of 10 µm in humans during nasal breathing (Ménache et al., 1995). Asgharian et al. (2003) suggested that an even more rapid decrease in inhalability with increasing d_{ae} may occur in rats, particularly for faster breathing rates. Asgharian et al. (2014) extended his model to calculate inhalability for mice which had a slightly more rapid decline in inhalability with increasing particle size than rats. Inhalability and nasal deposition are particularly important considerations influencing how much PM makes it into the lower respiratory tract of rodents relative to humans.

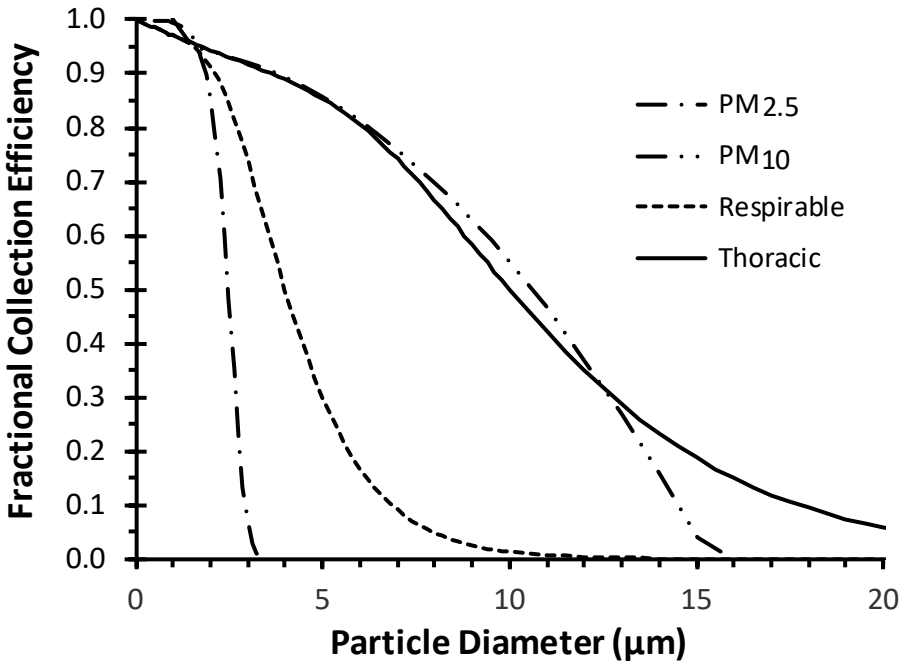
Kim et al. (2014) provide some computational fluid dynamics (CFD) simulations of inhalability for a 7-month old. Although the simulations were for an infant under a hood for drug delivery, these simulations may reasonably approximate inhalability from calm air. For a child sitting while quietly breathing (Q, 5 L/min), nasal inhalability decreased from 83% for 1 µm to 63% for 5 µm particles. For oronasal breathing, with 65% of air entering the mouth, inhalability was about 93% for 1 to 5 µm particles. These data suggest that particle inhalability of infants is much less than expected in adults.

4.1.6 Thoracic and Respirable Particles

This section describes sampling conventions that are used by in ambient and occupational settings. The particle sampling conventions are compared to demonstrate their similarities and differences. Finally, modeling is used to illustrate how the size of particles entering the lower respiratory tract (i.e., the thorax) is affected by route of breathing (see Section 4.1.3) and differs among species.

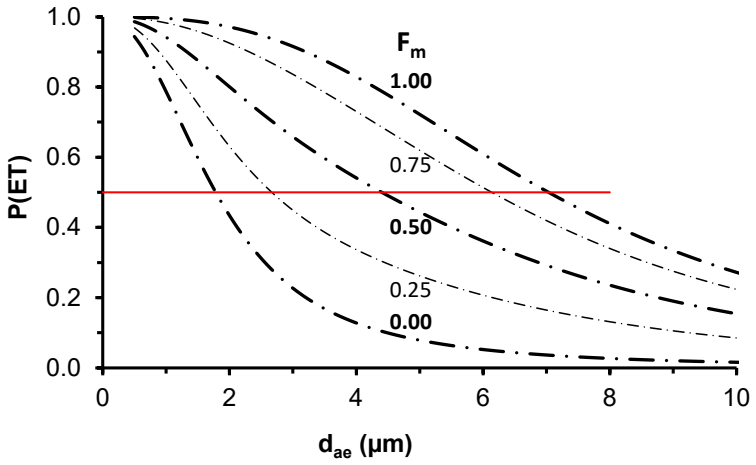
The terms thoracic particles and respirable particles refer to the fraction of particles that are able to enter the thoracic and gas exchange region of the lung, respectively. The European Committee for Standardization (CEN) specifically defines the thoracic fraction as the mass fraction of inhaled particles penetrating beyond the larynx (CEN, 1993). They further define the respirable fraction as the mass fraction of inhaled particles penetrating into the unciliated airways. More typically, the literature has defined the respirable fraction in relation to the fraction of particles entering the gas-exchange region or the fraction penetrating through the tracheobronchial region, the ciliated airways, or conducting airways. Relative to total airborne particles, the particle size having 50% penetration for the thoracic and respirable fractions are 10 µm and 4.0 µm (aerodynamic diameters), respectively (CEN, 1993). These criteria were specifically developed for workplace atmospheres. In 1987, the EPA adopted PM_{10} as the indicator of PM for the National Ambient Air Quality Standards (NAAQS) to delineate the subset of inhalable particles (referred to as thoracic particles) that were thought small enough to penetrate to the thoracic region (including the tracheobronchial and alveolar regions) of the respiratory tract.

Figure 4-2 illustrates the thoracic fraction and EPA's PM_{10} sampler collection efficiencies discussed above. These criteria are similar for particles smaller than 10 μm. However, the curves diverge between 12−13 μm, with a dramatic drop in collection efficiency for EPA's PM_{10} versus a more gradual decrease in sampler collection efficiency for the thoracic fraction criterion. The occupational respirable particle sampling convention and EPA's $PM_{2.5}$ are also illustrated in Figure 4-2. In 1997, EPA extended size-selective sampling to include fine particles indicated by $PM_{2.5}$ and retained PM_{10} as an indicator for the purposes of regulating the thoracic coarse particles or coarse fraction particles (i.e., the inhalable particles that remain if $PM_{2.5}$ particles are removed from a sample of PM_{10}). The selection of $PM_{2.5}$ by the EPA was mainly to delineate the atmospheric fine (combustion derived, aggregates, acid condensates, secondary aerosols) and coarse (crustal, soil-derived dusts) PM modes and for consistency with community epidemiologic health studies reporting various health effects associated with $PM_{2.5}$ (U.S. EPA, 1997). Although Miller et al. (1979) recommended a particle size cut-point of ≤2.5 μm as an indicator for fine PM based on consideration of particle penetration into the gas-exchange region, the selection of $PM_{2.5}$ was not based on dosimetric considerations and was not intended to represent a respirable particle sampling convention. The thoracic sampling convention intentionally over represents the true penetration of particles into the thoracic region (compare Figure 4-1 and Figure 4-3). The American Conference of Governmental Industrial Hygienist (ACGIH) committee that recommended a 50% cut-point at 10 μm for the thoracic fraction considering uncertainty related to individual biological variability in respiratory health status, breathing patterns (rate and route), and airways structure as well as differences in work rates, all of which can cause differences in inhaled aerosol deposition and dose. Facing those uncertainties, the committee afforded extra protection to exposed workers by choosing a 50% cut-point at 10 μm rather than in the range of 5−7 μm where experimental studies showed 50% penetration of particles into the lower respiratory tract during oral breathing at ventilation rates equivalent to light exercise (ACGIH, 1985).



Source: Permission pending, $PM_{2.5}$ from Equation 1 of Peters et al. (2001) and/or 40CFR53, Subpart F, Table F-5; PM_{10} from Equation 11.19 of Hinds (1999) and/or 40CFR53.43 Table D-3; Respirable and Thoracic fractions are from Appendix C of ACGIH (2005).

Figure 4-2 Sampling conventions for U.S. EPA's $PM_{2.5}$ and PM_{10} and occupational criteria for thoracic and respirable fractions.



Source: Permission pending, Brown et al. (2013).

Figure 4-3 Thoracic fraction, i.e., particle penetration through the extrathoracic region, P(ET), as a function of breathing route in adult male during light exercise (V_T, 1,250 mL; *f*, 20 min^{-1}). F_m is the fraction of breath passing through mouth.

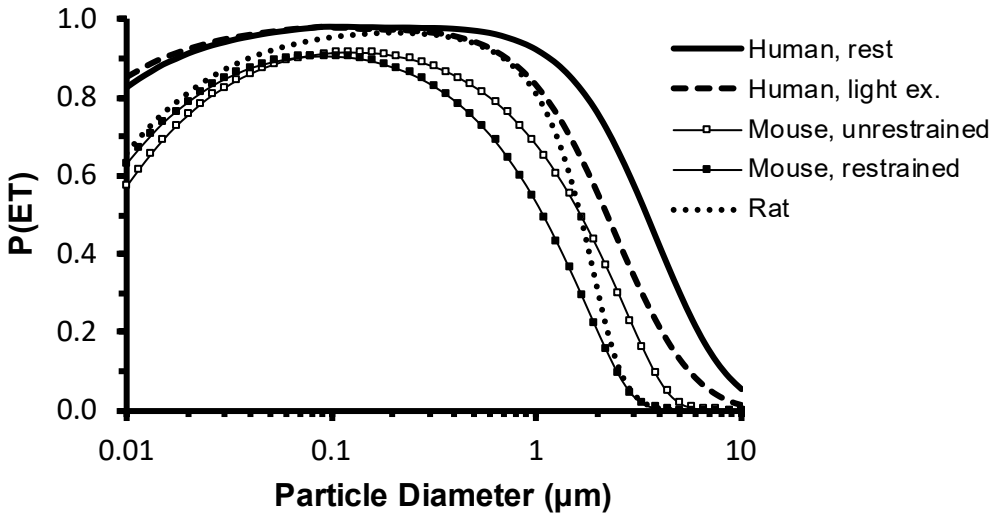
Brown et al. (2013) provide estimates of the thoracic and respirable fractions for healthy adult males, females, and a 10-year old child. The penetration of particles greater than 1 µm into the lower respiratory tract of humans was more affected by route of breathing than age, sex, activity level, or breathing pattern (i.e., V_T and *f*). Figure 4-3 illustrates this effect of route of breathing on the thoracic fraction. For typical activity levels and route of breathing, they estimated a 50% cut-size for the thoracic fraction at an aerodynamic diameter of around 3 µm in adults and 5 µm in children. The fraction of 10 µm particles entering the thorax was <20% for most activity levels and breathing habits. The penetration of 10 µm particles into the thorax was greatest, around 40%, for low levels of activity and purely oral breathing. Regardless of the breathing habit or activity level, the differences in the 50% cut-points for the thoracic and respirable fractions were far less than those used for occupational sampling. For oral breathing the 50% cut-point for the respirable fraction during oral breathing was within about 2 µm of the thoracic fraction cut-point, whereas it differs by 6 µm for occupational sampling criteria. For more typical breathing habits, the cut-points for the respirable and thoracic fractions were within about 0.5 µm. Two primary conclusions based on this study are: (1) PM_{10} over estimates the penetration of particles into the lower respiratory tract and (2) children are predicted to have greater particle penetration into the lower respiratory tract than adults.

Asgharian et al. (2014) recently provided estimates of the thoracic fraction in mice and rats as well as humans. The 50% cut-points for the thoracic fraction were roughly 1.1 µm in mice, 1.5 µm in rats,

and 3.7 µm in humans [see Figure 4 of Asgharian et al. (2014)]. The larger thoracic 50% cut-point for humans reported by Asgharian et al. (2014) relative to Brown et al. (2013) is, in part, due to the lower ventilation rate of 7.5 L/min used by the former versus average daily ventilation rates of 9 L/min and greater by the latter. One of the critical points that Asgharian et al. (2014) provide is that only a small fraction (2−5%) of particles greater than 3 µm reach the lower respiratory tract of the rodents. Thus, an appreciable fraction of inhaled thoracic coarse particles (i.e., $PM_{10-2.5}$) should not be expected to reach the lower respiratory tract of rodents during inhalation exposures.

Figure 4-4 illustrates the thoracic fraction in humans, rats, and mice calculated using the Multi-Path Particle Dosimetry model (MPPD; Version 3.04, ©2016).[42] For 50% cut-points are 3.4 µm (human, rest), 2.2 µm (human, light exercise), 1.6 µm (mouse, unrestrained), 1.1 µm (mouse, restrained), 1.6 µm (rat, rest). Note that although Table 4-1 shows increased breathing frequency and ventilation rates in restrained mice based on the review by Mendez et al. (2010), DeLorme and Moss (2002) consistently observed a lower breathing frequency and minute ventilation in restrained mice (f, 335 min^{-1}; minute ventilation, 70 mL/min) relative to unrestrained mice (f, 520 min^{-1}; minute ventilation, 120 mL/min). Regardless, with an increase in minute ventilation there is a decrease in the 50% cut-point for the thoracic fraction in both humans and mice.

[42]The MPPD model can be used to calculate particle deposition and clearance in multiple species. A description of the model, recent model improvements, and advancements incorporated into the MPPD model are provided by Miller et al. (2016). For additional information about the MPPD model (Version 3.04) or to obtain a copy, the reader is referred to: http://www.ara.com/products/mppd.htm.



Source: Permission pending, Estimates obtained using MPPD (Version 3.04).

Figure 4-4. Multispecies comparison of the thoracic fraction for nasal breathing with consideration for inhalability, i.e., particle penetration through the extrathoracic region, P(ET). Human, rest (V_T, 625 mL; *f*, 12 min^{-1}); Human, light exercise (V_T, 1,000 mL; *f*, 19 min^{-1}); Mouse, unrestrained (V_T, 0.19 mL; *f*, 145 min^{-1}); Mouse, restrained (V_T, 0.22 mL; *f*, 290 min^{-1}); Rat (V_T, 2.1 mL; *f*, 102 min^{-1}).

4.1.7 Dose and Dose Metrics

Assuming a constant exposure concentration, breathing rate, and aerosol particle size distribution, the total particle exposure or intake dose (ID) is given by:

$$ID = C \times f \times V_T \times I(d_{50\%}, \sigma_g) \times t$$

Equation 4-2

where: C is the mass concentration of the aerosol, *f* is breathing frequency, V_T is tidal volume, I(d50%, σ_g) is aerosol inhalability, and *t* is the duration of exposure. As discussed in Section 4.1.5, I(d50%, σ_g) should be considered for comparisons across species (e.g., human vs. rat), although this parameter should be negligible for particles under 1 µm. Intake doses characterized by Equation 4-2 are commonly normalized to body mass (Alexander et al., 2008). This may be particularly appropriate for soluble particles or materials expected to have systemic effects. Although C was specified as having units of particle mass per unit volume, other metrics such as particle surface area or number of particles per unit volume may be desired, especially for smaller particle sizes (e.g., <0.1 µm). Equation 4-2 is limited

in that it does not recognize that there are within-species differences as a function of particle size in total deposition (whole lung) and regional deposition (e.g., between TB and alveolar region) of particles.

The particle mass dose in a specific region (D_r) of the respiratory tract resulting from the particle inhalation may be given as:

$$D_r = ID \times DF_r$$

Equation 4-3

where: ID is the intake dose from Equation 4-2 and DF_r is the fraction of inhaled particles depositing in region *r* of the respiratory tract. The DF_r in Equation 4-3 can be calculated for a polydisperse aerosol by estimating the deposition fractions for a series of monodisperse aerosols as:

$$DF_r(d_{50\%}, \sigma_g) \approx \frac{1}{100} \sum_{P=0.01}^{0.99} DF_r(d_i)$$

Equation 4-4

where: $DF_r(d_i)$ in the summation is the deposition fraction in a region of the particle size associated with a given percentile, P, of the size distribution as calculated by Equation 4-1. Depending on health endpoints and particle size, the most appropriate dose metric choice for D_r may be mass, particle surface area, or number of particles deposited. The D_r may also be normalized to factors such as lung weight or surface area of specific regions of the respiratory tract. Because all of the variables potentially change over time, Equation 4-3 and Equation 4-4 are most appropriate for short duration exposures. Within an individual, the variability in DF_r over time is largely attributable to variations in inhaled particle size, *f*, V_T, and route of breathing (ICRP, 1994). Inter-subject and inter-species variability in DF_r is additionally affected by morphologic differences in the size and structure of the respiratory tract.

For chronic exposures, it is necessary to consider the retained dose. The particle dose retained in a region of the lung is determined by the balance between rate of input and the rate of removal. The particle burden (Br) in a region of lung may be expressed as:

$$B_r(t) = \dot{D}_r(t - \Delta t)\Delta t + B_r(t - \Delta t)[\exp(-\lambda_r \Delta t)]$$

Equation 4-5

where: $\dot{D}_r$ is the rate of deposition per unit time in region *r*, *t* is time, and λ_r is the clearance rate constant for region *r*, Δt is the time increment for the calculations (~1% [or less] of the clearance halftime [i.e., $0.693/\lambda_r$] of the region). $\dot{D}_r$ is calculated as D_r in Equation 4-3 except it is calculated for discrete Δt where parameters (namely, *f*, V_T, route of breathing, and DF_r) are relatively constant.

Under the premise that health effects from UFP are more associated with particle surface area of deposited particles than particle number or mass, some companies have started producing instruments to measure Lung Deposited Surface Area (LDSA). For a monodisperse ultrafine aerosol containing spherical

particles, the LDSA ($\mu m^2/cm^3$) is simply calculated as the particle surface area (μm^2) times particle number concentration ($\#/cm^3$) times the DF_r, where the DF_r is predicted for an adult male using the ICRP (1994) model under conditions of light exercise (V_T = 1.25 L and f = 20 min^{-1}) and nasal breathing (Asbach et al., 2009; Fissan et al., 2007). For a polydisperse aerosol, the estimated LDSA for specified particle size bins would be summed across aerosol distribution to obtain the total LDSA. Todea et al. (2015) assessed the accuracy of four types of commercially available devices available for the measurement of LDSA in the alveolar region.[43] The principle of operation is similar among the commercial devices with each imparting a unipolar charge on the incoming aerosol and subsequent measurement of electrical current from particles collected on a filter. Some conditioning of the incoming aerosol is typical, such as use of an impactor to remove large particles (roughly >1 µm) and/or an ion trap to remove small particles (generally <20 nm). The instruments do not actually measure the surface area of the particles, rather they provide an estimate of the particle surface area that is predicted to be deposited in the alveolar region of the lung. Theoretically, the measured LDSA most accurately matches predicted lung deposition for particles between 40 and 300 nm. However, measured values should be within ±30% from 20 to 400 nm. Studies characterizing LDSA in urban and microenvironments are becoming available [e.g., (Geiss et al., 2016; Kuuluvainen et al., 2016)] as are studies of health effects studies using LDSA [e.g., (Endes et al., 2017; Soppa et al., 2017)].

It should be noted that transfer into region *r* from another region may also occur. Such situations in which a region receives a portion of its burden from another region are common in the lung, for example, mucus clearance of the segmental bronchi into the lobar bronchi, which clear into the main bronchi, which in turn clear into the trachea. In addition, the clearance from one region can transfer burden into more than one other compartment, e.g., soluble particles in the airways may be cleared into the blood as well as via the mucus. Multiple pathways for clearance of insoluble particles exist. The main alveolar particle clearance pathway is macrophage mediated clearance with macrophage migration to the ciliated airways, but macrophage or particles themselves may also move from the alveoli into the lymph and remerge in the ciliated airways or blood. There are also considerable species differences in rates of clearance that should be considered for interspecies extrapolations evaluating chronic exposure scenarios.

4.2 Particle Deposition

Inhaled particles may be either exhaled or deposited in the ET, TB, or alveolar region. A particle becomes deposited when it moves from the airway lumen to the wall of an airway. The deposition of particles in the respiratory tract depends primarily on inhaled particle size, route of breathing (nasal or oronasal), tidal volume (V_T), breathing frequency (f), and respiratory tract morphology. The distinction between air passing through the nose versus the mouth is important since the nasal passages more effectively remove inhaled particles than the oral passage. Respiratory tract morphology, which affects

[43] One instrument offered the option of measuring LDSA for either the alveolar or the tracheobronchial region.

particle transport and deposition, varies between species, the size of an animal or human, and health status.

The fraction of inhaled aerosol becoming deposited in the human respiratory tract has been measured experimentally. Studies, using light scattering or particle counting techniques to quantify the amount of aerosol in inspired and expired breaths, have characterized total particle deposition for varied breathing conditions and particle sizes. The vast majority of in vivo data on the regional particle deposition has been obtained by scintigraphic methods where external monitors are used to measure gamma emissions from radiolabeled particles. These scintigraphic data have shown highly variable regional deposition with sites of highly localized deposition or "hot spots" in the obstructed lung relative to the healthy lung. Even in the healthy lung, "hot spots" occur in the region of airway bifurcations. Mathematical models aid in predicting the mixed effects of particle size, breathing conditions, and lung volume on total and regional deposition. Experimentally, however, there is considerable interindividual variability in total and regional deposition even when inhaled particle size and breathing conditions are strictly controlled. Section 4.2.4 on Biological Factors Modulating Deposition provides more detailed information on factors affecting deposition among individuals.

4.2.1 Mechanisms of Deposition

Particle deposition in the lung is predominantly governed by diffusion, impaction, and sedimentation. Most discussion herein focuses on these three dominant mechanisms of deposition. Simple interception, which is an important mechanism of fiber deposition, is not discussed in this chapter. Electrostatic and thermophoretic forces as mechanisms of deposition have not been thoroughly evaluated and receive limited discussion. Some generalizations with regard to deposition by these mechanisms follows, but should not be viewed as definitive rules. Both experimental studies and mathematical models have demonstrated that breathing patterns can dramatically alter regional and total deposition for all sized particles. The combined processes of aerodynamic and diffusive (or thermodynamic) deposition are important for particles in the range of 0.1 μm to 1 μm. Aerodynamic processes predominate above and thermodynamic processes predominate below this range. For detailed equations related to particle behavior in air and deposition in the human respiratory tract, the reader is referred to Annex D of ICRP (1994). Equations for calculation of deposition in the MPPD model are mostly summarized in Anjilvel and Asgharian (1995) and Asgharian and Price (2007) with physiological parameters summarized in Miller et al. (2016).

Diffusive deposition, by the process of Brownian diffusion, is the primary mechanism of deposition for particles having physical diameters of less than 0.1 μm. For particles having physical diameters of roughly between 0.05 and 0.1 μm, diffusive deposition occurs mainly in the small distal bronchioles and the pulmonary region of the lung. However, with further decreases in particle diameter

below ~0.05 μm, increases in particle diffusivity shift more deposition proximally to the bronchi and ET regions.

Governed by inertial or aerodynamic properties, impaction, and sedimentation increase with d_{ae}. When a particle has sufficient inertia, it is unable to follow changes in flow direction and strikes a surface thus depositing by the process of impaction. Impaction occurs predominantly at bifurcations in the proximal airways, where linear velocities are at their highest and secondary eddies form. Sedimentation, caused by the gravitational settling of a particle, is most important in the distal airways and pulmonary region of the lung. In these regions, residence time is the greatest and the distances that a particle must travel to reach the wall of an airway are minimal.

The electrical charge on some particles may result in an enhanced deposition over what would be expected based on size alone. With an estimated charge of 10−50 negative ions per particle, Scheuch et al. (1990) found deposition of 0.5 μm particles in humans (V_T = 500 mL, f = 15 min^{-1}) to increase from 13.4% (no charge) to 17.8% (charged). This increase in deposition is thought to result from image charges induced on the surface of the airway by charged particles. Yu (1985) estimated a charge threshold level above which deposition fractions would be increased of about 12, 30, and 54% for 0.3, 0.6, and 1.0 μm diameter particles, respectively. Electrostatic deposition is generally considered negligible for particles below 0.01 μm because so few of these particles carry a charge at Boltzmann equilibrium. This mechanism is also thought to be a minor contributor to overall particle deposition, but it may be important in some laboratory studies due to specific aerosol generation techniques such as nebulization. Laboratory methods such as passage of aerosols through a Kr-85 charge neutralizer prior to inhalation are commonly used to mitigate this effect.

The National Radiological Protection Board (NRPB) evaluated the potential for corona discharges from high voltage power lines to charge particles and enhance particulate doses (NRPB, 2004). They concluded that electrostatic effects would be the most important for particles in the size range from about 0.1−1 μm, where deposition may theoretically increase by a factor of three to ten. However, given that only a small fraction of ambient particles would pass through the corona to become charged, the small range of relevant particle sizes (0.1−1 μm), and the subsequent required transport of charged particles to expose individuals; the NRPB concluded that effects, if any, of electric fields on particle deposition in the human respiratory tract would likely be minimal.

When assessing particle behavior in the lower respiratory tract, it is important to consider how temperature affects their behavior. The mean free path of particles in air (i.e., the distance that particle travel in a given direction before colliding with an air molecule) and the dynamic viscosity of inhaled air are affected by the increased temperature in the lower respiratory tract relative to standard temperature and pressure. The mean free path increases from 66.4 nm at 20°C to 71.2 nm at 37°C (Briant, 1990). The dynamic viscosity of air increases from 1.82×10^{-4} poise at 20°C to 1.90×10^{-4} poise at 37°C (Briant, 1990). Due to these two parameters, the diffusivity of particles <0.1 μm is 1.08 times higher at 37 than 20°C. For micron sized particles, the time that it takes particles to change directions in response to a

change in the direction of airflow as well as the settling velocity of particles are decreased by about 4% at 37°C relative to 20°C. Thus, diffusive deposition is increased, whereas aerodynamic deposition is decreased at 37°C relative to 20°C.

There is less of an effect of body temperature on the particle behavior in the upper respiratory tract. Nasal mucosal temperatures decrease during inspiration and increase during expiration (Bailey et al., 2017; Lindemann et al., 2002). During inhalation of room temperature air (23−25°C), anterior mucosal temperatures can cycle 3−6°C between inspiration and expiration. More distally, 1°C fluctuations are observed at the nasopharynx, with average expiratory mucosal temperatures of 34°C (Lindemann et al., 2002). This indicates the temperature of inhaled air cannot achieve body temperature until it reaches the lower respiratory tract.

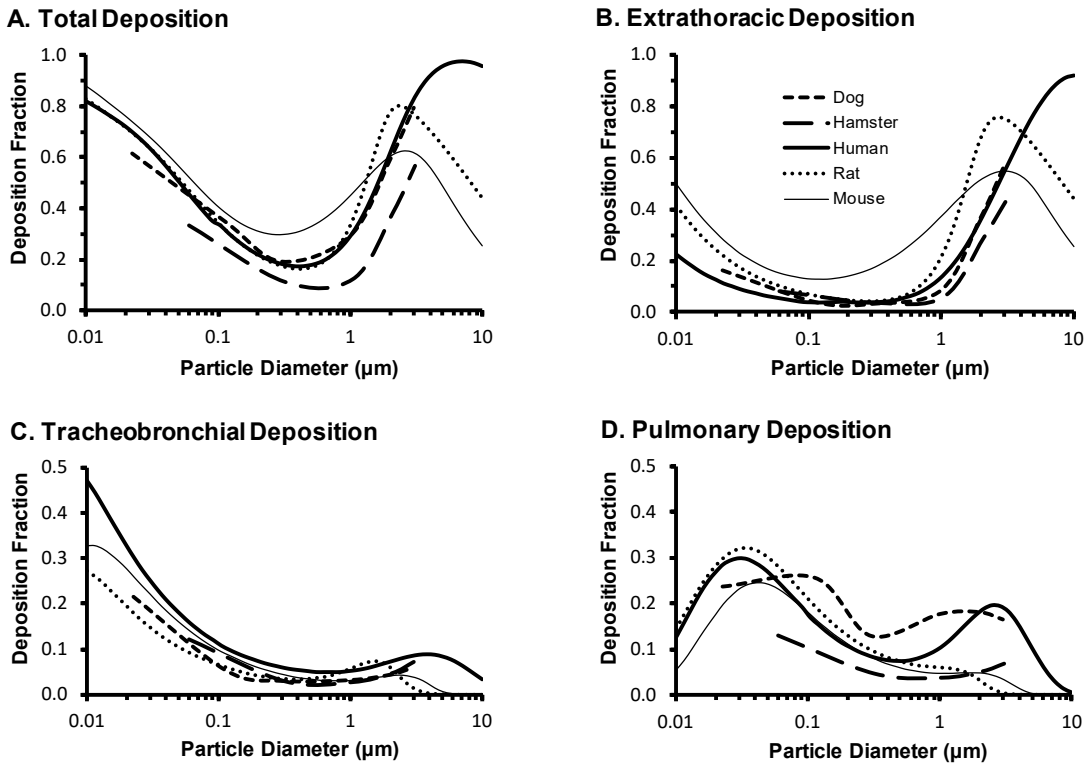
Thermophoretic forces on particles occur due to temperature differences between respired air and respiratory tract surfaces. Temperature gradients of around 20°C are thought to produce sufficient thermophoretic force to oppose diffusive and electrostatic deposition during inspiration and to perhaps augment deposition by these mechanisms during expiration (Jeffers, 2005). Thermophoresis is only relevant in the extrathoracic and large bronchi airways and reduces to zero as the temperature gradient decreases deeper in the lung. Theoretical analysis of thermophoresis has been done for smooth walled tubes and is important over distances that are several orders of magnitude smaller than the diameter of the trachea. The alteration of the flow patterns by airway surface features such as cartilaginous rings may affect particle transport and deposition over far greater distances than thermophoretic force.

4.2.2 Deposition Patterns

Knowledge of sites where particles of different sizes deposit in the respiratory tract and the amount of deposition therein is necessary for understanding and interpreting the health effects associated with exposure to particles. Particles deposited in the various respiratory tract regions are subjected to large differences in clearance mechanisms and pathways and, consequently, retention times. Deposition patterns in the human respiratory tract were described in considerable detail in dosimetry chapters of prior PM AQCD (U.S. EPA, 2004, 1996); as such, they are only briefly described here.

Predicted total and regional particle deposition in several mammalian species are illustrated in Figure 4-5. For all the species illustrated in Figure 4-5, ET deposition was based on experimental data at specific particle sizes or empirical fits to experimental data, while TB and pulmonary deposition were based on theoretical losses by diffusion, sedimentation, and impaction in species specific models of lower airways morphology. The predicted deposition for the human (male), mouse (unrestrained), and rat are for respiratory parameters in Table 4-1 using the MPPD model (Version 3.04, ©2016). Miller et al. (2016) reviews recent additions to the MPPD model that contribute to the ability to conduct cross-species extrapolations of both deposition and clearance. The effects of physiologic parameters on deposition in humans and rats free of respiratory disease are also described by de Winter-Sorkina and Cassee (2002).

The predicted deposition for the dog (V_T = 170 mL, f = 11.7 min^{-1}) and hamster (V_T = 0.72 mL, f = 59 min^{-1}) are based on Yeh (1980). The trends and magnitude of particle deposition are quite similar between the illustrated species. In the mouse and rat, due to particle inhalability, there is a gradual decrease in total and ET deposition for particles greater than about 2.5 to 3 µm. In the human, a similar decline in total deposition due to particle inhalability starts becoming apparent for particles above 7 to 8 µm.



Source: Permission pending, Adapted and updated from Brown (2015).

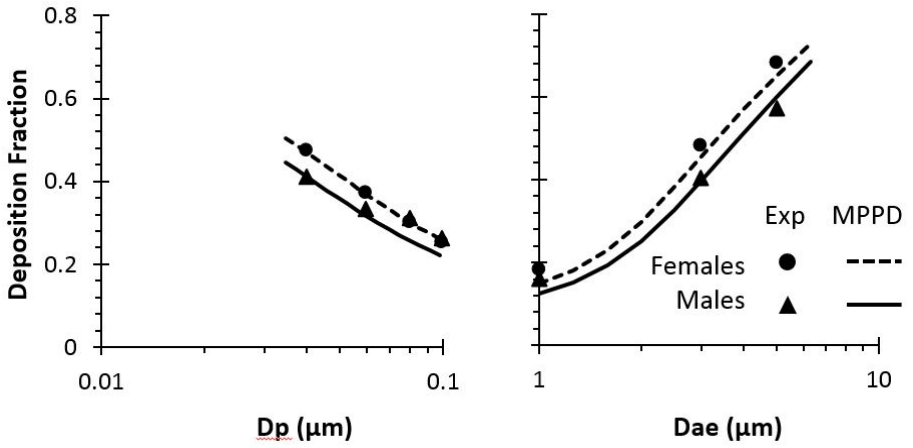
Figure 4-5. Predicted total and regional particle deposition adjusted for particle inhalability in select mammalian species. (A) Total deposition, (B) Extrathoracic deposition, (C) Tracheobronchial deposition, (D) Pulmonary deposition.

4.2.2.1 Total Respiratory Tract Deposition

Across mammalian species, the efficiency of deposition in the respiratory tract may generally be described as a "U shaped" curve on a plot of deposition efficiency versus the of log particle diameter as illustrated in Figure 4-5. Total deposition shows a minimum for particle diameters in the range of 0.1 to 1.0 µm, where particles are small enough to have minimal sedimentation or impaction and sufficiently

large so as to have minimal diffusive deposition. Total deposition does not decrease to zero for any sized particle, in part, because of mixing between particle laden tidal air and residual lung air. The particles mixed into residual air remain in the lung following a breath and are removed on subsequent breaths or gradually deposited. Total deposition approaches 100% for particles of roughly 0.01 µm due to diffusive deposition and for particles of around 10 µm due to the efficiency of sedimentation and impaction.

Total human lung deposition, as a function of particle size, is depicted in Figure 4-6. These experimental data were obtained by using monodisperse spherical test particles in healthy adults during controlled tidal breathing (V_T, 500 mL; f, 15 min^{-1}) on a mouthpiece. The experimental ultrafine data are for 11 males (age, 31 ± 4 years; FRC, 3,911 mL) and 11 females (age, 31 ± 4 years; FRC, 3,314 mL) from Jaques and Kim (2000). The fine and coarse data are for eight males (age, 31 ± 7 years; FRC, 3,730 mL) and seven females (age, 31 ± 6 years; FRC, 3,050 mL) from Kim and Hu (2006). The MPPD (Version 3.04) model used an upper airway volume of 40 mL and 50 mL for males and females, respectively, and the FRC from studies to predict particle deposition. Assuming isotropic expansion and contraction of the airways, scaling the airway morphology (length and diameters) to the cube root of volume, the model predictions are in good agreement with the mean experimental data.



Note: See text for more detail.

Source: Permission pending, Human data from Jaques and Kim (2000) and Kim and Hu (2006) with predicted deposition obtained from the MPPD model (Version 3.04).

Figure 4-6. Experimental (Exp) and predicted (MPPD) total lung deposition for controlled tidal breathing on a mouthpiece.

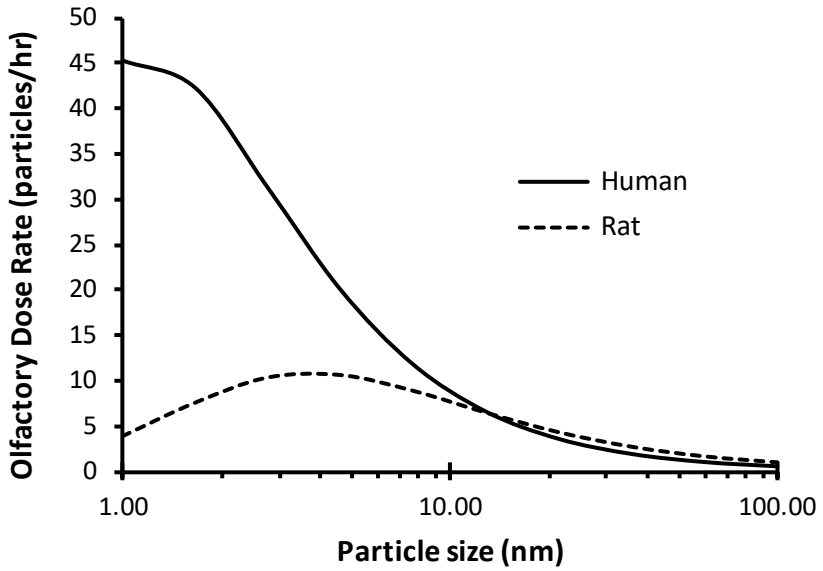
4.2.2.2 Extrathoracic Region

The first line of defense for protecting the lower respiratory tract from inhaled particles is the nose and mouth. Particle deposition in the ET region, especially the nasal passages, reduces the amount available for deposition in the TB and alveolar regions. Most of the new studies in the last PM ISA (U.S. EPA, 2009) were largely derived from computational fluid dynamics (CFD) modeling and experimental measurements in casts. Those studies generally reported that for particles >1 μm, deposition efficiency in the oral and nasal passages is a function of an impaction parameter (Stokes number) with the addition of a flow regime parameter (Reynolds number) for the oral passages. New studies are again largely derived from CFD modeling and experimental measurements in casts. Only a few new studies are discussed here, these were generally selected as those providing data for infants and children.

Several new papers from the same group describe nasal airway growth and particle deposition based on studies of nasal casts (Xi et al., 2014; Zhou et al., 2014; Zhou et al., 2013; Xi et al., 2012). The casts are for a 10-day old girl, 7-month old girl, a 5-year old boy, and a 53-year old man. The papers provide morphological data and total and regional deposition data (in vitro and CFD) for ultrafine and larger-sized particles (2−28 μm). For UFP, CFD simulations showed good agreement with other published studies of deposition in nasal casts for adults, infants, and children. Predicted ultrafine deposition was low (<10%) for particles larger than 10 nm, but rose rapidly to between 70 and 90% as particle size decreased to 1 nm (Xi et al., 2012). For particles ≤5 nm (not larger sizes), deposition also increased with decreasing flow (3 to 45 L/min), but this effect was less marked than the increase in deposition with decreasing particle size. Overall, the nasal deposition fractions of among the casts were rather similar when assessed as a function of a diffusion factor ($D^{0.5}Q^{-0.28}$; where, D is the particle diffusion coefficient and Q is flow rate). As a function of this diffusion factor, the deposition fractions were nearly identical for the 5-year old boy and 53-year old man with these two casts having greater deposition than those for the two younger girls' casts. For larger particles (monodisperse, 2−28 μm) delivered under resting breathing conditions, deposition data were well predicted and similar among all five casts as a function of a modified-impaction factor ($d_{ae}^2\Delta p^{2/3}$; where, Δp is the pressure drop across the nasal cast).

Another group has also recently published a series of experimental and CFD simulations of particle deposition in casts (Garcia et al., 2015; Schroeter et al., 2015; Garcia et al., 2009). The modified-impaction factor used by Zhou et al. (2014) was adopted from Garcia et al. (2009), who found that this factor better collapsed deposition factions among five adult nasal casts than several definitions of the Stokes number for nasal casts. More recently, Garcia et al. (2015) provided simulations of total ultrafine nasal deposition as well as that on the olfactory mucosa of humans and rats. Similar to Xi et al. (2012), these authors found that total nasal deposition in humans was low (<10%) for particles above about 10 nm, below which size deposition increased rapidly with decreasing particle size. Rats were predicted to have greater total and olfactory deposition than humans. However, due the much higher ventilation rate of humans than rats, humans were predicted to experience greater dose per olfactory

surface area for particles between 1 and 7 nm; above this size the dose per surface area was slightly greater in rats than humans. Figure 4-7 illustrates the olfactory dose rate of particles in humans and rats not normalized to olfactory surface area. Schroeter et al. (2015) provided experimental and CFD simulations for total and regional deposition of particles between 2.6 and 14.3 µm. For 5 to 14.3 µm particles inhaled during rest (Q, 16.5 L/min) about 2−5.5% deposition in the olfactory region was measured experimentally. In general, the CFD predicted pattern of deposition shifted proximally in the nose with increasing inspiratory flow and particle size. Nasal deposition was minimal for particles below 3 µm and 100% for the 14.3 µm particles.



Source: Permission pending, Based on empirical equations in Garcia et al. (2009) and Garcia et al. (2015).

Figure 4-7. Predicted nanoparticle olfactory dose rate (particles/hour) for resting ventilation (human, 7.5 L/min; rat, 0.288 L/min) and a concentration of one particle/cm^3 at any given particle size.

Some other recently published studies have used in vitro and in silico models to examine oral and nasal particle deposition in infants. Kim et al. (2014) used CFD simulations to evaluate particle inhalability (see Section 4.1.5) and penetration into the lower respiratory tract of a 7-month old. For quiet nasal breathing (Q, 5 L/min), the authors reported about 13.8% deposition of 2.5 µm particles in the nose, 0.4% in the lower-pharynx, and 11.8% in the larynx. As a point of clarification, the authors provided data separately for the nasopharynx which is the upper-pharynx and the pharynx.[44] For quiet oronasal

[44] Based on Figure 1a of Kim et al. (2014), it appears that the "pharynx" as used in the paper is the lower-pharynx or oropharynx which begins at the soft palate and extends to the openings of the larynx and esophagus.

breathing (Q, 5 L/min; 35% nasal, 65% oral), the authors reported about 3.9% deposition of 2.5 µm particles in the nose, 2.2% in the mouth, 6.9% in the lower-pharynx, and 17.2% in the larynx. Counter to studies in adults, oronasal breathing increased particle losses in the head by greatly increased deposition in the lower-pharynx and larynx. Amirav et al. (2014) also provide data suggesting greater ET removal of particles during oral than nasal breathing at typical breathing rates for 5-, 14-, and 20-month-olds. Aerosols were generated using a Respimat® soft mist inhaler which produces an aqueous aerosol with a mode in the range of 1.1−2.1 µm, although almost 50% of the aerosol mass associated with particles >3.3 µm (Zierenberg, 1999). Amirav et al. (2014) found for the 5- and 14-month-olds that the amount of aerosol penetrating the upper respiratory tract was significantly greater through the oral passages than the nose. At 20-months of age, the particle loses in the nasal and oral passages were equivalent. In contrast with adults, these studies suggest that the nasal airways of infants may have lower particle removal efficiency than the oral airway.

While these in silco (CFD) and in vitro (casts) data are informative, they are not in agreement with existing experimental data. Figure 4-8 illustrates experimental human nasal deposition data for adults and children (Bennett et al., 2008; Becquemin et al., 1991) and predictive equation fitting four children's' and an adult cast deposition data (Zhou et al., 2014). Becquemin et al. (1991) provide data for 20 children (6 M, 14 F; 5−15 years, mean 10 years) and 10 adults (5 M, 5 F; 21−54 years, mean 36 years) who inhaled 1, 2, and 3 µm particles under breathing conditions simulating rest and moderate exercise. Bennett et al. (2008) provide data for 12 children (9 M, 3 F; 6−10 years) and 11 adults (6 M, 5 F; 18−27 years) who inhaled 1 and 2 µm particles under breathing conditions simulating rest and light exercise. For Figure 4-8, mean total nasal deposition (η_{total}) data for particles were extracted from Table 2 of Becquemin et al. (1991) and Table 3 of Bennett et al. (2008). Assuming inspiratory and expiratory deposition efficiency were equivalent, inspiratory nasal deposition efficiency (η_{insp}) was calculated as:

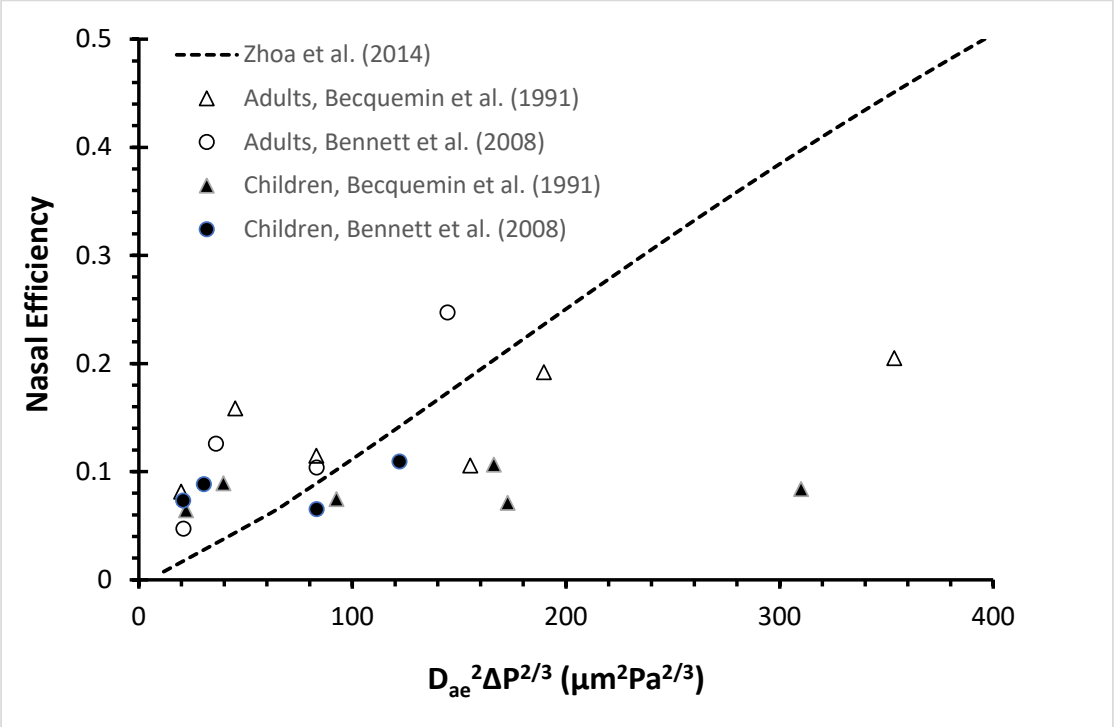
$$\eta_{insp} = 1 - \sqrt{1 - \eta_{total}}$$

Equation 4-6

The pressure drop (Δp) across the nose was calculated as the product of nasal resistance and inspiratory flow provided in the papers. The equation fitting deposition and in five nasal casts (4 children, 1 adult) of is not predictive of mean nasal deposition either in children or adults. The mean deposition for adults tends to exceed that of children.

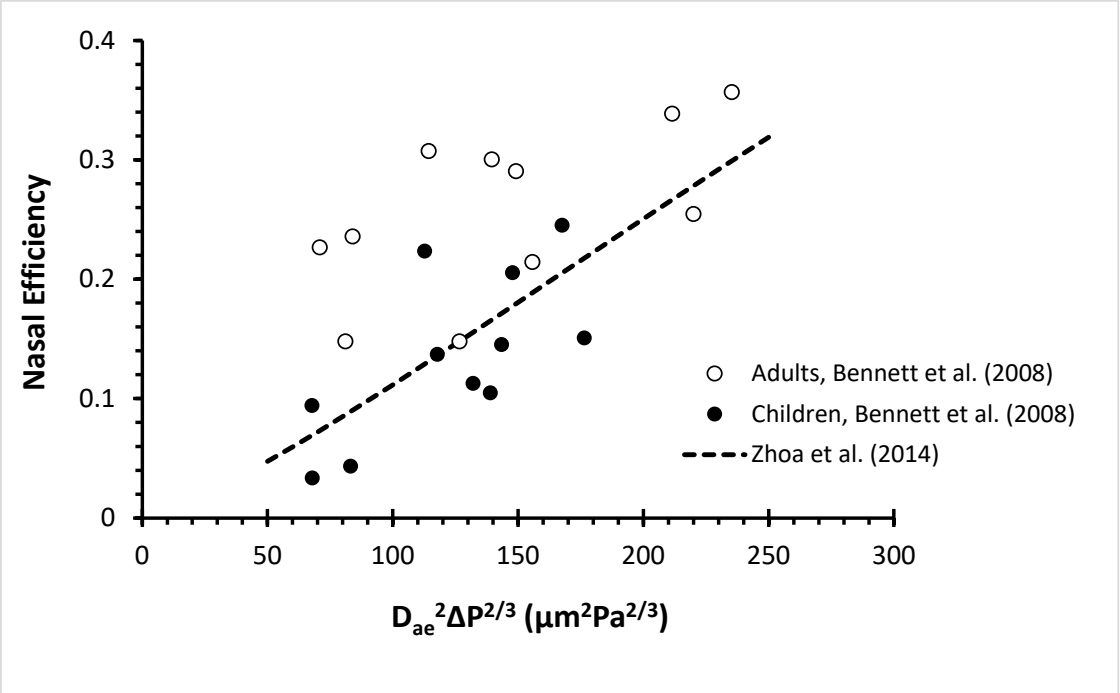
Figure 4-9 illustrates experimental human nasal deposition data for 2 µm particles in adults and children (Bennett et al., 2008) with the predictive equation fitting nasal cast deposition data (Zhou et al., 2014). The predictive equation fits the data for children fairly well ($r = 0.67$, $p = 0.024$). However, the fit of adults provides a negative r^2, showing that the mean is a better predictor or nasal deposition efficiency in adults than the Zhou et al. (2014) model. Bennett et al. (2008) used linear regression to examine the relationship between total nasal deposition and pressure drop and found that the intercept was significantly increased in adults relative to children. That is, as illustrated in Figure 4-9, there was overlap in $d_{ae}^2 \Delta p^{2/3}$ between adults and children, but adults had greater nasal deposition than children. Similarly,

Becquemin et al. (1991) provided plots of total nasal deposition against the modified-impaction factor, $d_{ae}^2\Delta p^{2/3}$. Although there was considerable overlap in $d_{ae}^2\Delta p^{2/3}$ between children and adults, nasal deposition again tended to be greater in adults than in children.



Source: Permission pending, Human data from Becquemin et al. (1991) and Bennett et al. (2008) with inspiratory nasal deposition efficiency estimated using Equation 4-6.

Figure 4-8. Comparison of group mean human nasal deposition data with nasal cast deposition data. Nasal efficiency during inspiration is plotted as a function of the modified impaction parameter. See text for more details.



Source: Permission pending, Human data extracted from Figure 5B of Bennett et al. (2008) with inspiratory nasal deposition efficiency estimated using Equation 4-6.

Figure 4-9. Comparison of individual level data for 2 µm inspiratory nasal deposition efficiency in during light exercise in adults and children with nasal cast model efficiency. Individual level deposition data are for 11 children and 11 adults. See text for more details.

Theory, CFD modeling, and research measuring deposition in nasal casts show that nasal deposition efficiency increases with increasing particle size and Δp across the cast. Consistent with that evidence, the ICRP (1994) Human Respiratory Tract Model recommends the use of scaling factors to increase nasal deposition in children relative to adults. For the children (V_T, 478 mL; *f*, 28 min^{-1}; 6−10 years of age) and adults (V_T, 940 mL; *f*, 20 min^{-1}) in Figure 4-9, the ICRP model predicts a η_{insp} for 2 µm particles of 0.275−0.338 (scaling factor of 1.26 for 10 year olds and 1.58 for 6 year-olds) and η_{insp} of 0.217 (scaling factor of 1.0 for adults). The mean experimental η_{insp} were 0.136 and 0.257 in children and adults, respectively. Recognizing that experimental data showed lower nasal deposition in children than adults, Brown et al. (2013) recommended using a scaling factor of one for estimates of nasal efficiency in children. Using a scaling factor of one for children (V_T, 478 mL; *f*, 28 min^{-1}), the ICRP model predicts η_{insp} of 0.173 for 2 µm particles. The scaling factor needs to be reduced to 0.89 to match the experimental η_{insp} of 0.136 for 2 µm particles in the Bennett et al. (2008) study. Although theory and studies using casts suggest increase nasal deposition efficiency with increasing Δp across the nose, experimental data show less nasal deposition in children than adults.

4.2.2.3 Tracheobronchial and Alveolar Region

Inhaled particles passing the ET region enter and may become deposited in the lungs. For any given particle size, the pattern of particle deposition influences clearance by partitioning deposited material among lung regions. Deposition in the tracheobronchial airways and alveolar region cannot be directly measured in vivo. Much of the available deposition data for the TB and alveolar regions have been obtained from experiments with radioactively labeled, poorly soluble particles (U.S. EPA, 1996) or by use of aerosol bolus techniques (U.S. EPA, 2004). In general, the ability of these experimental data to define specific sites of particle deposition is limited to anatomically large regions of the respiratory tract such as the head, larynx, bronchi, bronchioles, and alveolar region. Mathematical modeling can provide more refined predictions of deposition sites. Highly localized sites of deposition within the bronchi are described in Section 4.2.2.4. Both experimental and modeling techniques are based on many assumptions that may be relatively good for the healthy lung but not for the diseased lung. For discussion of these issues, the reader is referred to Section 4.2.4.4 and Section 4.2.4.5.

The ICRP (1994) relied on scintigraphic and aerosol bolus techniques to estimate TB deposition. Due to concern that these methods may have led to an overestimation of deposition in the TB airways, Brown et al. (2013) used the MPPD model to determine particle penetration through the TB airways. That is, in ascertaining regional lung deposition, there are uncertainties in the ICRP (1994) assessment of TB deposition due to slow particle clearance from the TB airways and the penetration of even shallowly inhaled aerosol boluses into the alveolar region. These would lend toward an overestimation of TB particle deposition and likewise an underestimation of alveolar deposition using ICRP (1994) formulas. However, the ICRP (1994) model might be preferable since it was based on human experimental data, whereas the MPPD model is a deterministic model based on theoretical deposition in a series of tubes. Accordingly, a comparison of the models was provided by Brown et al. (2013). Most apparent for oral breathing due to low ET particle removal, the 50% cut points were between 0.5 and 1 μm smaller using the ICRP (1994) versus the MPPD model. This finding is consistent with the supposition that the ICRP (1994) model overestimates TB deposition.

4.2.2.4 Sites of Localized Deposition

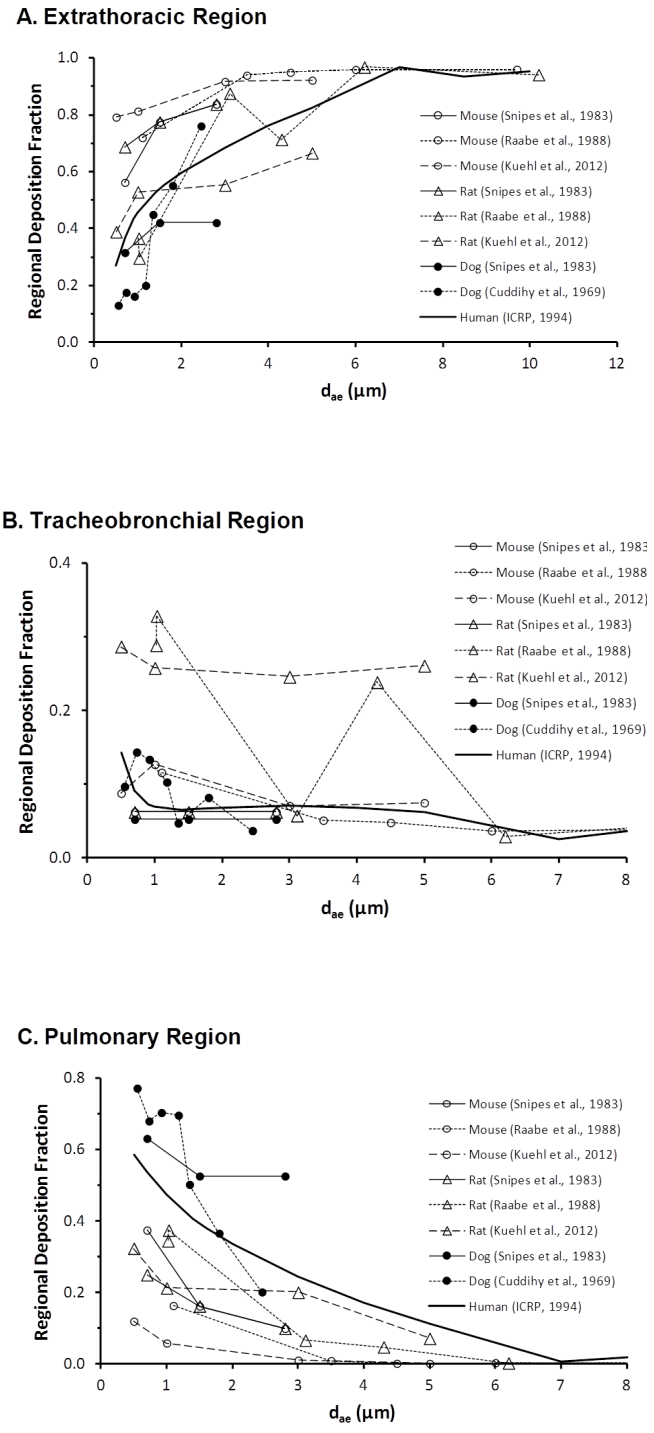
From a toxicological perspective, it is important to realize that not all epithelial cells in an airway will receive the same dose of deposited particles. Localized deposition in the vicinity of airway bifurcations has been analyzed using experimental and mathematical modeling techniques as described in prior reviews (U.S. EPA, 2009, 2004, 1996). Although there are a couple of new papers describing localized ultrafine, fine, and coarse particle deposition in the olfactory region of humans (see Section 4.3.3.1, Olfactory Delivery), there do not appear to be recent papers describing localized deposition in the tracheobronchial airways.

In the 1996 PM AQCD (U.S. EPA, 1996), experimental data were available illustrating the peak deposition of coarse particles (3, 5, and 7 μm d_{ae}) in daughter airways during inspiration and the parent airway during expiration, but always near the carinal ridge (Kim and Iglesias, 1989). In the 2004 PM AQCD (U.S. EPA, 2004), mathematical models predicted distinct "hot spots" of deposition in the vicinity of the carinal ridge for both coarse (10 μm) and ultrafine (0.01 μm) particles (Heistracher and Hofmann, 1997; Hofmann et al., 1996). In a model of lung Generations 4−5 during inspiration, hot spots occurred at the carinal ridge for 10 μm d_{ae} particles due to inertial impaction and for 0.01 μm particles due to secondary flow patterns formed at the bifurcation. During expiration, preferential sites of deposition for both particle sizes occurred (1) approaching the juncture of daughter airways on the walls forming and across the lumen from the carinal ridge; and (2) the top and bottom (visualizing the Y-shaped geometry laying horizontal) of the parent airway downstream of the bifurcation.

Studies reviewed in the 2009 ISA (U.S. EPA, 2009) further support these findings. Most of these studies quantified localized deposition in terms of an enhancement factor. Typically, the enhancement factor was the ratio of the deposition in a prespecified surface area (e.g., 100 × 100 μm which corresponds to ~10 × 10 epithelial cells) to the average deposition density for the whole airway geometry. Enhancement factors are very sensitive to the size of the surface considered (Balashazy et al., 1999). The deposition of 0.001 μm is rather uniform, however, the deposition pattern became increasingly less uniform with increasing particle size (Farkas and Balásházy, 2008; Farkas et al., 2006). For particles greater than ~0.01 μm, some cells located near the carinal ridge of bronchial bifurcations may receive hundreds to thousands of times the average dose (particles per unit surface area) of the parent and daughter airways. The inertial impaction of particles ≥1 μm d_{ae} at the carinal ridge of large bronchi also increases with increasing inspiratory flows.

4.2.3 Interspecies Patterns of Deposition

Across species comparisons of the modeling of total, extrathoracic, tracheobronchial, and alveolar deposition were provided in Figure 4-5. In general, there are consistent patterns in predicted deposition among species with the exception of rodents having lower deposition of particles larger than 2.5−3 μm due to lower inhalability of rodents relative to larger mammals. Figure 4-10 illustrates the experimental regional deposition in mice, rats, dogs, and humans. Regional deposition is the fraction of particles found in each compartment relative to total respiratory tract deposition.



Source: Permission pending, Brown (2015).

Figure 4-10. Experimental regional particle deposition (normalized to total deposition) in select mammalian species. (A) extrathoracic deposition (nasal breathing); (B) tracheobronchial deposition; and (C) pulmonary deposition.

Within a given species, considerable between study variability is apparent (see Figure 4-10). Some of the within species variability may be attributable to breathing pattern. Kuehl et al. (2012) reported breathing patterns for mice (V_T = 0.20 mL, f = 275 min^{-1}) and rats (V_T = 1.71 mL, f = 181 min^{-1}). The f reported by Kuehl et al. (2012) for mice are similar to those of restrained mice in Table 4-1. Neither Raabe et al. (1988) nor Snipes et al. (1983) reported breathing patterns. On average, Cuddihy et al. (1969) reported a V_T of 164 mL and f of 12 min^{-1} in dogs. However, there was considerable within dog variability among the aerosol exposures in the Cuddihy et al. (1969) study, with V_T ranging from 130 to 200 mL and f ranging from 8 to 20 min^{-1}. The human data are for a male with resting breathing pattern (V_T = 625 mL, f = 12 min^{-1}) as predicted by the ICRP (1994) Human Respiratory Tract Model. There are some limited scintigraphic regional deposition data for three baboons (10−14 kg; 6.3 ± 0.5 years of age) from Albuquerque-Silva et al. (2014). Similar to data in Figure 4-10, the baboon data showed increasing extrathoracic deposition with increasing particle size from 0.23 to 2.8 µm (activity median aerodynamic diameter).

Despite the within and between species differences, some trends become apparent from this figure. First, the ET fraction generally increases with decreasing species size and increasing particle size. Second, the pulmonary fraction generally decreases with decreasing species size and increasing particle size. Third, the TB fraction is a small component of the overall deposition. With respect to this third observation, however, it should be noted that due to relatively small surface area of the TB region, delivered surface doses can be quite high.

4.2.4 Factors Modulating Deposition

4.2.4.1 Physical Activity

The activity level of an individual is well recognized to affect their minute ventilation and route of breathing. Changes in minute ventilation during exercise are accomplished by increasing both V_T and f (Table 4-2). As discussed in Section 4.1.3, route of breathing generally changes from the nose when at rest to increasingly through the mouth with increasing activity level. There is considerable variability in both the route by which people breathe and is affected by sex, age, nasal resistance, and upper airway infection and inflammation.

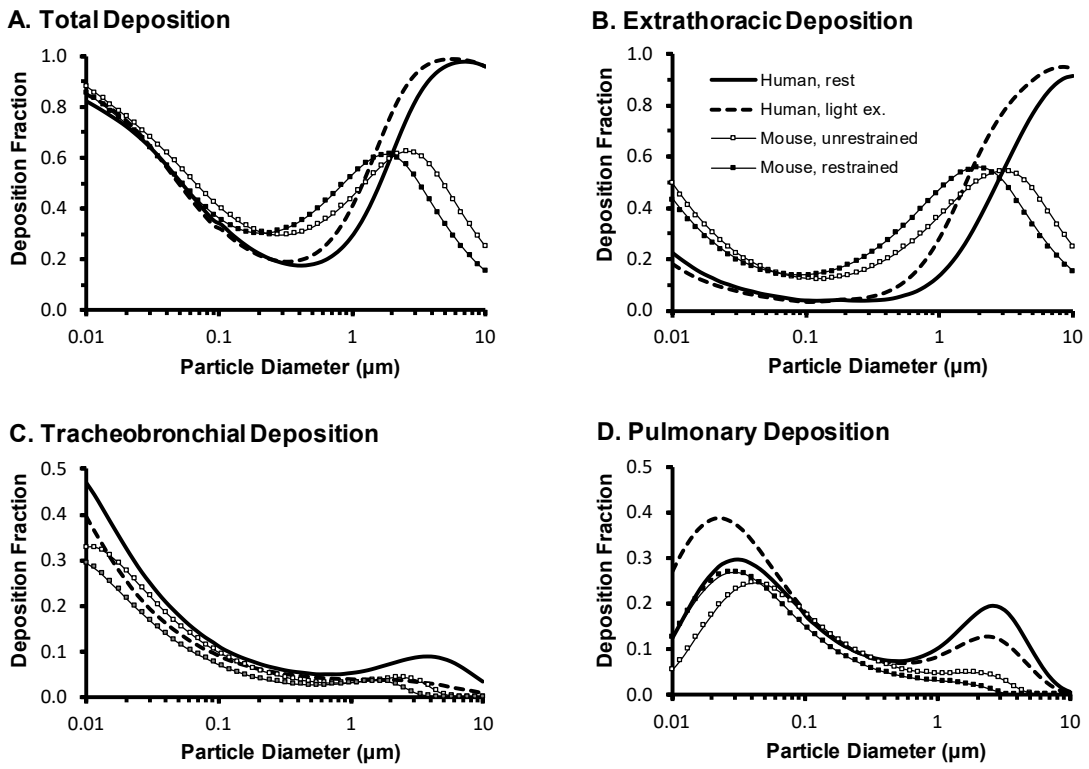
Table 4-2. Breathing patterns with activity level in adult human male.

Activity	Awake Rest[a]	Slow Walk[a]	Light Exertion[a]	Moderate Exertion[a]	Heavy Exertion[b]
Breaths/min	12	16	19	28	26
Tidal volume, mL	625	813	1,000	1,429	1,923
Minute ventilation, L/min	7.5	13	19	40	50

[a]de Winter-Sorkina and Cassee (2002).
[b]ICRP (1994).

When individuals increase their ventilation with activity the total number of particles inhaled per unit time (i.e., exposure rate) increases, but the fractional deposition of particles in each breath also changes with breathing pattern. Figure 4-11 illustrates the particle deposition at two breathing patterns in both a human and mouse. During exercise, both V_T and *f* increase. Fractional deposition for all particles increases with increased V_T. Increasing the *f*, however, decreases the fractional deposition of $PM_{2.5}$ and UFPs due to decreased time for gravitational and diffusive deposition. For particles of larger than a d^{ae} of roughly 3 μm, increasing *f* can increase the deposition fraction due to increased impaction in the extrathoracic and TB airways. Thus, it should be expected that the change in deposition fraction with activity will vary among individuals depending on the relative influences of these two variables (i.e., V_T and *f*) in a given subject and the particle size to which they are exposed.

Experimentally, the lung deposition fractions of fine particles during moderate exercise and mouth breathing are unchanged between rest and exercise (Bennett et al., 1985; Morgan et al., 1984). Löndahl et al. (2007) also found no difference in deposition fractions of particles (hygroscopic and hydrophobic; 0.013−0.290 μm mobility diameter of dry particles) between rest (V_T = 0.72 ± 0.15 L; *f* = 12 ± 2 min^{-1}) and exercise (V_T = 2.1 ± 0.5 L; *f* = 17 ± 4 min^{-1}). Kim (2000) evaluated differences in deposition of 1, 3, and 5 μm particles under varying breathing patterns (simulating breathing conditions of sleep, resting, and mild exercise). Total lung deposition increased with increasing V_T at a given flow rate and with increasing flow rate at a given breathing period. These experimental studies suggest that the total deposited dose rate (i.e., deposition per unit time) of particles will generally increase in direct proportion to the increase in minute ventilation associated with exercise.



Source: Permission pending, Deposition fractions estimated using MPPD (Version 3.04) model.

Figure 4-11. Effect of increasing minute ventilation on total and regional deposition. Human, rest (V_T, 625 mL; *f*, 12 min^{-1}); Human, light exercise (V_T, 1,000 mL; *f*, 19 min^{-1}); Mouse, unrestrained (V_T, 0.19 mL; *f*, 145 min^{-1}); Mouse, restrained (V_T, 0.22 mL; *f*, 290 min^{-1}).

The changes in ventilation, i.e., breathing pattern and flow rate, may also alter the regional deposition of particles. Coarse particle deposition increases in the TB and ET regions during exercise due to the increased flow rates and associated impaction. A rapid-shallow breathing pattern during exercise may result in more bronchial airway versus alveolar deposition, while a slow-deep pattern will shift deposition to deeper lung regions (Valberg et al., 1982). Bennett et al. (1985) showed for 2.6 μm particles that moderate exercise shifted deposition from the lung periphery towards ET and larger, bronchial airways. Similarly, Morgan et al. (1984) showed that even for fine particles (0.7 μm) TB deposition was enhanced with exercise. This shift in deposition toward the bronchial airways results in a much greater dose per unit surface area of tissue in those regions. Morgan et al. (1984) also found that the apical-to-basal distribution of fine particles increased with exercise, i.e., a shift towards increased deposition in the lung apices. This shift may be less likely for larger particles, however, whose deposition

in large airway bifurcations may preclude their transport to these more apical regions (Bennett et al., 1985).

4.2.4.2 Age

Airway structure and respiratory conditions vary with age, and these variations may alter the amount and site of particle deposition in the respiratory tract. It was concluded in the 2004 PM AQCD (U.S. EPA, 2004) that significant differences between adults and children had been predicted by mathematical models and observed in experimental studies. Modeling studies generally indicated that ET and TB deposition was greater in children and that children received greater doses of particles per lung surface area than adults. Experimental studies show lower nasal particle deposition in children than adults (see Figure 4-9). Relative to adults, children also tend to breathe more through their mouth (see Section 4.1.3 Route of Breathing) which is less efficient for removing inhaled particles than the nose (see Section 4.1.6 Thoracic and Respirable Particles). For typical activity levels and route of breathing, the 50% cut-size for the thoracic fraction is at an aerodynamic diameter of around 3 μm in adults and 5 μm in children. These findings suggest that the lower respiratory tract of children may receive a higher intake dose of ambient PM compared to adults. Recent experimental studies suggest increased lower respiratory tract deposition fraction of particles in children relative to adults, but this may be an artifact of the methodology.

As discussed in the last PM ISA (U.S. EPA, 2009), during oral breathing on a mouthpiece, Bennett and Zeman (1998) measured the deposition fraction of inhaled, fine particles (2 μm d_{ae}) in children (age 7−14 years, n = 16), adolescents (age 14−18 years, n = 11), and adults (age 19−35 years, n = 12) as they breathed the aerosol with their natural, resting breathing pattern. The deposition fraction of particles was not significantly different among age groups. Among the children, variation in deposition fractions was highly dependent on inter-subject variation in V_T, but not height which is a predictor of lung volume. However, there was no difference in deposition fractions between children and adults for these fine particles. This finding and the modeling predictions (Hofmann et al., 1989) are explained, in part, by the smaller V_T and faster breathing rate of children relative to adults for natural breathing conditions. Bennett et al. (2008) also reported measures of fine particle (1 and 2 μm) deposition at ventilation rates typical of rest and light exercise in children (age 6−10 years, n = 12) and adults (age 18−27 years, n = 11). This study also found that the deposition of 2 μm d_{ae} particles during oral breathing and under conditions of rest and light exercise did not differ significantly between children and adults. However, the DF of 1 μm d_{ae} particles during oral breathing was significantly increased in adults relative to children for both breathing rates. The authors attributed increased DF in adults to mixing of inhaled aerosol with reserve air. Deposition during nasal inhalations, were significantly increased in adults relative to children for the 2 μm particles at both breathing patterns (rest and light exercise) and for the 1 μm particles during light exercise. Across all children and adults, the deposition of both 1 and 2 μm particles was generally a function of residences time within the lungs and depth of breathing. Because children breathe at higher

minute ventilations relative to their lung volumes, the rate of deposition of fine particles normalized to lung surface area may be greater in children versus adults (Bennett and Zeman, 1998).

Rissler et al. (2017a) also measured deposition in children and adults, but who were spontaneous breathing on a mouthpiece. On average, across all particle sizes (15 nm to 5 µm), the deposition fraction tended to be greater by 11% ($1\text{-}DF_{child}/DF_{adult}$) in children (n = 7; 7−12 years; V_T, 0.51 ± 0.13 L; *f*, 16 ± 3 min^{-1}) than adults (n = 60; 20−67 years; V_T, 0.73 ± 0.22 L; *f*, 11 ± 3 min^{-1}). Absolute difference in the deposition fractions between children and adults were 5% for 15 nm to 50 nm particles; 3−4% for 50 nm to 1.9 µm particles; 6−10% for 1.9 µm to 5 µm particles. Generally consistent with Bennett and Zeman (1998) and Bennett et al. (2008), stepwise regression showed the best predictors of deposition for prespecified size ranges (e.g., 15−30 nm and 1.3−1.9 µm) to be V_T, time of breathing cycle, anatomic dead space, and a measure of airway resistance. For most particle sizes, deposition decreased increasing anatomic dead space; deposition increased with increasing V_T, time of breathing cycle, and airway resistance.

Olvera et al. (2012) measured hygroscopic particle deposition during spontaneous breathing on a mouthpiece in healthy men (n = 5; age, 26 ± 7 years; V_T, 0.66 ± 0.34 L; *f*, 13 ± 2 min^{-1}), healthy boys (n = 8; age, 13 ± 2 years; V_T, 0.37 ± 0.20 L; *f*, 18 ± 10 min^{-1}), and boys with asthma (n = 9; age, 12 ± 3 years; V_T, 0.38 ± 0.20 L; *f*, 16 ± 5 min^{-1}). The authors estimated a total deposition fraction for a polydisperse UFPs (median, 40 nm; GSD, 1.9) of 0.48 for the healthy children and 0.54 for the asthmatic children, the latter of which was significantly ($p = 0.002$) greater than 0.36 for the adults.

The tendencies for increased deposition in healthy children versus healthy adults in the Rissler et al. (2017a) and Olvera et al. (2012) studies could, in large part, be due to spontaneous breathing on a mouthpiece. Spontaneous breathing on a mouthpiece generally results in increases in V_T and decreases in *f* (long breathing period) relative to natural unencumbered breathing (Bennett et al., 1996). Both of these changes in breathing pattern (i.e., the increase in V_T and decrease in *f*) cause increases in deposition by diffusion and sedimentation. If these changes were equivalently affecting both children and adults, then a comparison of the relative deposition fractions may be unaffected. For natural breathing, Bennett et al. (2008) found that V_T as a fraction of resting lung volume (i.e., $V_T/(FRC + V_T)$) was not different between adults and children (0.14 ± 0.03 vs. 0.16 ± 0.04, respectively); whereas, for spontaneous breathing on a mouthpiece in the Rissler et al. (2017a) study, the different between adults and children (0.21 ± 0.16 vs. 0.25 ± 0.05, respectively) is statistically significant by a two-tailed *t*-test ($p = 0.011$) based on data in supplemental materials (Rissler et al., 2017b). Spontaneous breathing on a mouthpiece resulted in an increase in V_T relative to lung volume that was larger for children than adults which in and of itself may have led to the tendency for greater deposition in children versus adults.

In 62 healthy adults with normal lung function aged 18−80 years, Bennett et al. (1996) showed there was no effect of age on the whole lung deposition fractions of 2-µm particles under natural breathing conditions. Across all subjects, the deposition fractions were found to be independent of age, depending on breathing period ($r = 0.58$, $p < 0.001$) and airway resistance ($r = 0.46$, $p < 0.001$). In the

same adults breathing with a fixed pattern (360 mL V_T, 3.4 s breathing period), there was a mild decrease in deposition with increasing age, which could be attributed to increased peripheral airspace dimensions in the elderly.

4.2.4.3 Sex

Males and females differ in body size, conductive airway size, and ventilatory parameters; therefore, sex differences in deposition might be expected. In some of the controlled studies, however, the men and women were constrained to breathe at the same V_T and *f*. Since women are generally smaller than men, the increased minute ventilation of women compared to their normal ventilation could affect deposition patterns. This may help explain why sex related effects on deposition have been observed in some studies. As discussed in Section 4.1.3, females have a greater nasal breathing contribution than males across all ages. This reduces exposure and deposition of particles in the lower respiratory tract of females relative to males under normal breathing conditions.

(Kim and Hu, 1998) assessed the regional deposition patterns of 1-, 3-, and 5-µm particles in healthy adult males and females using controlled breathing on a mouthpiece. The total fractional deposition in the lungs was similar for both sexes with the 1-µm particle size, but was greater in women for the 3- and 5-µm particles. Deposition also appeared to be more localized in the lungs of females compared to those of males. Kim and Jaques (2000) measured deposition in healthy adults using sizes in the ultrafine mode (0.04−0.1 µm). Total fractional lung deposition was greater in females than in males for 0.04- and 0.06-µm particles. The region of peak fractional deposition was shifted closer to the mouth and peak height was slightly greater for women than for men for all exposure conditions. The total lung deposition data for these ultrafine aerosols in men and women are illustrated in Figure 4-6 in Section 4.2.2.1, data for the coarse particles are form a different study (Kim and Hu, 2006) than discussed above. As illustrated in Figure 4-6, difference between males and females were relatively well predicted by the MPPD model. These differences can generally be attributed to the smaller size of the upper airways, particularly of the laryngeal structure, and smaller airways in the lungs of females than males.

In another study by Bennett et al. (1996), the total respiratory tract deposition of 2-µm particles was examined in adult males and females aged 18−80 years who breathed with a normal resting pattern. There was a tendency for a greater deposition fractions in females compared to males. However, since males had greater minute ventilation, the deposition rate (i.e., deposition per unit time) was greater in males than in females. Bennett and Zeman (2004) found no difference in the deposition of 2-µm particles in boys versus girls aged 6−13 years (n = 36).

4.2.4.4 Body Mass Index

Bennett and Zeman (2004) expanded their measures of fine particle deposition during resting breathing to a larger group of healthy children (6−13 years; 20 boys, 16 girls) and found again that the variation in total deposition, was best predicted by V_T ($r = 0.79$, $p < 0.001$). But both V_T and resting minute ventilation increased with both height and body mass index (BMI) of the children. Interestingly, these data suggest that for a given height and age, children with higher BMI have larger minute ventilations and V_T at rest than those with lower BMI. These differences in breathing patterns as a function of BMI translated into increased deposition of fine particles in the heaviest children. The rate of deposition (i.e., particles depositing per unit time) in the overweight children was 2.8 times that of the leanest children ($p < 0.02$). Among all children, the rate of deposition was significantly correlated with BMI ($r = 0.46$, $p < 0.004$). Some of the increase in deposition fractions of heavier children may be due to their elevated V_T, which was well correlated with BMI ($r = 0.72$, $p < 0.001$).

Consistent with the findings of Bennett and Zeman (2004), ventilation rates are increased in overweight individuals compared to those of normal weight (Brochu et al., 2014). For example, median daily ventilation rates (m^3/d) are about 1.2 times greater in overweight (>85th percentile body mass index [BMI]) than normal weight children (5−10 years of age). In 35−45-year-old adult males and females, ventilation rates are 1.4 times greater in overweight (BMI ≥ 25 kg/m^2) than normal weight (18.5 to <25 kg/m^2 BMI) individuals. Across all ages, overweight/obese individuals respire greater amounts of air and associated pollutants than age matched normal weight individuals. As discussed in Section 4.1.3 (Route of Breathing), some studies suggest that obese children may breathe a higher fraction through the mouth than normal weight children. Increased minute ventilation, a potentially lower nasal breathing fraction, and increased DF with increasing BMI would all lead to greater rates of deposition in the lung as well.

4.2.4.5 Anatomical Variability

Anatomical variability, even in the absence of respiratory disease, can affect deposition throughout the respiratory tract. The ET region is the first exposed to inhaled particles and, therefore, deposition within this region would reduce the amount of particles available for deposition in the lungs. Variations in relative deposition within the ET region will, therefore, propagate through the rest of the respiratory tract, creating differences in calculated doses among individuals.

The influence of variations in nasal airway geometry on particle deposition has been investigated. Cheng et al. (1996) examined nasal airway deposition in healthy adults using particles ranging in size from 0.004 to 0.15 μm and at two constant inspiratory flow rates, 167 and 333 mL/s. Interindividual variability in deposition was correlated with the wide variation of nasal dimensions; in that, greater surface area, smaller cross-sectional area, and increasing complexity of airway shape were all associated

with enhanced deposition. Bennett and Zeman (2005) have also shown that nasal anatomy influences the efficiency of particle uptake in the noses of adults. For light exercise breathing conditions in adults, their study demonstrated that nasal deposition efficiencies for both 1 and 2 μm monodisperse particles were significantly less in African Americans versus Caucasians. The lesser nasal efficiencies in African-Americans were associated with both lower nasal resistance and less elliptical nostrils compared to Caucasians.

Within the lungs, the branching structure of the airways may also differ between individuals. Zhao et al. (2009) examined the bronchial anatomy of the left lung in patients (132 M, 84 W; mean age 47 years) who underwent conventional thoracic computed tomography scans for various reasons. At the level of the segmental bronchus in the upper and lower lobes, a bifurcation occurred in the majority of patients. A trifurcation, however, was observed in 23% of the upper and 18% of the lower lobes. Other more unusual findings were also reported such as four bronchi arising from the left upper lobe bronchus.

Anatomic variability is also seen in other species. Miller et al. (2014) provide noticeably differing TB morphologies between two Sprague-Dawley rats of quite similar weight and lung volume. Although the patterns of depositing between lung regions were nearly identical, the morphometric differences in the TB airways caused slightly increased deposition (1−4% absolute difference) of 1 to 3 μm in this region of one rat relative to the other. However, across rat strains, Miller et al. (2014) found large differences in deposition patterns across all particle sizes (0.01−10 μm) with Sprague-Dawley having increased TB and decreased PU particle deposition relative to a Long-Evans rat. For example, with endotracheal exposure the deposition fractions in the TB region for 0.03 and 3 μm particles were 30 and 80% (respectively) in the Sprague-Dawley, whereas they were only 10 and 30% (for 0.03 and 3 μm, respectively) in the Long-Evans rat. However, the PU deposition was much greater for particles <0.1 and >1 μm in the Long-Evans than the Sprague-Dawley rat. More interesting, for the case of an endotracheal exposure, particles >3 μm were able to penetrate through the TB airways to deposit in the PU region of the Long-Evans rat, whereas the PU deposition was effectively zero by 4 μm in the Sprague-Dawley.

As described in Section 4.2.2.4, deposition can be highly localized near the carinal ridge of bifurcations. The effect of a bifurcation versus other branching patterns on airflow patterns and particle deposition has not been described in the literature. Martonen et al. (1994) showed that a wide blunt carinal ridge shape dramatically affected the flow stream lines relative to a narrower and more rounded ridge shape. Specifically, there were high flow velocities across the entire area of the blunt carinal ridge versus a smoother division of the airstream in the case of the narrow-rounded ridge shape. The implication may be that localized particle deposition on the carinal ridge would increase with ridge width. A similar situation might be expected for a trifurcation versus a bifurcation. These differences in branching patterns provide a clear example of anatomical variability among individuals that might affect both air flow patterns and sites of particle deposition.

4.2.4.6 Ventilation Distribution

Regional deposition in excess of regional ventilation to poorly ventilated areas has been reported for aerosols in the 0.5 to 1.0 μm size range and attributed to increased residence time in obstructed areas (Susskind et al., 1986; Trajan et al., 1984). However, others show increasing deposition with increasing ventilation. For instance, a significant association of increased aerosol (1.2 μm) deposition in better ventilated regions has been observed in lung transplant patients with bronchiolitis obliterans (O'Riordan et al., 1995). The trend for increased aerosol (0.78 μm) deposition with increasing ventilation has also been reported in normal individuals and asymptomatic smokers (Chamberlain et al., 1983). Other studies using similar sized aerosols, have found no association between ventilation distribution and particle deposition (O'Riordan and Smaldone, 1994; Smaldone et al., 1991). All of these studies compared regional ventilation to the regional particle deposition using scintigraphic methods. The mixed results in these studies may be due to deposition not having a simple monotonic relationship with ventilation.

Brown et al. (2001) examined the relationship of 5 μm particles in healthy adults (n = 11) and patients with cystic fibrosis (n = 12) using scintigraphic techniques. Deposition of particles in the TB airways followed the pattern of ventilation in the healthy individuals, whereas it was inversely related to ventilation in the patients. This is consistent with Kim et al. (1983) who found the pattern of particle deposition (3.0 μm) followed ventilation distribution in a three generation model, but was enhanced in the vicinity of obstructions. Consistent with Brown et al. (2001) data in healthy individuals, Verbanck et al. (2016) recently found experimentally and using CFD modeling that the regional deposition of coarse particles (6 μm) followed regional ventilation in a human airway cast which extended out to the fifth airway generation at inspiratory flows mimicking light and heavy exercise.

In the alveolar region, Brown et al. (2001) found deposition very strongly associated with ventilation distribution in the patients, i.e., the well-ventilated regions received increased alveolar deposition of particles relative to poorly ventilated regions. A similar trend was observed in the healthy individuals, but a more uniform pattern of ventilation lead to smaller differences in ventilation and deposition between lung regions. The recent experimental study of healthy adults (n = 7) by Sá et al. (2017) supports that alveolar deposition of coarse particles (5 μm) is directory proportional ventilation. As extreme example of no regional ventilation in patients with mild-to-moderate asthma, (King et al., 1998) reported large wedge-shaped regions of the lung which were absent the deposition of 0.12 μm particles.

With regard to interpreting the above discussion of coarse particle (5−6 μm) deposition in the lungs, it should be stress that the experimental and modeling work done with oral breathing on a mouthpiece. Referring back to Section 4.1.6 and Figure 4-3, these coarse particles would not be expected to reach the lower respiratory tract during nasal breathing.

4.2.4.7 Respiratory Tract Disease

The presence of respiratory tract disease can affect airway structure and ventilatory parameters, thus altering deposition compared to that occurring in healthy individuals. The effect of airway diseases on deposition has been studied extensively, as described in the 1996 and 2004 PM AQCD (U.S. EPA, 2004, 1996) and the 2009 PM ISA (U.S. EPA, 2009). Studies described therein showed that people with chronic obstructive pulmonary disease (COPD) had very heterogeneous deposition patterns and differences in regional deposition compared to healthy individuals. People with obstructive pulmonary diseases tended to have greater deposition in the TB region than did healthy people. Furthermore, there tended to be an inverse relationship between bronchoconstriction and the extent of deposition in the alveolar region, whereas total respiratory tract deposition generally increased with increasing degrees of airway obstruction. There are some limited new data available for children with asthma.

Olvera et al. (2012) measured hygroscopic particle deposition during spontaneous breathing on a mouthpiece in healthy men (n = 5; age, 26 ± 7 years; V_T, 0.66 ± 0.34 L; *f*, 13 ± 2 min^{-1}), healthy boys (n = 8; age, 13 ± 2 years; V_T, 0.37 ± 0.20 L; *f*, 18 ± 10 min^{-1}), and boys with asthma (n = 9; age, 12 ± 3 years; V_T, 0.38 ± 0.20 L; *f*, 16 ± 5 min^{-1}). The children with asthma had about 2−4% (absolute difference) greater deposition than healthy children for particles between 10−90 nm, and above this size the data converged. Across all particles sizes, the children with asthma had 8% (absolute difference) greater deposition than adults, this difference ranged from 3% for 11 nm particles to 10% for 200 nm particles. The authors estimated a total deposition fraction for a polydisperse UFPs (median, 40 nm; GSD, 1.9) of 0.48 for the healthy children and 0.54 for the asthmatic children, the latter of which was significantly (p = 0.002) greater than 0.36 for the adults. As discussed in Section 4.2.4.2, spontaneous breathing on a mouthpiece may have resulted in an increase in V_T relative to lung volume that was larger for children than adults which may have led to the tendency for greater deposition in children versus adults. It is not clear if asthma additionally affected breathing patterns. A prior study of adults using a fixed breathing pattering showed a greater deposition fraction of 1 µm particles in individuals with asthma relative to healthy adults (22 vs. 14%, respectively) (Kim and Kang, 1997).

The vast majority of deposition studies in individuals with respiratory disease have been performed during controlled breathing, i.e., all subjects breathed with the same V_T and *f*. However, although resting V_T is similar or elevated in people with COPD compared to healthy individuals, the former tend to breathe at a faster rate, resulting in higher than normal tidal peak flow and resting minute ventilation. Thus, given that breathing patterns differ between healthy and obstructed individuals, particle deposition data for controlled breathing may not be appropriate for estimating respiratory doses or dose rates from ambient PM exposures.

Bennett et al. (1997) measured the fractional deposition of insoluble 2 µm particles in moderate-to-severe COPD patients (n = 13; mean age 62 years) and healthy older adults (n = 11; mean age 67 years) during natural resting breathing. COPD patients had about a 1.6-times greater deposition fraction and a 1.5-times greater resting minute ventilation relative to the healthy adults. As a result, the

patients had an average deposition rate of about 2.4-times that of healthy adults. Similar to previously reviewed studies (U.S. EPA, 2004, 1996), these investigators observed an increase in deposition with an increase in airway resistance, suggesting that deposition increased with the severity of airway disease. Across a broad range of obstructive disease severity using a fixed breathing pattern, Kim and Kang (1997) previously reported the deposition of 1 μm particles to be well associated with several measures of lung function.

Brown et al. (2002) measured the deposition of UFPs (CMD = 0.033 μm) during natural resting breathing in 10 patients with moderate-to-severe COPD (mean age 61 years) and nine healthy adults (mean age 53 years). The COPD group consisted of seven patients with chronic bronchitis and three patients with emphysema. The total deposition fraction in the bronchitic patients (DF, 0.67) was significantly ($p < 0.02$) greater than in either the patients with emphysema (DF, 0.48) or the healthy subjects (DF, 0.54). Minute ventilation increased with disease severity (healthy, 5.8 L/min; chronic bronchitic, 6.9 L/min; emphysema, 11 L/min). Relative to the healthy subjects, the average dose rate was significantly ($p < 0.05$) increased by 1.5 times in the COPD patients, whereas the average deposition fraction only tended to be increased by 1.1 times. These data further demonstrate the need to consider dose rates (which depend on minute ventilation) rather than just deposition fractions when evaluating the effect of respiratory disease on particle deposition and dose.

Most of the available literature on particle deposition in the diseased lung have considered obstructive lung disease. There are some limited data showing ultrafine and fine particle (0.02−0.25 μm) deposition fractions are similar between healthy adults and those with restrictive lung disease (Anderson et al., 1990). However, individuals with restrictive lung disease have an increased minute ventilation relative to individuals with normal lungs (Tobin et al., 1983b). Thus, as described above for individuals with obstructive disease, it should be expected that dose rate for particulate matter would be increased in individuals with restrictive lung disease due to their increased ventilation rates comparted to individuals free of lung disease.

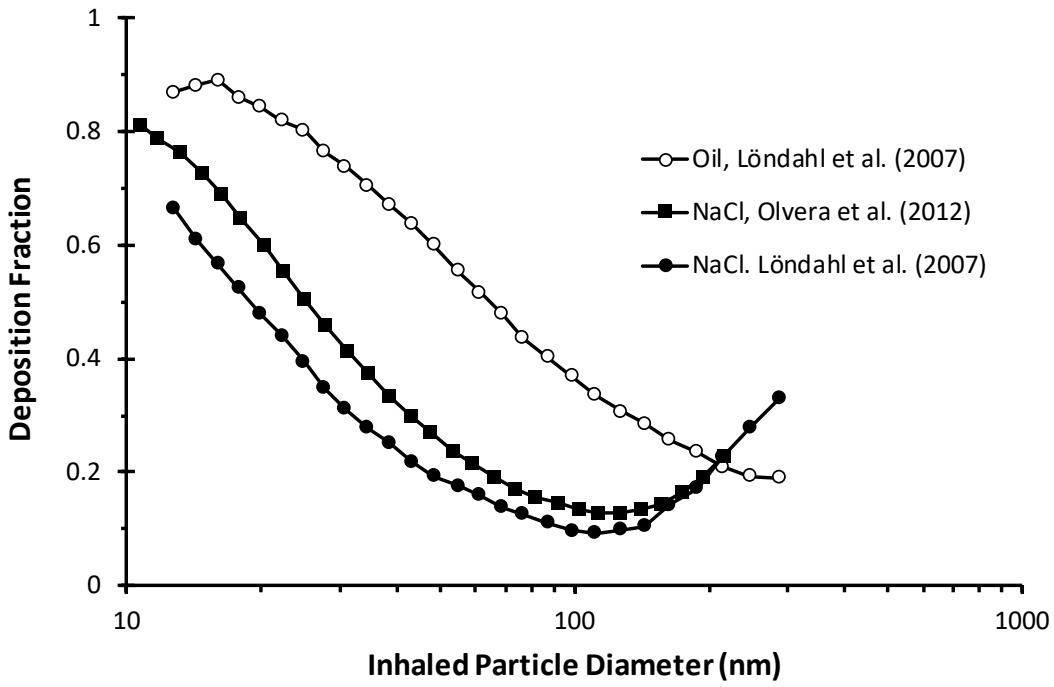
4.2.4.8 Particle Hygroscopicity

In an individual during controlled breathing (V_T = 0.75−1.0 L; f = 15 min^{-1}), Tu and Knutson (1984) found minimal deposition in the range of 0.06 to 0.09 μm for hygroscopic particles, whereas it was in the range 0.3 to 0.6 μm for hydrophobic particles. The deposition curves for hygroscopic and hydrophobic particles intersected at approximately 0.15 μm in the Tu and Knutson (1984) study. This implies that hygroscopic growth reduced diffusive deposition below 0.15 μm and increased aerodynamic deposition above this particle size. Nonhygroscopic particles around 0.3 μm have minimal intrinsic mobility and low total deposition in the lungs. Hygroscopic 0.3 μm (dry diameter) salt particles will grow to nearly 2 μm in the respiratory tract and deposit to a far greater extent than hydrophobic 0.3 μm particles (Anselm et al., 1990).

Löndahl et al. (2007) measured particle deposition in 29 individuals (20 M, 9 F; median age, 25 years) who inhaled hygroscopic and hydrophobic particles between 0.013 and 0.290 μm (mobility diameter of dry particles) by mouth during spontaneous breathing (not their natural breathing pattern measured prior to being on a mouthpiece) while engaged in rest ($V_T = 0.72 \pm 0.15$ L; $f = 12 \pm 2$ min^{-1}) or exercise ($V_T = 2.1 \pm 0.5$ L; $f = 17 \pm 4$ min^{-1}). Deposition fractions for each particle type were minimally affected by sex or activity. The prior study by Tu and Knutson (1984) found the deposition curves for hygroscopic and hydrophobic particles were also generally unaffected by route of breathing. Figure 4-12 illustrates deposition curves for hygroscopic and hydrophobic particles inhaled during rest in the Löndahl et al. (2007) study. From this figure, it is seen that the growth of 0.02 to 0.03 μm hygroscopic particles lowers their diffusive deposition to that of 0.07 μm hydrophobic particles. Deposition of the hygroscopic particles reached a minimum in the range of 0.1 to 0.14 μm. Hygroscopic growth reduced diffusive deposition below 0.2 μm and increased aerodynamic deposition above this particle size.

Olvera et al. (2012) also measured hygroscopic particle deposition during spontaneous breathing on a mouthpiece in five healthy men (age, 26 ± 7 years; V_T, 0.66 ± 0.34 L; f, 13 ± 2 min^{-1}), eight healthy boys (age, 13 ± 2 years; V_T, 0.37 ± 0.20 L; f, 18 ± 10 min^{-1}), and nine boys with asthma (age, 12 ± 3 years; V_T, 0.38 ± 0.20 L; f, 16 ± 5 min^{-1}). The data for the adult males appear in Figure 4-12 for comparison with the data by Löndahl et al. (2007).

Ferron et al. (2013) provide a model for hygroscopic particle deposition in the rat lung and compare with the predicted deposition in humans (adult male only). The paper illustrates the effect of particle size on the time required to its equilibrium size in the respiratory tract. As particle size is increased from 0.05 to 0.5 and to 2.0 μm, the time to reach equilibrium increased from 0.01 s to 1 s and to 10 s, respectively. The effect of varied hygroscopicity on particle equilibrium size and deposition were also provided. For example, given the same inhaled particle size, sodium chloride grows to about twice as large as zinc sulfate. Relative to hydrophobic particles, total deposition decreased for sodium chloride particles <0.3 μm and decreased for zinc sulfate particles <0.4 μm due to the reduction in diffusivity with increasing size due to particle growth. Above these sizes (i.e., 0.3 to 0.4 μm), total deposition increased due to the increase in inertial properties relative to hydrophobic particles. The reduction in diffusive deposition and increase in inertial deposition were more pronounced for sodium chloride than zinc sulfate relative to hydrophobic particles. For relaxed, resting breathing, Ferron et al. (2013) predicted that hygroscopic growth would affect deposition mainly for particles between 0.02 and 5 μm in the rat and between 0.02 and 6 μm in adult human males.



Source: Permission pending, Adapted from Löndahl et al. (2007) and Olvera et al. (2012).

Figure 4-12. Total deposition fraction of hygroscopic sodium chloride (NaCl) and hydrophobic diethylhexylsebacate oil aerosols in adults during oral breathing at rest as a function of dry particle diameter.

4.2.5 Summary

Particle deposition in the respiratory tract occurs predominantly by diffusion, impaction, and sedimentation. Deposition is minimal for particle diameters in the range of 0.1 to 1.0 μm, where particles are small enough to have minimal sedimentation or impaction and sufficiently large so as to have minimal diffusive deposition. In humans, total respiratory tract deposition approaches 100% for particles of roughly 0.01 μm due to diffusive deposition and for particles of around 10 μm due to the efficiency of sedimentation and impaction.

The first line of defense for protecting the lower respiratory tract from inhaled particles is the nose and mouth. Nasal deposition approaches 100% in the average human for 10 μm particles. Experimental studies show lower nasal particle deposition in children than adults. Relative to adults, children also tend to breathe more through their mouth which is less efficient for removing inhaled particles than the nose. These findings suggest that the lower respiratory tract of children may receive a higher dose of ambient PM compared to adults. Since children breathe at higher minute ventilations

relative to their lung volumes, the rate of particle deposition normalized to lung surface area may be further increased relative to adults.

People with COPD generally have greater total deposition and more heterogeneous deposition patterns compared to healthy individuals. The observed increase in deposition correlates with increases in airway resistance, suggesting that deposition increases with the severity of airway obstruction. Destruction of peripheral airspaces, such as with emphysema, can decrease particle deposition on a breath by breath basis. However, COPD patients also have an increased resting minute ventilation relative to the healthy adults. This demonstrates the need to consider dose rates (which depend on minute ventilation) rather than just deposition fractions when evaluating the effect of respiratory disease on particle deposition and dose.

Modeling studies indicate that, for particles greater than ~0.01 μm, some cells located near the carinal ridge of bronchial bifurcations may receive hundreds to thousands of times the average dose (particles per unit surface area) of the parent and daughter airways. The inertial impaction of particles ≥1 μm at the carinal ridge of large bronchi increases with increasing inspiratory flows. Airway constriction can further augment the overall deposition efficiency of coarse particles at downstream bifurcations. These findings suggest that substantial doses of particles may be justified for in vitro studies using tracheobronchial epithelial cell cultures.

Our ability to extrapolate between species has improved since the 2009 ISA (U.S. EPA, 2009). However, some considerations related to coarse particles warrant comment. The inhalability of particles having of 2.5, 5, and 10 μm is 80, 65, and 44% in rats, respectively, whereas it remains near 100% for 10 μm particles in humans. In most laboratory animal species (rat, mouse, hamster, guinea pig, and dogs), deposition in the extrathoracic region is near 100% for particles greater than 5 μm. By contrast, in humans, nasal deposition approaches 100% for 10 μm particles. Oronasal breathing versus obligate nasal breathing further contributes to greater penetration of coarse particles into the lower respiratory tract of humans than rodents.

4.3 Particle Clearance

This section discusses the clearance and translocation of poorly soluble particles that have deposited in the respiratory tract. The term "clearance" is used here to refer to the processes by which deposited particles are removed by mucociliary action or phagocytosis from the respiratory tract. "Translocation" is used here mainly to refer to the movement of free particles across cell membranes and to extrapulmonary sites. In the literature, translocation may also refer to the extra and intracellular dissolution of particles and the subsequent transfer of dissociated material to the blood through extra and intracellular fluids and across the various cell membranes and lung tissues.

A basic overview of biological mechanisms and clearance pathways from various regions of the respiratory tract are presented in the following sections. Then regional kinetics of particle clearance are addressed. Subsequently, an update on interspecies patterns and rates of particle clearance is provided. The translocation of UFPs is also discussed. Finally, information on biological factors that may modulate clearance is presented.

4.3.1 Clearance Mechanisms

For any given particle size, the deposition pattern of poorly soluble particles influences clearance by partitioning deposited material between lung regions. Tracheobronchial clearance of poorly soluble particles in humans, with some exceptions, is thought (in general) to be complete within 24−48 hours through the action of the mucociliary escalator. Clearance of poorly soluble particles from the alveolar region is a much slower process which may continue from months to years.

4.3.1.1 Extrathoracic Region

Particles deposited in either the nasal or oral passages are cleared by several mechanisms. Particles depositing in the mouth may generally be assumed to be swallowed or removed by expectoration. Particles deposited in the posterior portions of the nasal passages are moved via mucociliary transport towards the nasopharynx and swallowed. Mucus flow in the most anterior portion of the nasal passages is forward, toward the vestibular region where removal occurs by sneezing, wiping, or nose blowing.

Smith et al. (2014) updates the extrathoracic clearance portion of the ICRP (1994) human respiratory tract model. Deposition in the extrathoracic regions is considered as divided among the anterior and posterior nasal passage, oropharynx, and, depending on route of breathing, the mouth. Regardless of inhaled particle size, deposition in the nasal passages is portioned to have 65% in the anterior and 35% in the posterior nose. Of the deposition in the anterior nose, 29% is cleared by nose blowing, 71% is cleared to the posterior nose from which nearly all is cleared to the gastro-intestinal (GI) tract with only 0.05% sequestered in the nose. This new model was based on a study of nasal clearance in healthy adults (8 M, 1 F; 43 ± 10 years) who inhaled ^{111}In-labeled particles of 1.5, 3, or 6 µm under conditions of rest and light exercise (Smith et al., 2011).

4.3.1.2 Tracheobronchial Region

Mucociliary clearance in the TB region has generally been considered to be a rapid process that is relatively complete by 24−48 hours post-inhalation in humans. Mucociliary clearance is frequently

modeled as a series of "escalators" moving material proximally from one generation to the next. As such, the removal rate of particles from an airway generation increases with increasing tracheal mucus velocity. Assuming continuity in the amount of mucus between airway generations, mucus velocities decrease and transit times within an airway generation increase with distal progression. Although clearance from the TB region is generally rapid, experimental evidence discussed in the 1996 and 2004 PM AQCD (U.S. EPA, 2004, 1996), showed that a fraction of material deposited in the TB region is retained much longer.

The slow-cleared TB fraction (i.e., the fraction of particles deposited in the TB region that are subject to slow clearance) was thought to increase with decreasing particle size. For instance, Roth et al. (1993) showed approximately 93% retention of UFPs (30 nm median diameter) thought to be deposited in the TB region at 24 hours post-inhalation. The slow phase clearance of these UFPs continued with an estimated half-time ($t_{1/2}$) of around 40 days. Using a technique to target inhaled particles (monodisperse 4.2 µm MMAD) to the conducting airways, Möller et al. (2004) observed that 49 ± 9% of particles cleared rapidly ($t_{1/2}$ of 3.0 ± 1.6 hours), whereas the remaining fraction cleared considerably slower ($t_{1/2}$ of 109 ± 78 days). The ICRP (1994) human respiratory tract model assumes particles ≤2.5 µm (physical diameter) to have a slow-cleared TB fraction of 50%. The slow-cleared fraction assumed by the ICRP (1994) decreases with increasing particle size to <1% for 9 µm particles. Considering the UFP data of Roth et al. (1993) in addition to data considered by the ICRP (1994), Bailey et al. (1995) estimated a slow-cleared TB fraction of 75% for UFPs. At that time, they (Bailey et al., 1995) also estimated the slow-cleared fraction to decrease with increasing particle size to 0% for particles ≥6 µm. Experimental evidence from the same group (Smith et al., 2008) showed no difference in TB clearance among humans for particles with geometric sizes of 1.2 µm versus 5 µm, but the same d_{ae} (5 µm) so as to deposit similarly in the TB airways. For at least micron-sized particles, these findings do not support the particle size dependence of a slow-cleared TB fraction. As discussed further below, much of the apparent slow-cleared TB fraction may be accounted for by differences in deposition patterns, i.e., greater deposition in the alveolar region than expected based on symmetric, bulk flow into the lungs without longitudinal mixing.

A portion of the slow cleared fraction from the TB region appears to be associated with the smaller, more distal bronchioles. For large particles (d_{ae} = 6.2 µm) inhaled at a very slow rate to theoretically deposit mainly in small ciliated airways, 50% had cleared by 24 hours post-inhalation. Of the remaining particles, 20% cleared with a $t_{1/2}$ of 2.0 days and 80% with a $t_{1/2}$ of 50 days (Falk et al., 1997). Using the same techniques, Svartengren et al. (2005) also reported the existence of long-term clearance in humans from the small airways. It should be noted that the clearance rates for the slow-cleared TB fraction still exceeds the clearance rate of the alveolar region in humans. Kreyling et al. (1999) targeted inhaled particle (2.5 µm) deposition to the TB airways of adult beagle dogs and subsequently quantified particle retention using scintigraphic and morphometric analyses. Despite the use of shallow aerosol bolus inhalation to a volumetric lung depth of less than the anatomic dead space, 25% of inhaled particles deposited in alveoli. At 24 and 96 hours post-inhalation, more than 50% of the retained particles were in alveoli. However, 40% of particles present at 24 and 96 hours were localized to

small bronchioles of between 0.3 and 1 mm in diameter. Collectively, these studies suggest that although mucociliary clearance is fast and effective in healthy bronchi and larger bronchioles, it is less effective and sites of longer retention exist in smaller bronchioles.

The underlying sites and mechanisms of long-term retention in the bronchioles remain largely unknown. Several factors may contribute to the existence or experimental artifact of slow clearance from the smaller TB airways. Even when inhaled to very shallow lung volumes, some particles reach the alveolar region (Kreyling et al., 1999). Therefore, experiments utilizing bolus techniques to target inhaled particle deposition to the TB airways may have had some deposition in the alveolar region. This may occur due to variability in path length and the number of generations to the alveoli (Asgharian et al., 2001) and/or differences in regional ventilation (Brown and Bennett, 2004). Nonetheless, the experimentally measured clearance rates measured for the slow cleared TB fraction are faster than that of the alveolar region in both humans and canines. Thus, although experimental artifacts likely occur, they do not discount the existence of a slow cleared TB fraction. To some extent, it is possible that the slow cleared TB fraction may be due to distal bronchioles that do not have a continuous ciliated epithelium as in the larger bronchi and more proximal bronchioles. Neither path length, ventilation distribution, nor a discontinuous ciliated epithelium explains an apparently slow cleared TB fraction with decreasing particle size below 0.1 μm. As discussed in Section 4.3.3 on Particle Translocation, UFPs cross cell membranes by mechanisms different from larger (~1 μm) particles. Based on that body of literature, particles smaller than a micron may enter epithelial cells resulting in their prolonged retention, particularly in the bronchioles where the residence time is longer and distances necessary to reach the epithelium are shorter compared to that in the bronchi.

4.3.1.3 Alveolar Region

The primary alveolar clearance mechanism is macrophage phagocytosis and migration to terminal bronchioles where the cells are cleared by the mucociliary escalator. Alveolar macrophages originate from bone marrow, circulate briefly as monocytes in the blood, and then become pulmonary interstitial macrophages before migrating to the luminal surfaces. Under normal conditions, a small fraction of ingested particles may also be cleared through the lymphatic system. This may occur by transepithelial migration of alveolar macrophage following particle ingestion or free particle translocation with subsequent uptake by interstitial macrophages. Snipes et al. (1997) have also demonstrated the importance of neutrophil phagocytosis in clearance of particles from the alveolar region. Rates of alveolar clearance of poorly soluble particles vary between species and are briefly discussed in Section 4.3.2. The translocation of particles from their site of deposition is discussed in Section 4.3.3. The effect particle dissolution on retention in the alveolar region was recently reviewed by Oberdörster and Kuhlbusch (2018).

The efficiency of macrophage phagocytosis is thought to be greatest for particles between 1.5 and 3 μm (Oberdörster, 1988). The decreased efficiency of alveolar macrophage for engulfing UFPs increases the time available for these particles to be taken up by epithelial cells and moved into the inter-stitium (Ferin et al., 1992). Consistent with this supposition (i.e., translocation increases with time), an increase in titanium dioxide (TiO_2) particle transport to lymph nodes has been reported following inhalation of a cytotoxin to macrophages (Greenspan et al., 1988). Interestingly, the long-term clearance kinetics of the poorly soluble ultrafine (15−20 nm CMD) iridium (Ir) particles were found to be similar to the kinetics reported in the literature for micrometer-sized particles (Semmler-Behnke et al., 2007; Semmler et al., 2004). For rats, Semmler-Behnke et al. (2007) concluded that ultrafine Ir particles are less phagocytized by alveolar macrophage than larger particles, but are effectively removed from the airway surface into the inter-stitium. Particles are then engulfed by interstitial macrophages which then migrate to the airway lumen and are removed by mucociliary clearance to the larynx. The major role of macrophage-mediated clearance was supported by lavage of relatively few free particles versus predominantly phagocytized particles at time-points of up to 6 months. It is also possible that some free UFP as well as particle-laden macrophage were carried from interstitial sites via the lymph flow to bronchial and bronchiolar sites, including bronchial-associated lymphatic tissue, where they were excreted again into the airway lumen (Semmler-Behnke et al., 2007; Brundelet, 1965). In addition to macrophage phagocytosis and migration to the ciliated airways, these studies suggest that alveolar particle clearance via interstitial translocation and uptake into the lymphatics may be an important clearance pathway for UFP.

There is evidence that particle aggregates may disassociate once deposited in the lungs. This disassociation makes inhaled aggregate size the determinant of deposition amount and site, but primary particle size the determinant of subsequent clearance (Bermudez et al., 2002; Ferin et al., 1992; Takenaka et al., 1986). Following disaggregation, the ultrafine TiO_2 particles are cleared more slowly and cause a greater inflammatory response (neutrophil influx) than fine TiO_2 particles (Bermudez et al., 2002; Oberdorster et al., 2000; Oberdörster et al., 1994a; Oberdörster et al., 1994b; Ferin et al., 1992). (Balasubramanian et al., 2013) also suggested that disaggregation of following inhalation lead to differential organ concentration of 7 nm versus 20 nm gold particles. The differences in inflammatory effects and possibly lymph burdens between fine and ultrafine TiO_2 in many studies appear related to lung burden in terms of particle surface area and not particle mass or number (Oberdorster et al., 2000; Tran et al., 2000; Oberdorster, 1996; Oberdörster et al., 1992). There is some uncertainty related to these conclusions since the crystal form of TiO_2, anatase versus rutile, may have affected some results. Others have noted that particle surface area is not an appropriate metric across all particle types (Warheit et al., 2006). Surface characteristics such as roughness can also affect protein binding and potentially clearance kinetics, with smoother TiO_2 surfaces being more hydrophobic (Sousa et al., 2004).

4.3.2 Interspecies Clearance and Retention

There are differences between species in both the rates of particle clearance from the lung and manner in which particles are retained in the lung. For instance, based on models of mucociliary clearance from undiseased airways, >95% of particles deposited in the tracheobronchial airways of rats are predicted to be cleared by 5 hours post deposition, whereas it takes nearly 40 hours for comparable clearance in humans (Hofmann and Asgharian, 2003). As noted in Section 4.3.1.2, however, there is some evidence that a sizeable fraction of particles deposited at the bronchiolar level of the ciliated airways in humans (as well as canines) are cleared at a far slower rate. Some evidence suggests that the slow cleared TB fraction increases with decreasing particle size.

From interspecies comparisons of alveolar clearance, the path length from alveoli to ciliated terminal bronchioles may affect the particle transport rate (Kreyling and Scheuch, 2000). The average path length from alveoli to ciliated terminal bronchioles is longer in humans, monkeys, and dogs, than in sheep, rats, hamsters, and mice. Transport time and hence retention times may increase with path length. This hypothesis fits with all species in this comparison, except guinea pigs, which have a short path length yet particle retention that is nearly as long as in humans, monkeys, and dogs. However, sheep have a short path length and particle transport as fast as rodents. In general, alveolar clearance rates appear to increase with increasing path length from the alveoli to ciliated airways. This supports the important role of particle laden macrophage migration from the alveolar region to the ciliated airways with subsequent clearance from the lungs.

There are also distinct differences in the normal sites of particle retention that affect clearance pathways between species. Large mammals retain particles in interstitial tissues under normal conditions, whereas rats retain particles on epithelial surfaces and in alveolar macrophages (Snipes, 1996). The influence of exposure concentration on the pattern of particle retention in rats (exposed to diesel soot) and humans (exposed to coal dust) was examined by Nikula et al. (2001). In rats, the diesel particles were found to be primarily in the lumens of the alveolar duct and alveoli; whereas in humans, retained dust was found primarily in the interstitial tissue within the respiratory acini. With chronic high doses, there is a shift in rat's pattern of dust accumulation and response from that observed at lower doses in the lungs (Snipes, 1996; Vincent and Donaldson, 1990). Rats chronically exposed to high concentrations of insoluble particles experience a reduction in their alveolar clearance rates and an accumulation of interstitial particle burden (Bermudez et al., 2004; Bermudez et al., 2002; Warheit et al., 1997; Oberdörster et al., 1994a; Oberdörster et al., 1994b; Ferin et al., 1992). Even at lower acute doses of particles, the temporary impairment of alveolar clearance results in increased movement of particles into the interstitial tissues of rats (Snipes et al., 1997). However, the results of Semmler-Behnke et al. (2007) and other older studies (Brundelet, 1965; Gross and Westrick, 1954) suggest that alveolar particle clearance via interstitial translocation and uptake into the lymphatics may be an important clearance pathway for UFP.

Following transport of particles from the alveolar epithelium via macrophages or as free particles into interstitial tissues, fluid flow can draw particles into pulmonary lymphatics. Whether it is free particles that enter the inter-stitium and lymphatics or whether macrophage emigrate from pulmonary capillaries into the alveoli and then immigrate back into the inter-stitium after phagocyting particles has been debated since the 1870s (Gross and Westrick, 1954). Gross and Westrick (1954) demonstrated that free particles themselves can enter interstitial tissues and migrate to peribronchial (possibly via the lymphatics) and perivascular positions. Pulmonary particle clearance of via lymphatics has generally been considered minimal and its importance debated (Oberdörster, 1988). Particle transport in the pulmonary lymphatics is typically considered to terminate in lymph nodes (Stober and McClellan, 1997). Semmler-Behnke et al. (2007) concluded that, in rats, ultrafine Ir particles are less phagocytized by alveolar macrophage than larger particles, but are effectively removed from the airway surface into the inter-stitium. They further suggested that some free particles as well as particle-laden macrophage are carried from interstitial sites via the lymph flow to bronchial and bronchiolar sites, including bronchial-associated lymphatic tissue, where they are excreted again into the airway lumen.

4.3.3 Particle Translocation

Mucociliary and macrophage mediated clearance of poorly soluble particles from the respiratory tract was discussed in Section 4.3.1. There is growing evidence that a small fraction of particles may cross cell membranes and move from their site of deposition by other mechanisms. The following subsections discuss the movement of particles from the olfactory mucosa to the brain and from the luminal surfaces of the alveolar region into lung tissues and other organs. The clearance and distribution of soluble particles and soluble components of particles are also considered. There are pathways that particles could reach extrapulmonary organs by means other than direct translocation from the alveoli into the blood. For example, mucociliary clearance moves particles proximally until they are eventually swallowed. Recognizing this, the organ distribution of particles following gastrointestinal and intravenous delivery are also discussed. Finally, there are a few recent studies examining particle translocation to the fetus that are discussed.

In the last PM ISA (U.S. EPA, 2009) it was concluded that olfactory transport to the brain was likely unimportant in humans, it was not clear what portion of inhaled nanoparticles reached extrapulmonary sites via the lung's air-blood barrier versus clearance to the gastrointestinal tract with subsequent absorption and distribution to the organs, and there were data supporting translocation of poorly soluble particles from the human lung. It is now concluded that olfactory transport may be important in humans as well as rodents. A comparison of particle translocation following instillation versus ingestion also shows translocation of particles from the lungs occurs in a size dependent manner and that GI absorption of particles cleared from the respiratory tract is relatively minor route into circulation. A new human study shows that following inhalation, a small fraction of gold nanoparticles enters circulation.

4.3.3.1 Olfactory Delivery

Studies reviewed in the last PM ISA (U.S. EPA, 2009) demonstrated the translocation of soluble solutions (manganese chloride and sulfate, zinc) and poorly soluble particles (hureaulite, manganese oxide and tetroxide, silver, titanium dioxide, iridium) from the olfactory mucosa via axons to the olfactory bulb of the brain. Translocation via the axon to the olfactory bulb was observed for numerous compounds of varying composition, particle size, and solubility. Studies showed that the rate of translocation was rapid, less than an hour. The vast majority of these studies were conducted by instillation in rodents. However, DeLorenzo (1970) also observed the rapid (within 30−60 min) movement of 50 nm silver-coated colloidal gold particles instilled on the olfactory mucosa to the olfactory bulb of squirrel monkeys. Information on transport from the olfactory bulb to the olfactory tubercle, stratum, or other brain regions is limited.

Based on the diameter of the axon, the transport of insoluble particles from the olfactory mucosa via axons to the olfactory bulb should be limited to particles of less than about 200 nm (Griff et al., 2000; Plattig, 1989; De Lorenzo, 1957). These thin olfactory axons bundle into thicker filaments (aka fila olfactoria or olfactory nerves) and pass directly into the olfactory bulb through numerous foramina in the cribriform plate of the ethmoid bone (Plattig, 1989; De Lorenzo, 1957). Analysis of 40 skulls of known age and sex by Kalmey et al. (1998) showed a reduction in the area of the foramina in the cribriform plate with increasing age that did not differ significantly between the sexes. The reduction of the foramina area with aging has been postulated as a cause of a reduced sense of smell with aging and would suggest that olfactory translocation may also decrease with age.

A number of inhalation studies have investigated the transport of soluble and poorly soluble manganese compounds to the brain of rats. While most of this discussion and the available literature focuses on transport from the olfactory mucosa, it should be noted that Lewis et al. (2005) reported an accumulation of manganese in the trigeminal ganglia in rats following a 10-day inhalation exposure to soluble manganese chloride particles. Following a 13-week inhalation exposure to 0.1 mg Mn/m^3, relative to air controls, more soluble manganese sulfate reached the olfactory bulb of rats than was observed for the less soluble manganese phosphate in the form of hureaulite (Dorman et al., 2004). Manganese concentration in the olfactory bulb increased 2.3-times with exposure to Mn sulfate and only 1.5-times with exposure to hureaulite (Dorman et al., 2004). As part of this same study, exposures to 0.01 and 0.5 mg Mn/m^3 of Mn sulfate resulted in olfactory bulb concentrations of 1.3-times and 3.5-times relative to air control, respectively. Since the inhaled hureaulite particles were 1.0−1.1 µm (physical diameter) and so not likely due to their size to move along axons, these data suggest that around 20−30% of the hureaulite was solubilized to reach the olfactory bulb. However, insufficient hureaulite was solubilized find increased Mn in the striatum as occurred following the Mn sulfate exposures of 0.1 and 0.5 mg Mn/m^3.

Using smaller sized particles, a 2-day inhalation exposure to poorly soluble manganese oxide (~30 nm) with the right nostril blocked showed an accumulation of the Mn oxide in the left olfactory bulb

(Elder et al., 2006). This study demonstrates neuronal uptake and translocation of UFPs following inhalation without particle dissolution and in the absence of mucosal injury that may occur with instillation. For a longer 12-day inhalation exposure to poorly soluble manganese oxide (~30 nm) with both nostrils patent, Elder et al. (2006) also found Mn concentration was significantly increased in several brain regions (striatum, 1.6×; frontal cortex, 1.4×; cortex, 1.2× cerebellum, 1.2×), but most notably increased in the olfactory bulb (3.4×). Additionally, following nasal instillation of particles, similar amounts of Mn were found in the left olfactory bulb of rats instilled with soluble manganese chloride (8.2 ± 3.6% of instilled) and small poorly soluble particles (30 nm; 1.5% dissolution per day) of manganese oxide (8.2 ± 0.7% of instilled) at 24 hours post instillation. This finding supports the conclusion that poorly soluble manganese particles, if of a sufficiently small size, do not need to be solubilized to reach the olfactory bulb. The slow solubilization process would have resulted lesser amounts of the manganese oxide than manganese chloride in the brain by 24 hours similar to the finding by Dorman et al. (2004) following 13 week inhalation exposures to manganese sulfate versus less soluble hureaulite described in the preceding paragraph.

Leavens et al. (2007) modeled the transport of Mn from soluble and poorly soluble particles to the olfactory bulb and stratum based on the experimental studies by Brenneman et al. (2000) and Dorman et al. (2002), respectively. In both of these experimental studies rats were exposed to Mn-aerosol for a single 90 minute period. Leavens et al. (2007) estimated that 92−93% Mn from soluble particles reached the striatum via the blood with the additional 6−8% arriving via the olfactory transport. However, only small amount of Mn reaching the olfactory bulb from the inhaled soluble Mn chloride (0.1%) and poorly soluble Mn phosphate (3.3%) particles was estimated to reach the striatum. That is, Mn reached the olfactory bulb, but generally did not proceed to the adjacent stratum. The transport of Mn to the stratum from the olfactory bulb was estimated based on data from animals where one nostril was plugged while the other was left patent. Thus, the olfactory transport of Mn to the stratum only occurs on the side of the animal with a patent nostril. Mn in that stratum on the plugged side of the animal is presumably derived from the blood. At least two issues affect the interpretation of these data. First, rats having a plugged nostril reduce their minute ventilation by about 50% (Brenneman et al., 2000), this lowers the signal to noise ratio in these studies versus animals with fully patent nostrils. Second, rather large sized particles were delivered to the rats in these studies, 2.51 µm MMAD (GSD 1.17) by Brenneman et al. (2000) and 1.68 µm MMAD (GSD 1.42) (Dorman et al., 2002). Referring back to Figure 4-4 and Figure 4-5, only a small fraction of these sized particles are expected to penetrate through the head to reach the lower respiratory tract. The majority of deposition occurs in the extrathoracic airways, in this case, the nasal passages of the rat. Although Leavens et al. (2007) attributed all Mn in the blood as derived from the lungs, Mn reaching circulation through areas such as the turbinates following nasal particle deposition should not be ignored.

More recently, Kreyling (2016) determined the fraction of iridium-192 (^{192}Ir) nanoparticles reaching the brain via transport from the upper versus the lower respiratory tract. Female Wistar-Kyoto rats (8−10 weeks old, 270-300 g body weight) were exposed to aerosols (20 nm; GSD, 1.6) via nose-only

inhalation or intratracheal inhalation. Estimates of particle translocation at 24 hours post inhalation excluded activity of particles on the skin or rapidly cleared to the gut and feces. Of the delivered particles (excluding skin and rapidly cleared), at 24 hours post inhalation, 0.012% of what deposited in the upper respiratory tract and 0.0014% of what deposited in the lower respiratory tract reached the brain. That is, there was 9-times more in the brain derived from the upper than the lower respiratory tract. The predicted deposition was 3-times higher in the alveolar region than in the upper respiratory tract for the nose-only exposure. These results suggest that olfactory transport to the brain was 27-times (i.e., 9×3) greater than translocation from the alveolar region. This work, however, does not indicate what brain regions contained particles or how those brain regions differed between the exposures.

Antonini et al. (2009) exposed rats to welding fumes (0.31 µm MMAD) via inhalation or filtered air for 10 days. The poorly soluble particles (soluble/insoluble ratio, 0.0139 in water) were composed primarily of iron (80.6%), manganese (14.7%), silicon (2.75%), and copper (1.79%). The welding fume was reported to be highly insoluble in water (pH, 7.4; 37°C) with dissolution of 1.4% in 24 hours. The most marked increases in iron, manganese, and copper relative to control were found in the lungs. There was no evidence of pulmonary inflammation or injury despite exposure to 40 mg/m^3 of welding fume. Consistent with studies described in Section 4.3.3.2 on translocation from the lungs, there was a slight increase in iron and manganese concentrations in the liver, heart, kidney, and spleen at 1-day post-exposure relative to controls. Metal content was also assessed in seven brain regions: hippocampus, cerebellum, striatum, thalamus, cortex, olfactory bulb, and midbrain. Manganese concentrations, but not iron or copper, were significantly increased relative to controls in the cortex (1.3×) and cerebellum (1.2×), and especially the olfactory bulb (2.2×). Of the brain regions examined, only the thalamus showed a slight insignificant reduction in manganese relative to controls. Interestingly, although there was only a tendency for a small increase in Mn concentrations within the striatum (1.1×), proinflammatory chemokines and cytokines were significantly increased by about 1.5 times in the striatum. The lower relative increase in the olfactory bulb in this study as compared to the Elder et al. (2006) study (2.2× vs. 3.4×, respectively) may, in part, be due to the larger inhaled particle size with only around 30−40% (assuming log-normal particle size distribution with a GSD of 2−4) of the welding fume being less than 200 nm, the particle size necessary for olfactory translocation, whereas all the particles in the Elder et al. (2006) study were well under 200 nm. Less than 5% of the welding fume would be smaller than the 30 nm particles used by Elder et al. (2006). Given the distribution of manganese among brain regions, the Antonini et al. (2009) study supports the transport of manganese from welding fume particles depositing on the olfactory mucosa to the olfactory bulb. However, finding increased Mn concentrations but not other metals in the brain, suggests the differential solubilization and mobilization of the Mn rather than the movement of particles themselves along axons to the brain.

New modeling studies contradict the conclusion in the 2009 PM ISA that between species differences may predispose rats, more so than humans, to deposition of particles in the olfactory region with subsequent particle translocation to the olfactory bulb. The 2009 conclusion was based on two main differences between rodents and primates. First, the olfactory mucosa covers approximately 50% of the

nasal epithelium in rodents versus only about 5% in primates (Aschner et al., 2005). Second, a greater portion of inhaled air passes through the olfactory region of rats relative to primates (Kimbell, 2006). More recently, Garcia et al. (2015) provided CFD simulations of total ultrafine nasal deposition as well as that in the olfactory region of humans and compared to prior simulations (Garcia and Kimbell, 2009) for rats. Rats were predicted to have greater total and olfactory deposition than humans. However, due the much higher ventilation rate of humans than rats, humans were predicted to experience greater dose rate to the olfactory mucosa for particles between 1 and 13 nm, above this size the dose rate was slightly greater in rats than humans (Section 4.2.2.2 and Figure 4-7). Schroeter et al. (2015) provided experimental replica cast data and CFD simulations for total and regional deposition of particles between 2.6 and 14.3 µm. The olfactory region was assumed to be 14% of the nasal surface area. For 5 µm to 11 µm particles inhaled during light activity (flow = 30 L/min), greater than 1% deposition in the olfactory region was predicted with a maximum of 6% predicted for 8 µm particles. During a resting inhalation (flow = 15 L/min), the predicted olfactory deposition exceeded 1% for particles between 9 and 19 µm, with a maximum of 8% for 13 µm particles. Although the larger particles would not themselves be expected to move along to axon from the olfactory region of the nose to the olfactory bulb, soluble materials associated with large particles could be solubilized and pass along the axon to the olfactory bulb. Greater particle deposition was predicted to occur in the turbinates than the olfactory region by Schroeter et al. (2015), soluble materials could also move into the blood from this well perfused area and reach the brain. These newer modeling studies suggest that ultrafine particle translocation as well as soluble components associated with all sized particles could reach the olfactory bulb of humans as well as rodents in a measurable amount depending on the exposure concentration.

Human autopsy data are becoming available that also suggest the importance of translocation of material from the olfactory mucosa to the olfactory bulb. Although their source is unknown, the presence of UFP in the olfactory bulb was reported in 2 of 35 Mexico City residents (Calderon-Garciduenas et al., 2010). Presumably metal components of urban PM, statistically significant increases in manganese, nickel, and chromium have been reported in the frontal lobe of Mexico City residents relative to lower air pollution areas (Calderón-Garcidueñas et al., 2013). More recently, Maher et al. (2016) examined magnetite particles in the frontal lobes from subjects that lived in Mexico City and Manchester, U.K. The magnetite (Fe_3O_4) particles were found in two forms: smooth spherical particles and, more rarely, as angular cuboctahedrons. The authors attributed the presence of the smooth spherical particles to inhaled ambient combustion-related particles, whereas the angular cuboctahedral particles were attributed to endogenous formation. The spherical particles showed a median diameter around 14−18 nm with a maximum size of about 150 nm, sizes that can be transported to the olfactory bulb from the olfactory mucosa. As discussed in Section 4.3.3.2, some of these particles may have also reached the brain via the circulation following deposition in the alveolar region of the lung. The combined literature for animal toxicological studies, CFD modeling studies, and human autopsy data support the existence of olfactory translocation in animals and suggest its relevance in humans. Although olfactory translocation is rapid with particles appearing in the olfactory bulb within an hour following instillation on the olfactory mucosa, the relative amount of particles translocated is relatively small. For example, based on Garcia et

al. (2015) only 0.001% of 20 nm particles would potentially deposit on the olfactory mucosa in humans at rest or 0.03% in rats. Based on Elder et al. (2006), around 10% of the particles on the olfactory mucosa would translocate to the olfactory bulb. Thus, only a small fraction of poorly soluble particles inhaled through the nose might be expected to reach the olfactory bulb via the axons in humans or rats. However, absolute number of particles potentially reaching the olfactory bulb over time can be considerable (see Figure 4-7).

4.3.3.2 Pulmonary Delivery

4.3.3.2.1 Membrane Translocation

It was first demonstrated by Gross and Westrick (1954) that free particles can enter interstitial tissues and migrate to peribronchial (possibly via the lymphatics) and perivascular positions. Both in vitro and in vivo studies support the rapid (≤1 hour) translocation of free ultrafine TiO_2 particles across cell membranes (Geiser et al., 2005; Churg et al., 1998; Ferin et al., 1992). Geiser et al. (2005) conducted a detailed examination of the disposition of inhaled ultrafine TiO_2 in 20 healthy adult rats. They found that distributions of particles among lung tissue compartments appeared to follow the volume fraction of the tissues and did not significantly differ between 1 and 24 hours post-inhalation. Averaging 1 and 24-hour data, 79.3 ± 7.6% of particles were on the luminal side of the airway surfaces, 4.6 ± 2.6% were in epithelial or endothelial cells, 4.8 ± 4.5% were in connective tissues, and 11.3 ± 3.9% were within capillaries. Particles within cells were not membrane bound. It is not clear why the fraction of particles identified in compartments such as the capillaries did not differ between 1 and 24 hours post-inhalation. These findings were consistent with the smaller study of five rats by Kapp et al. (2004) who reported identifying TiO_2 aggregates in a Type II pneumocyte; a capillary close to the endothelial cells; and within the surface-lining layer close to the alveolar epithelium immediately following a 1 hour exposure. These studies effectively demonstrate that some inhaled ultrafine TiO_2 particles, once deposited on the pulmonary surfaces, can rapidly (≤1 hour) translocate beyond the epithelium and potentially into the vasculature.

A few studies have characterized differences in the behavior of fine and UFPs in vitro. Geiser et al. (2005) found that both ultrafine and fine (0.025 µm gold, 0.078 µm TiO_2, and 0.2 µm TiO_2) particles cross cellular membranes by nonendocytic (i.e., not involving vesicle formation) mechanisms such as adhesive interactions and diffusion, whereas the phagocytosis of larger 1 µm TiO_2 particles is ligand-receptor mediated. Gross and Westrick (1954) surmised that free particle translocation from the alveolar surface to interstitial tissues may be limited to smaller fine particles (<0.5 µm). Edetsberger et al. (2005) found that UFPs (0.020 µm polystyrene) translocated into cells by first measurement (~1 min after particle application). Intracellular agglomerates of 88−117 nm were seen by 15−20 min and of 253−675 nm by 50−60 min after particle application. These intracellular aggregates were thought to result

from particle incorporation into endosomes or similar structures since Genistein or Cytochalasin treatment generally blocked aggregate formation. Interestingly, particles did not translocate into dead cells, rather they attached to the outside of the cell membrane. Amine- or carboxyl-modified surfaces (46 nm polystyrene) did not affect translocation across cultures of human bronchial epithelial cells with about 6% regardless of the surface characteristics (Geys et al., 2006).

4.3.3.2.2 Extrapulmonary Distribution

Soluble material can move rapidly from the alveolar surface into the blood, but poorly soluble particles generally remain in the lung for an extended period of time. A number of human studies are available confirming that the majority of poorly soluble UFP deposited in the alveolar region undergo slow clearance and do not rapidly enter circulation. However, animal studies (primarily of rats) show that UFPs cross cell membranes by mechanisms different from larger (~1 μm) particles and that a small fraction of these particles enter capillaries and distribute systemically. Some evidence suggests that a small degree of pulmonary inflammation increases interstitial hydraulic pressure sufficiently to exceed pulmonary capillary pressure, resulting in a flux of fluid and any associated particles or fibers into pulmonary capillaries (Miserocchi et al., 2008). This is consistent with the presence of airway inflammation in a variety of airway diseases (e.g., asthma, fibrosis, ARDS, pulmonary edema, inflammation from smoking) and altered epithelial integrity, allowing more rapid movement of solutes into the bloodstream [see Section 4.4.2 of U.S. EPA (2009)]. In general, increased alveolar permeability to ^{99m}Tc-DTPA is associated with any lung syndrome characterized by pulmonary edema. Fluid flow and particle migration would be from the alveolar surface into the inter-stitium as inflammation and edema resolve.

Several human studies have investigated the pulmonary retention of radiolabeled UFPs (Wiebert et al., 2006a; Brown et al., 2002; Roth et al., 1994) or fine aggregates of UFPs (Möller et al., 2008; Mills et al., 2006; Wiebert et al., 2006b; Roth et al., 1997; Burch et al., 1986). All of these studies used technician-99m (^{99m}Tc; $t_{1/2}$ = 0.25 days; pure gamma emitter) labeled carbon, except for Roth et al. (1994) who used indium-111 (^{111}In; $t_{1/2}$ = 2.8 days; pure gamma emitter) oxide. All of these studies reported ≥80% pulmonary retention of particles at 24 hours post-inhalation. However, of the fraction cleared from the lungs in the studies using ^{99m}Tc-labeled particles, it is not entirely clear how much was deposited in the ciliated airways and cleared versus how much of the radiolabel leached from the particles and was cleared in its soluble pertechnetate form. Highly soluble in normal saline, pertechnetate clears rapidly from the lung with a $t_{1/2}$ of ~10 min and accumulates most notably in the bladder, stomach, thyroid, and salivary glands (Isawa et al., 1995; Monaghan et al., 1991). Wiebert et al. (2006a) were able to reduce leaching of the ^{99m}Tc-labeled carbon (35 nm CMD inhaled) and found effectively 100% retention at 24 hours post-inhalation. Similarly, Wiebert et al. (2006b) minimized leaching of ^{99m}Tc-labeled carbon (87 nm CMD inhaled) and found negligible particle clearance from the lungs by 70 hours post-inhalation. Using the longer half-life ^{111}In-oxide aerosol (18 nm CMD), Roth et al. (1994) found 93% retention in the

human lung at 24 hours and 80% retention at 9 days post inhalation. ^{111}In-oxide is poorly soluble and as such was not expected to move into circulation as pertechnetate does. The 7% clearance of the 18 nm ^{111}In-oxide versus near 0% clearance of the 35 nm ^{99m}Tc-labeled carbon may be, in part, caused by a more proximal deposition pattern of the smaller particles (see Figure 4-5C). These human data show that the majority of poorly soluble UFP remain in the lung.

Miller et al. (2017) investigated the translocation of gold nanoparticles having primary particle sizes of approximately 4−5 nm and 34 nm in a series of two separate inhalation experiments involving young healthy adults. In experiment one, 14 young healthy adult males inhaled (3.8 nm primary particle size) 18.7 nm agglomerates (1.5 GSD) via a face mask for 2 hours with intermittent exercise (exercise target of 25 L/min/m^2 body surface area, BSA). By 15 minutes post-exposure, gold was identified in the blood of three subjects. Gold was found in the blood of 12 subjects at 6 hours, 11 subjects at 24 hours, and 7 subjects at 3 months post-exposure.[45] Gold was also identified in the urine in an unspecified number of subjects at 24 hours and 3 months post-exposure. In experiment two, groups of healthy adult males inhaled gold nanoparticles with primary particle sizes of 4.1 nm (n = 10 subjects) and 34 nm (n = 9 subjects) as agglomerates of 17.8 nm (GSD, 1.2) and 52.4 nm (GSD, 1.4). The authors observed higher gold concentrations in the blood following inhalation of the smaller than larger primary sized particles. However, relative to the larger particles, the aerosol concentration of the smaller sized particles was, on average, 1.3 times higher (192 vs. 146 µg/m^3) and the predicted deposition is about double (total deposition fractions are 72 and 35% for smaller and larger agglomerates, respectively), leading to an estimated 2.7 times greater dose of the smaller sized particles.[46] This difference in delivered dose may have been adequate to account for differences in the amounts of gold in the blood out to 7 days post-exposure, but not necessarily at the 28 day time point. The authors also observed gold in urine for the smaller particles, but gold in urine was below the limit of detection for the larger particles. The relatively small estimated difference in delivered doses does not appear sufficient to large differences in gold in urine by 28 days post-exposure. This study demonstrates the presence of gold in the blood and urine of humans following the inhalation of gold nanoparticles.

The finding of material in the blood in this human study, Miller et al. (2017), but not prior human studies described above may, in part, be a matter of an increased signal to noise afforded in this new work and/or an indication that there is a difference in particle translocation from the lung depending on the inhaled particle type. There is uncertainty related to the actual fraction of the deposited dose that translocated from the lungs and interpretation of study results. Using data from experiment one (described above), based on the concentration of gold in urine (35 ng/L) at 24 hours and average urinary volume of

[45] The number having detectable gold in blood is based on Figure 1C of Miller et al. (2017).
[46] Deposition estimated using the MPPD model (Version 3.04) for exposure to 17.8 nm (GSD, 1.2) or 52.4 nm (GSD, 1.4) particle agglomerates during two hours of intermittent exercise with 15-minute periods of exposure at rest (V_T, 0.800 L; f, 15 min^{-1}) and 15-minute periods of exposure during exercise (V_T = 1.923 L; f = 26 min^{-1}) and default airway morphology for an adult male (i.e., Yeh/Schum symmetric morphology, FRC of 3.3 L, and upper respiratory tract volume of 0.05 L). A BSA of 2.0 m^2 was assumed (not provided by authors). The breathing pattern for rest was selected to have a minute ventilation of 6 L/min per m^2 BSA based on Mcdonnell et al. (2012). The heavy exercise breathing pattern was selected from ICRP (1994).

2.4 L, it can be estimated that about 84 ng gold was excreted from the body. This can be used as a lower end estimate of translocation from the lungs since (as described below) there is evidence from animal studies of particle accumulation in various organs. Based on the exposure concentration of 116 μg/m^3 and the ventilation rates of 12 L/min at rest and 50 L/min during exercise, the total amount of aerosol inhaled was 430 μg gold. The estimated total deposition fraction of the 18.7 nm (GSD 1.5) agglomerates is 60%.[47] The alveolar deposition fraction during periods of rest and exercise are about 30 and 40%, respectively, giving combined volume-weighted alveolar deposition fraction of 38% of the inhaled aerosol. Based on total deposition, about 0.03% translocation may have occurred given the urinary excretion at 24 hours (i.e., 0.084/256). It may be more appropriate to consider deposition in the alveolar region since the movement of particles from the gastrointestinal tract into circulation is minimal by comparison to that from the alveolar region (Kreyling et al., 2014). Translocation from the alveolar deposition to urinary excretion at 24 hours is estimated to be around 0.05% (i.e., 0.084/163). Based on the log-log plot in Figure 3i of Kreyling et al. (2014), excretion via urine as a percent of material in the lungs not cleared in 24 hours by mucus clearance in rats is about 0.42% for 2.8 nm particles and 0.006% for 5 nm particles, which provides an estimate of 0.05% for 3.8 nm particles by linear interpolation on log-log scale. The comparisons developed herein place the urinary elimination by 24 hours of 3.8 nm gold particles in humans by Miller et al. (2017) as nearly identical to those obtained in rats by Kreyling et al. (2014).

A greater amount of information on particle translocation from the lungs is available from animal studies. These studies fairly consistently show that a small portion (generally <1%) of particles delivered to the lungs via inhalation or instillation are translocated from the pulmonary surfaces to extrapulmonary organs. For example, as reviewed in the last PM ISA (U.S. EPA, 2009), extrapulmonary translocation was described for poorly soluble ultrafine gold and Ir particles. In male Wistar-Kyoto rats exposed by inhalation to ultrafine gold particles (5−8 nm), Takenaka et al. (2006) reported a low, but significant, fraction (0.03 to 0.06% of lung concentration) of gold in the blood from 1 to 7 days post inhalation. Semmler et al. (2004) also found small but detectable amounts of poorly soluble Ir particle (15 and 20 nm CMD) translocation from the lungs of female Wistar-Kyoto rats to secondary target organs like the liver, spleen, brain, and kidneys. Each of these organs contained about 0.2% of deposited Ir. The peak levels in these organs were found 7 days post inhalation. The translocated particles were largely cleared from extrapulmonary organs by 20 days and Ir levels were near background at 60 days post inhalation. Particles may have been distributed systemically via the gastrointestinal tract. Immediately after the 6-hour inhalation exposure, 18 ± 5% of the deposited Ir particles had already cleared into the gastrointestinal tract. After 3 weeks, 31 ± 5% of the deposited particles were retained in the lung. By 2 and 6 months post inhalation, lung retention was 17 ± 3 and 7 ± 1%, respectively. The particles appeared

[47] For 18.7 nm (GSD 1.5) using MPPD (Version 3.04) with intermittent exercise as described for Experiment Two. Although the authors provided a BSA of 2.76 m^2 in their Table S1, a BSA of 2.0 m^2 was assumed as a more reasonable value for males being 180 cm height and 79 kg mass. Breathing patterns used for Experiment Two were used again here.

to be cleared predominantly from the peripheral lung via the mucociliary escalator into the GI tract and were found in feces.

A considerable number of new studies have become available since the last PM ISA (U.S. EPA, 2009). Studies continue to show the translocation of a small fraction of particles following inhalation or instillation increases with decreasing particle size (Kreyling et al., 2014; Kreyling et al., 2009). However, the dissolution of poorly soluble particles increases with decreasing pH and decreasing particle size (Kreyling et al., 2002; Kreyling and Scheuch, 2000; Kreyling, 1992). Dissolution and absorption of UFPs in the gastrointestinal tract subsequent to clearance from the respiratory tract cannot be fully discounted as contributing to organ concentrations of inhaled or instilled particles. The organ distribution of particles may differ depending on the route by which they are reaching circulation. For example, in humans, the liver receives about 6.5% of arterial blood flow and all blood flow coming from the GI tract (ICRP, 2002). Additionally, the proteins that particles may encounter and potentially bind to will vary depending on the route by which they entered circulation. Recognizing such issues, a series of experiments have been conducted to quantify translocation using a ^{198}Au gamma-spectrometry[48] in female Wistar-Kyoto rats (8−10 weeks old, 250 g body weight) of negatively charged gold nanoparticles of 1.4, 2.8, 5, 18, 80, and 200 nm primary particle size and positively charged 2.8 nm primary particle size following intratracheal instillation (Kreyling et al., 2014), ingestion (Schleh et al., 2012), and intravenous delivery (Hirn et al., 2011). Although additional studies have become available since the last PM ISA, the primary focus will be on the careful comparison across these routes of delivery.

Following particle instillation, Kreyling et al. (2014) measured translocation from the lungs as a function of peripheral lung dose (i.e., ignoring particles found in the trachea, GI tract, and feces). Translocation from the lung by 24 hours of particles with a negative surface charge decreased from 5.6% for 1.4 nm particles, to 3.2% for 2.8 nm, to 0.22% for 5 nm, to 0.12% for 18 nm, to only 0.06% for 80 nm, and 0.2% for 200 nm particles.[49] Most of the translocation from the lungs appears to have occurred within 1−3 hours post-instillation, but continued up to 24 hours for the largest, 200 nm particles. The estimated translocation excluded the fraction of particles found in the trachea, GI tract and feces by 24 hours post-instillation, which was 30% (averaged across all particle sizes) of the instilled dose.[50] Potential GI tract absorption was considered negligible since a prior study by Schleh et al. (2012) of particle ingestion found only a small fraction of particles entered circulation (0.37% for 1.4 nm particles, 0.37% for 2.8 nm, 0.05% for 5 nm, 0.12% for 18 nm, 0.03% for 80 nm, and 0.01% for 200 nm particles).[51] Considering the fraction of instilled particles found in GI tract and feces and GI absorption of particles, about 4% (median of all particle sizes) to 7% (mean of all particle sizes) of the apparent translocation from the lung may have derived from the GI tract (i.e., 93−96% of the particles appearing in

[48] Gamma-spectrometry is a highly sensitive technique relative to inductively coupled plasma mass spectrometry.
[49] Values from Figures 2B and 6A of Kreyling et al. (2014) for the 24-hour time point.
[50] Data from Supplement Table S1 of Kreyling et al. (2014) for the 24-hour time point.
[51] Data estimated from Table III of Schleh et al. (2012).

circulation were derived from the lung).[52] For both instillation and ingestion, less positively charged than negatively charged 2.8 nm particles entered circulation. The organ distribution of particles following intravenous administration differed greatly from instillation. At 24 hours post intravenous delivery, 51% of 1.4 nm particles, 82% of 2.8 nm particles, and 92−97% of 5−200 nm particles were found in the liver (Hirn et al., 2011). Of the material translocating from the lungs following instillation, independent of particle size, only about 10% of particles are found in the liver with the majority (43% of 1.4 nm; 55% of 7 nm; 71% of 18 nm; 96% of 80 nm) of translocated particles found in the carcass (skeleton, soft tissues, and fat) (Kreyling et al., 2014). This difference in organ distribution following intravenous versus instillation was attributed to the proteins that particles may have encountered and bound with in the lungs prior to entering circulation. This series of studies shows that translocation of particles from the lungs occurs in a size-dependent manner, that GI absorption of particles cleared from the respiratory tract is a relatively minor route into circulation, and that organ distribution can vary depending on how particles are delivered to animals.

Following translocation from the lung or intravenous injection, particles appear to be rather rapidly cleared from the blood. This clearance from the blood occurs due to accumulation in extrapulmonary organs and elimination from the body. The blood concentrations of the smallest gold nanoparticles studied (1.4 nm) are 46% cleared in rats by one-hour post-injection and by 93% at 24 hours post-injection.[53] By 24 hours, about 10% of 1.4 nm particles had moved, in roughly equal portions, into feces and urine. Larger nanoparticles (18 and 80 nm) were roughly 99% cleared from blood by one-hour post-injection. By 24 hours post-injection, most of the organ retention, 92−97% for 5−200 nm particles, is in the liver (Hirn et al., 2011). Of these larger particles eliminated (0.1 to 1%) by 24 hours post-injection, most is via the feces.[54] Others have also reported similar dependence of organ accumulation of particle size in mice, with smaller gold nanoparticles (1.5−5 nm) persisting more in blood and excreted via urine than larger (30−70 nm) nanoparticles (Miller et al., 2017; Yang et al., 2014). This was similarly demonstrated in humans with 4.1 nm particles found in urine, but not 34.3 nm particles (Miller et al., 2017). A limited number of studies have shown the continued existence in the blood at 28 days post-delivery of inhaled gold nanoparticles (4.1 and 34.3 nm) in humans and instilled TiO_2 (70 nm) in rats (Kreyling et al., 2017b; Miller et al., 2017). It is likely that the particles in the blood at 28 days post-delivery were due to additional movement/clearance from the lungs.

The long-term health implications of translocation following acute or chronic PM exposures is uncertain. Heringa et al. (2018) recently reported the existence of TiO_2 in the livers and spleens of humans (9 F, 6 M; 84 ± 13 years) on autopsy. The average titanium content in was 40 µg/kg (TiO_2 mass/tissue mass) in the liver and 80 µg/kg in the spleen. Two of the subjects had received titanium implants, but had titanium content below the limit of detection in the liver and low amounts in the spleen

[52] Kreyling et al. (2017b) reported that at 24-hour post-instillation, 5% of TiO_2 (70 nm) reaching the blood was absorbed in the GI tract (i.e., 95% crossed the alveolar air-blood barrier). Due to long-term clearance of the lung, this percentage increased to 13% by 7 days post instillation and 21% at 28 days post instillation.
[53] Data from Table S1 of Semmler-Behnke et al. (2014).
[54] Data from Figure S4 of Semmler-Behnke et al. (2014).

relative to the other individuals. Titanium dioxide particles having diameters of 85−440 nm were identified. By count with a limit of detection at 85 nm, nearly 27% of the particles in the liver and 21% of the particles in the spleen were ≤100 nm. By count, about 75% of particles were ≤200 nm. Gamma-spectrometry studies of 70 nm TiO_2 particle translocation in rats show about 4% translocation into circulation following intratracheal instillation and about 0.6% following ingestion (Kreyling et al., 2017b; Kreyling et al., 2017c). As occurs for gold nanoparticles instillation, the translocated TiO_2 distribute around the body and accumulate in organs, but are found primarily (91% at 24-hour post instillation) in the carcass (skeleton, soft tissues, and fat). This differs from 24 hours post-intravenous injection where TiO_2 accumulates predominately (95.5%) in the liver (Kreyling et al., 2017a). Following rather high doses (25−30 mg/day) of ingested TiO_2 nanoparticles (10 nm) to rat dams from gestational day 2 to 21, pups sacrificed 1 day after birth have increased titanium content in the hippocampus (Mohammadipour et al., 2014). Quantification of translocation to fetuses is provided in Section 4.3.3.3. Particle accumulation in the liver and spleen of autopsied humans is consistent with accumulation in these organs in rodents following intratracheal instillation and ingestion of particles.

4.3.3.3 Transplacental Barrier Transport

A number of studies have become available since the last PM ISA (U.S. EPA, 2009) examining particle translocation to the fetus. The route of exposure in these studies is generally oral or intravenous delivery. These papers may be important regardless of the delivery method (with the exception of intraperitoneal) since they add biological plausibility for effects during pregnancy. However, as indicated in Section 4.3.3.2.2, the sites of accumulation differ greatly between intravenous delivery versus instillation into the lung and ingestion. Specifically, the majority of particles found in circulation following intravenous delivery accumulate in the liver, whereas as the majority of particles are found in the carcass (skeleton, soft tissues, and fat) following instillation and ingestion.

The primary focus herein is given to Semmler-Behnke et al. (2014). This study utilizes the highly sensitive ^{198}Au gamma-spectrometry technique and provides a mass balance for the full body and excrement. This study was also discussed in Section 4.3.3.2.2 and was conducted by the same German research group having many years of experience and numerous publications evaluating particle deposition, clearance, and translocation in humans and rodents. The principal finding of the Semmler-Behnke et al. (2014) study relevant to this section is the accumulation in rat fetuses following delivery of particles at gestational Day 18. This time point was selected because the nutrition of the fetus is primarily the dam's blood versus the yoke sac earlier in gestation. Following intravenous injection, 0.06% of 1.4 nm and 0.004% of 18 nm gold nanoparticles were found in fetuses. No 80 nm particles (<0.0004%, the detection limit) were found in fetuses. The authors attributed the decreasing translocation as a function of increasing particle size to the role of transtrophoblasitic channels (canaliculi of 20−25 nm in diameter) in transporting particles from the maternal blood to the fetuses. The organ distribution between pregnant and nonpregnant rats was generally similar. Yang et al. (2014) also reported similar organ distributions

between pregnant and nonpregnant animals at 5 hours post intravenous injection of gold nanoparticles (1.5, 4.5, 13, 30, and 70 nm diameter). Tsyganova et al. (2014) found increased gold content in liver and spleen of fetuses following intravenous injection of gold nanoparticles (5 and 30 nm) into pregnant rats. Following rather high doses (25−30 mg/day) of ingested TiO_2 nanoparticles (10 nm) to rat dams from gestational day 2 to 21, pups sacrificed 1 day after birth have increased titanium content in the hippocampus (Mohammadipour et al., 2014). Overall, these studies show that a small fraction of nanoparticles entering circulation may reach fetuses.

4.3.4 Factors Modulating Particle Clearance

4.3.4.1 Age

It was previously concluded that there appeared to be no clear evidence for any age-related differences in clearance from the lung or total respiratory tract, either from child to adult, or young adult to elderly (U.S. EPA, 2004, 1996). Studies showed either no change or some slowing in mucus clearance with age after maturity. Although some differences in alveolar macrophage function were reported between mature and senescent mice, no age-related decline in macrophage function had been observed in humans. A comprehensive review of the literature provided in the last PM ISA (U.S. EPA, 2009) supported a decrease in mucociliary clearance with increasing age beyond adulthood in humans and animals. Limited animal data also suggest macrophage-mediated alveolar clearance may also decrease with age. This evidence is briefly paraphrased below.

Ho et al. (2001) demonstrated that nasal mucociliary clearance rates were about 40% lower in old (age >40−90 years) versus young (age 11−40 years) men and women. Tracheal mucus velocities in elderly (or aged) humans and beagle dogs are about 50% that of young adults (Whaley et al., 1987; Goodman et al., 1978). Several human studies have demonstrated decreasing rates of mucociliary particle clearance from the large and small bronchial airways with increasing age (Svartengren et al., 2005; Vastag et al., 1985; Puchelle et al., 1979). Linear fits to the data show that rapid clearance (within 1 hour) from large bronchi and prolonged clearance (between 1−21 days) from the small bronchioles in an 80-year old is only about 50% of that in 20-year old (Svartengren et al., 2005; Vastag et al., 1985). One study reported that alveolar particle clearance rates decreased by nearly 40% in old versus young rats (Muhle et al., 1990). Another study has reported that older rats have an increased susceptibility to pulmonary infection due to altered alveolar macrophage function and slowed bacterial clearance (Antonini et al., 2001). Although data are somewhat limited, they consistently show a depression of clearance throughout the respiratory tract with increasing age from young adulthood in humans and laboratory animals.

4.3.4.2 Sex

Sex was not found to affect clearance rates in prior reviews (U.S. EPA, 2004, 1996). Studies included in the most recent review (U.S. EPA, 2009) also showed that human males and females have similar nasal mucus clearance rates (Ho et al., 2001), tracheal mucus velocities (Yeates et al., 1981), and large bronchial airway clearance rates (Vastag et al., 1985).

4.3.4.3 Respiratory Tract Disease

At the time of the last two reviews (U.S. EPA, 2004, 1996), it was well recognized that obstructive airways disease may influence both the site of initial deposition and the rate of mucociliary clearance from the airways. When deposition patterns are matched, mucociliary clearance rates are reduced in patients with COPD relative to healthy controls. The effects of acute bacterial/viral infections and cough on mucociliary clearance were briefly summarized in Section 10.4.2.5 (U.S. EPA, 1996) and Section 6.3.4.4 (U.S. EPA, 2004) of past reviews. While cough is generally a reaction to some inhaled stimulus, in some cases, especially respiratory disease, it can also serve to clear the upper bronchial airways of deposited substances by dislodging mucus from the airway surface. One of the difficulties in assessing effects on infection on mucociliary clearance is that spontaneous coughing increases during acute infections. Cough has been shown to supplement mucociliary clearance of secretions, especially in patients with obstructive lung disease and primary ciliary dyskinesia.

Using a bolus technique to target specific lung regions, Möller et al. (2008) examined particle clearance from the ciliated airways and alveolar region of healthy subjects, smokers, and patients with COPD. Airway retention after 1.5 hours was significantly lower in healthy subjects (89 ± 6%) than smokers (97 ± 3%) or COPD patients (96 ± 6%). At 24 and 48 hours, retention remained significantly higher in COPD patients (86 ± 6% and 82 ± 6%, respectively) than healthy subjects (75 ± 10% and 70 ± 9%, respectively). However, these findings are confounded by the more central pattern of deposition in the healthy subjects than in the smokers and COPD patients. Alveolar retention of particles was similar between the groups at 48 hours post-inhalation.

The effect of asthma on lung clearance of particles may depend on disease status. Lay et al. (2009) found significantly ($p < 0.01$) more rapid particle (0.22 µm) mucociliary clearance over a 2-hour period post-inhalation in mild asthmatics than in healthy volunteers. Although the pattern of deposition tended to be more central in the asthmatics, there was not a statistically significant difference from healthy controls ($p = 0.24$). The extent of central relative to peripheral airways deposition was well correlated with the lung retention at 2 hours post-inhalation in the subjects with asthma ($r = -0.78$, $p < 0.01$) but not the healthy subjects. In vivo uptake by airway macrophages in mild asthmatics was also enhanced relative to healthy volunteers ($p < 0.01$). In an ex vivo study, airway macrophages from individuals with more severe asthma had impaired phagocytic capacity relative to less severely affect

asthmatics and healthy volunteers (Alexis et al., 2001). Lay et al. (2009) concluded that enhanced uptake and processing of particulate antigens could contribute to the pathogenesis and progression of allergic airways disease in asthmatics and may contribute to an increased risk of exacerbations with particulate exposure.

Chen et al. (2006) investigated the effect of endotoxin on the disposition of particles. Healthy rats and those pretreated with endotoxin (12 hours before particle instillation) were instilled with ultrafine (56.4 nm) or fine (202 nm) particles. In healthy rats, there were no marked differences in lung retention or systemic distribution between the ultrafine and fine particles. In healthy animals, UFPs were primarily retained in lungs (72 ± 10% at 0.5−2 hours; 65 ± 1% at 1 day; 62 ± 5% at 5 days). Particles were also detected in the blood (2 ± 1% at 0.5−2 hours; 0.1 ± 0.1% at 5 days) and liver (3 ± 2% at 0.5−2 hours; 1 ± 0.1% at 5 days) of the healthy animals. At 1-day post-instillation, about 13% of the particles were excreted in the urine or feces of the healthy animals. In rats pretreated with endotoxin, by 2 hours post-instillation, the UFPs accessed the blood (5 vs. 2%) and liver (11 vs. 4%) to a significantly greater extent than fine particles. The endotoxin-treated rats also had significantly greater amounts of UFPs in the blood (5 vs. 2%) and liver (11 vs. 3%) relative to the healthy control rats. This study demonstrates that acute pulmonary inflammation caused by endotoxin increases the migration of UFPs into systemic circulation.

Adamson and Prieditis (1995) investigated the possibility that particle deposition into an already injured lung might affect particle retention and enhance the toxicity of "inert" particles. Bleomycin was instilled into mice to induce epithelial necrosis and subsequent pulmonary fibrosis. Instilled 3 days following bleomycin treatment, while epithelial permeability was compromised, carbon black particles in treated mice were translocated to the inter-stitium and showed increased pulmonary retention relative to untreated mice. When instilled at 4 weeks post bleomycin treatment, after epithelial integrity was restored, carbon black particle retention was similar between treated and untreated mice with minimal translocation to the inter-stitium. The instillation of carbon particles did not appear to increase lung injury in the bleomycin treated mice at either time point. This study shows that integrity of the epithelium affects particle retention and translocation into interstitial tissues.

4.3.4.4 Particle Overload

Unlike other laboratory animals, rats appear susceptible to "particle overload" effects due to impaired macrophage-mediated alveolar clearance. Numerous reviews have discussed this phenomenon and the difficulties it poses for the extrapolation of chronic effects in rats to humans (Oberdorster, 2002; ILRI Risk Science Institute, 2000; Miller, 2000; Oberdorster, 1995; Morrow, 1994). Large mammals have slow pulmonary particle clearance and retain particles in interstitial tissues under normal conditions, whereas rats have rapid pulmonary clearance and retain particles in alveolar macrophages (Snipes, 1996). With chronic high doses of PM there is a shift in the pattern of dust accumulation and response from that

observed at lower doses in rat lungs (Snipes, 1996; Vincent and Donaldson, 1990). Rats chronically exposed to high concentrations of insoluble particles experience a reduction in their alveolar clearance rates and an accumulation of interstitial particle burden (Bermudez et al., 2004; Bermudez et al., 2002; Warheit et al., 1997; Oberdörster et al., 1994a; Oberdörster et al., 1994b; Ferin et al., 1992). With continued exposure, some rats eventually develop pulmonary fibrosis and both benign and malignant tumors (Warheit et al., 1997; Lee et al., 1986; Lee et al., 1985a, b). Oberdorster (2002, 1996) proposed that high-dose effects observed in rats may be associated with two thresholds. The first threshold is the pulmonary dose that results in a reduction in macrophage-mediated clearance. The second threshold, occurring at a higher dose than the first, is the dose at which antioxidant defenses are overwhelmed and pulmonary tumors develop. Intrapulmonary tumors following TiO_2 exposures are exclusive to rats and are not found in mice or hamsters (Mauderly, 1997). Moreover, Lee et al. (1985a) noted that the squamous cell carcinomas observed with prolonged high concentration TiO_2 exposures developed from the alveolar lining cells adjacent to the alveolar ducts, whereas squamous cell carcinomas in humans which are generally linked with cigarette smoking are thought to arise from basal cells of the bronchial epithelium. Quoting Lee et al. (1986), "Since the lung tumors were a unique type of experimentally induced tumor under exaggerated exposure conditions and have not usually been seen in man or animals, their relevance to man in questionable."

4.3.5 Summary

For any given particle size, the pattern of particle deposition influences clearance by partitioning deposited material between regions of the respiratory tract. Particles depositing in the mouth may generally be assumed to be swallowed or removed by expectoration. About 80% of particles deposited in nasal passages and the majority deposited in the tracheobronchial airways move via mucociliary transport towards the nasopharynx and are swallowed. The primary alveolar clearance mechanism of poorly soluble particles is macrophage phagocytosis and migration to terminal bronchioles where the cells are cleared by the mucociliary escalator. Movement of particles into the lymphatics, both as free particles and in macrophages, also contributes to alveolar clearance. Clearance from both the tracheobronchial and alveolar region is more rapid in rodents than humans. Mucociliary and macrophage-mediated clearance decreases with age beyond adulthood.

A small fraction of nanoparticles (≤100 nm) depositing in the alveolar region translocate rapidly (≤1 hour) from the lungs in a size dependent manner. The fraction of nanoparticles translocating from the peripheral lung into circulation is generally low (less than a fraction of a percent) for larger nanoparticles (18−80 nm), but can approach several percent for extremely small particles (1.4−2.8 nm). Particle translocation has not been reported for particles larger than 200 nm. Translocation has now been reported in both a human study as well as numerous animal studies. Of particles found in circulation following delivery to the lung, the majority (~95%) arrive via the lung's air blood barrier with the remainder (~5%) coming from gastrointestinal absorption. These particles are cleared from circulation fairly rapidly (hours

to days) by accumulation predominately in the skeleton, soft tissues, and fat and secondarily by accumulation within the liver and spleen. Particles injected into circulation, however, accumulate predominately within the liver, suggesting a differing protein corona from those derived from the lung and gastrointestinal tract. Following nanoparticle inhalation or ingestion, particles may be identified in the blood out to a month post-delivery. This longer-term presence of particles in the blood is believed to result from continued particle clearance from the lung. Some limited new evidence in rodents suggests a small fraction of nanoparticles may also reach fetuses.

The translocation of particles from the olfactory mucosa via axons to the olfactory bulb has been reported in primates, rodents, and freshwater pike for numerous compounds of varying composition, particle size, and solubility. The rate of translocation is rapid, perhaps less than an hour. Axonal transport of poorly soluble particles is thought to be limited to those under 200 nm in diameter. It is unclear to what extent translocation to the olfactory bulb and other brain regions may occur. The most extensive study of olfactory translocation has been for manganese compounds. For manganese particles, most of the manganese found in brain regions beyond the olfactory bulb is believed to derive from the blood rather than from the olfactory bulb. New particle deposition modeling suggests that deposition on the olfactory mucosa with subsequent translocation to the olfactory bulb may be important in humans as well as rodents.

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CHAPTER 5 RESPIRATORY EFFECTS

Summary of Causality Determinations for Short- and Long-Term Particulate Matter (PM) Exposure and Respiratory Effects

This chapter characterizes the scientific evidence that supports causality determinations for short- and long-term PM exposure and respiratory effects. The types of studies evaluated within this chapter are consistent with the overall scope of the ISA as detailed in the Preface (see Section P.3.1). In assessing the overall evidence, strengths and limitations of individual studies were evaluated based on scientific considerations detailed in the Appendix. The evidence presented throughout this chapter support the following causality determinations. More details on the causal framework used to reach these conclusions are included in the Preamble to the ISA (U.S. EPA, 2015).

Size Fraction	Causality Determinations
Short-term exposure	
$PM_{2.5}$	Likely to be causal
$PM_{10-2.5}$	Suggestive of, but not sufficient to infer
UFP	Suggestive of, but not sufficient to infer
Long-term exposure	
$PM_{2.5}$	Likely to be causal
$PM_{10-2.5}$	Inadequate
UFP	Inadequate

5.1 Short-Term $PM_{2.5}$ Exposure and Respiratory Effects

The 2009 PM ISA (U.S. EPA, 2009) concluded that a "causal relationship is likely to exist" between short-term $PM_{2.5}$ exposure and respiratory effects (U.S. EPA, 2009).[55] This conclusion was based mainly on epidemiologic evidence demonstrating associations between short-term $PM_{2.5}$ exposure and various respiratory effects. The more limited evidence from controlled human exposure and animal toxicological studies provided coherence and biological plausibility for a subset of respiratory effects for which $PM_{2.5}$-related associations were observed in epidemiologic studies. In addition, the 2009 PM ISA described epidemiologic evidence as consistently showing $PM_{2.5}$-associated increases in hospital

[55] As detailed in the Preface, risk estimates are for a 10 $\mu g/m^3$ increase in 24-hour average $PM_{2.5}$ concentrations unless otherwise noted.

admissions and emergency department (ED) visits for chronic obstructive pulmonary disease (COPD) and respiratory infection among adults or people of all ages, as well as increases in respiratory mortality. Epidemiologic evidence was inconsistent for hospital admissions or ED visits for asthma but supported associations with increased respiratory symptoms and decreases in lung function in children with asthma. Studies examining copollutant models showed that $PM_{2.5}$ associations with respiratory effects were robust to inclusion of CO or SO_2 in the model, but often were attenuated with inclusion of O_3 or NO_2. Evidence supporting an independent effect of $PM_{2.5}$ exposure on the respiratory system was provided by animal toxicological studies of $PM_{2.5}$ concentrated ambient particles (CAPs) demonstrating changes in some pulmonary function parameters, as well as inflammation, oxidative stress, injury, enhanced allergic responses, and reduced host defenses. Many of these effects have been implicated in the pathophysiology for asthma exacerbation, COPD exacerbation, or respiratory infection. Some of these effects were also observed with diesel exhaust (DE) or woodsmoke exposures; however, there was no attempt to attribute the effect to the particulate or gaseous components of the mixture. In the few controlled human exposure studies conducted in individuals with asthma or COPD, $PM_{2.5}$ exposure mostly had no effect on respiratory symptoms, lung function, or pulmonary inflammation. Short-term $PM_{2.5}$ exposure was not clearly related to respiratory effects in healthy people. Evidence integrated across scientific disciplines linked respiratory effects to several $PM_{2.5}$ components such as elemental carbon/black carbon (EC/BC), organic carbon (OC), and metals and $PM_{2.5}$ sources such as wildfires and traffic. However, there were few studies on any given component or source, and disparate outcomes were examined across studies and disciplines, complicating the overall interpretation of results. As a result, the 2009 PM ISA did not make a conclusion with respect to PM sources and components specifically for respiratory effects, but broadly concluded that "many [components] of PM can be linked with differing health effects and the evidence is not yet sufficient to allow differentiation of those components or sources that are more closely related to specific health outcomes" (U.S. EPA, 2009).

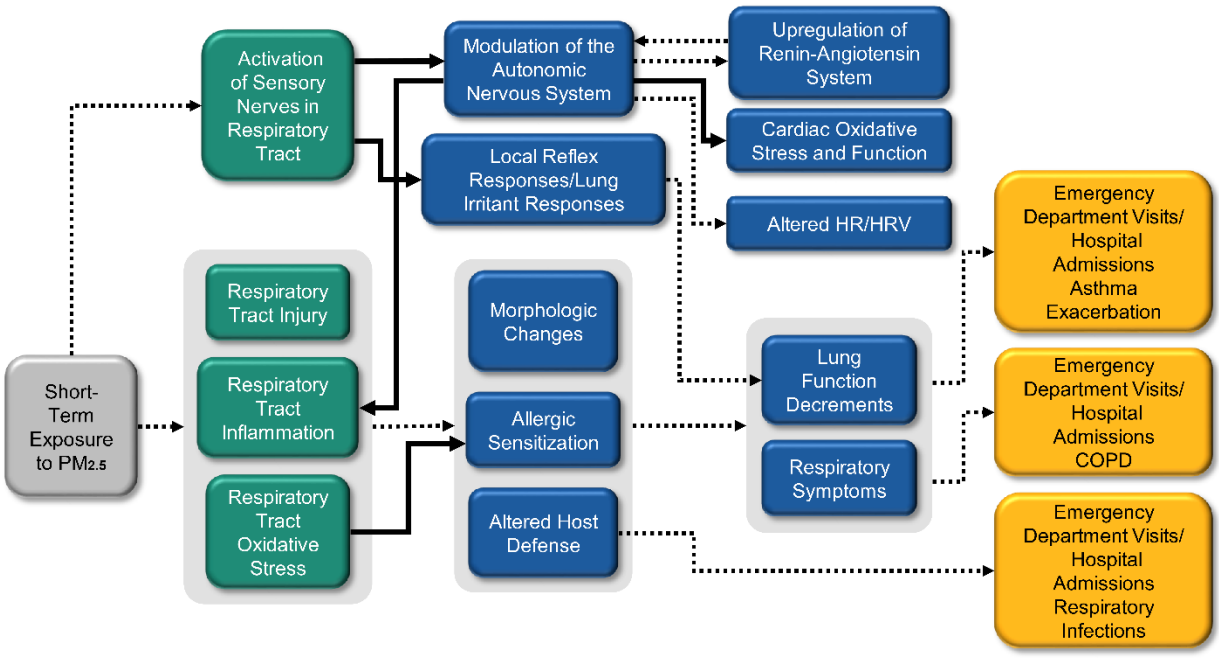
The following section on short-term $PM_{2.5}$ exposure and respiratory effects opens with a discussion of biological plausibility (Section 5.1.1) that provides background for the subsequent sections in which groups of related endpoints are presented in the context of relevant disease pathways. The organization of sections by outcome group aims to clearly characterize the extent of coherence among related endpoints (e.g., hospital admissions, symptoms, inflammation) and biological plausibility of $PM_{2.5}$ effects. These outcome groups include asthma exacerbation (Section 5.1.2), COPD exacerbation (Section 5.1.4), respiratory infection (Section 5.1.5), combinations of respiratory-related disease hospital admissions and ED visits (Section 5.1.6), and respiratory mortality (Section 5.1.9). New to this ISA are distinct discussions of allergy exacerbation (Section 5.1.3), respiratory effects in healthy populations (Section 5.1.7), and respiratory effects in populations with cardiovascular disease (Section 5.1.8). Section 5.1.10 comprises an integrated discussion of policy-relevant considerations across the epidemiologic studies evaluated within Section 5.1. The evaluation of whether there is evidence of differential associations by various $PM_{2.5}$ components and sources, compared to $PM_{2.5}$ mass, is detailed in Section 5.1.11.

5.1.1 Biological Plausibility

This section describes biological pathways that potentially underlie respiratory health effects resulting from short-term exposure to $PM_{2.5}$. Figure 5-1 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" short-term exposure to $PM_{2.5}$ may lead to respiratory health effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 5.1.

Once $PM_{2.5}$ deposits in the respiratory tract, it may be retained, cleared, or solubilized (see CHAPTER 4). Insoluble and soluble components of $PM_{2.5}$ may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate reactive oxygen species (ROS) and this capacity is termed "oxidative potential." Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see CHAPTER 4). Immune system responses due to the presence of particles in the interstitial space may contribute to respiratory health effects.

Evidence that short-term exposure to $PM_{2.5}$ may affect the respiratory tract generally informs two proposed pathways (Figure 5-1). The first pathway begins with injury, inflammation, and oxidative stress responses, which are difficult to disentangle. Inflammation generally occurs as a consequence of injury and oxidative stress, but it can also lead to further oxidative stress and injury due to secondary production of ROS by inflammatory cells. The second pathway begins with the activation of sensory nerves in the respiratory tract that can trigger local reflex responses and transmit signals to regions of the central nervous system that regulate autonomic outflow.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Solid arrows denote direct evidence of the relationship as provided, for example, by an inhibitor of the pathway or a genetic knock-out model used in an experimental study. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 5-1 Potential biological pathways for respiratory effects following short-term $PM_{2.5}$ exposure.

Injury, Inflammation, and Oxidative Stress

Regarding the first pathway, a large body of evidence from controlled human exposure (Section 5.1.7.2) and animal toxicological studies (Section 5.1.7.3 and Section 5.1.8) found injury, inflammation, and oxidative stress responses in healthy individuals and animals. These responses are highly variable. In studies involving concentrated ambient particles (CAPs) exposure, variability may be due to differences in concentration and sources of $PM_{2.5}$ present in the airshed. Multiday exposures generally resulted in more robust responses than exposures of a few hours. Some studies in humans and animals that examined markers in bronchoalveolar lavage fluid (BALF) found increased numbers of macrophages and neutrophils. Animal toxicological studies examining responses in lung tissue found markers of injury and oxidative stress, such as increased lung water and protein carbonyl content (Rhoden et al., 2004; Gurgueira et al., 2002), and markers of inflammation such as recruitment of macrophage populations (Xu et al., 2013). Other studies found evidence of mild morphologic changes, such as hyperplasia of the bronchoalveolar duct (Batalha et al., 2002) and changes in the mucus content of the nasal epithelium (Yoshizaki et al., 2016), that could be downstream effects of inflammation following

inhalation of $PM_{2.5}$. Inflammation may lead to other downstream effects, such as lung function decrements. A decrease in maximal mid-expiratory flow coupled with a decrease in oxygen saturation, possibly indicating dysfunction of small peripheral airways, was observed in healthy humans following inhalation of $PM_{2.5}$ (Gong et al., 2005). It is not clear whether the decrement in lung function seen in this study was due to inflammation or to autonomic nervous system (ANS) responses, which are discussed below.

Some experimental evidence focuses on respiratory responses in specific disease states, such as asthma and COPD, in which inflammation is known to play an important role. In animal models of allergic airway disease, which share many phenotypic features with asthma in humans, short-term exposure to $PM_{2.5}$ led to morphologic changes due to allergic responses and airway remodeling (Section 5.1.2.4). These morphologic changes could lead to lung function decrements and respiratory symptoms, both of which are associated with $PM_{2.5}$ concentrations in epidemiologic panel studies of humans with asthma (Section 5.1.2.2 and Section 0). Further, evidence from epidemiologic panel studies in children with asthma linked $PM_{2.5}$ concentrations to the inflammatory marker leukotriene E4, asthma symptoms, medication use (Section 5.1.2.2 and Section 5.1.2.4) and decrements in lung function (Section 0). Overall, these results provide plausibility for epidemiologic findings of hospital admissions and ED visits for asthma (Section 5.1.2.1).

Injury and inflammatory responses to inhaled CAPs were more robust in animal models of COPD than in healthy animals (Saldiva et al., 2002; Kodavanti et al., 2000; Clarke et al., 1999). Lung function-related changes in oxygen saturation, FEV_1, and tidal volume were seen in controlled human exposure studies involving human subjects with COPD and in animal models of COPD following short-term exposure to $PM_{2.5}$ (Gong et al., 2005; Saldiva et al., 2002; Clarke et al., 1999) and provide plausibility for epidemiologic findings of exacerbation of COPD (Section 5.1.4). Whether these COPD-related changes in lung function were due to inflammation or to ANS responses, which are discussed below, is not clear.

In animal toxicological studies, inhalation of $PM_{2.5}$ resulted in additional effects on the immune system subsequent to respiratory tract inflammation and oxidative stress. Allergic sensitization occurred in one study using diesel exhaust particles (DEPs) (Whitekus et al., 2002). It was blocked by treatment with antioxidants (depicted by the solid line connecting oxidative stress and allergic sensitization in Figure 5-1), indicating a role for oxidative stress in mediating the response. Allergic sensitization is an early step in the development of an allergic phenotype, which could contribute to both lung function decrements and respiratory symptoms. Another study found altered macrophage function and increased susceptibility to an infectious following inhalation of CAPs (Zelikoff et al., 2003). This demonstration of impaired host defense provides plausibility for epidemiologic findings of respiratory infection (Section 5.2.6).

Activation of Sensory Nerves

Regarding the second pathway, activation of sensory nerves, animal toxicological studies described in the previous ISA and later in this chapter demonstrated changes in respiratory rate and lung volumes (i.e., rapid, shallow breathing) (Section 5.1.7 and Section 5.1.8). These responses are characteristic of lung irritant responses. Activation of sensory nerves in the respiratory tract can trigger local reflex responses resulting in lung irritation. Evidence that lung irritant responses are mediated by parasympathetic pathways involving the vagus nerve is provided by a study in which DEPs were intra-tracheally instilled into a rodent (Mcqueen et al., 2007) (depicted as a solid line connecting activation of sensory nerves and local reflex responses in Figure 5-1). In this study, pretreatment with atropine, an inhibitor of parasympathetic pathways, and vagotomy, which involves severing of the vagus nerve, blocked the irritant response to DEP. Lung irritation serves as an adaptive response to a noxious chemical that can potentially decrease exposure to that chemical. While some studies in humans and animals involving inhalation of $PM_{2.5}$ found FEV_1 changes, it is not clear whether this effect was mediated by lung irritant responses or by inflammation.

Activation of sensory nerves in the respiratory tract can also transmit signals to regions of the central nervous system that regulate autonomic outflow and influence all the internal organs, including the heart. Involvement of specific receptors on the sensory nerves, the transient receptor potential (TRP) sensory nerve receptors, was demonstrated by (Ghelfi et al., 2008), since TRP antagonists blocked downstream effects of exposure to $PM_{2.5}$ on the heart (depicted by the solid line connecting activation of sensory nerves and cardiac oxidative stress and function in Figure 5-1). In this study, modulation of the ANS resulted in altered autonomic outflow, which was manifest as a change in heart rate (see Section 8.1.1 and Section 6.1.1).

Furthermore, studies suggest connections between $PM_{2.5}$-mediated modulation of the ANS and other effects. A study in mice found that short-term exposure to $PM_{2.5}$ increased sympathetic nervous system (SNS) activity, as indicated by increased norepinephrine levels in lung and brown adipose tissue (Chiarella et al., 2014). Furthermore, inhalation of $PM_{2.5}$ increased BALF cytokine levels, an effect which was enhanced by β_2 adrenergic receptor agonists, which mimic the actions of norepinephrine. Using knock-out mice lacking the β_2 adrenergic receptor specifically in alveolar macrophage, it was demonstrated that inhalation of $PM_{2.5}$ enhanced cytokine release from alveolar macrophages. This involvement of the SNS in $PM_{2.5}$-mediated inflammatory responses is depicted by the solid line connecting modulation of the ANS and respiratory tract inflammation in Figure 5-1. The SNS is one arm of the ANS (the other arm being the parasympathetic nervous system). This is likely to represent a positive feed-back mechanism by which ANS responses may enhance inflammation. Another study found upregulation of the renin-angiotensin system (RAS), as indicated by an increase in mRNA for angiotensin receptor Type 1 and angiotensin converting enzyme, in the lung (Aztatzi-Aguilar et al., 2015). Angiotensin receptor Type 1 mediates the effects of angiotensin II, which is a potent vasoconstrictor and mediator in the vasculature. The SNS and the RAS are known to interact in a positive feedback fashion

(Section 8.1.2) with important ramifications in the cardiovascular system. However, it is not known whether SNS activation or some other mechanism mediated the changes in the RAS observed in the respiratory tract in this study.

Summary

As described here, there are two proposed pathways by which short-term exposure to $PM_{2.5}$ may lead to respiratory health effects. One pathway involves respiratory tract injury, inflammation, and oxidative stress that may lead to morphologic changes and lung function decrements, which are linked to asthma and COPD exacerbations. Respiratory tract inflammation may also lead to altered host defense, which is linked to increased respiratory infections. The second pathway involves the activation of sensory nerves in the respiratory tract leading to lung function decrements, which are linked to asthma and COPD exacerbations. While experimental studies involving animals or human subjects contribute most of the evidence of upstream effects, epidemiologic studies found associations between exposure to $PM_{2.5}$ and both respiratory tract inflammation and lung function decrements. Together, these proposed pathways provide biological plausibility for epidemiologic evidence of respiratory health effects and will be used to inform a causality determination, which is discussed later in the chapter (Section 5.1.12).

5.1.2 Asthma Exacerbation

Asthma is a chronic inflammatory lung disease characterized by reversible airway obstruction and increased airway responsiveness. Exacerbation of disease is associated with symptoms such as wheeze, cough, chest tightness, and shortness of breath. Symptoms may be treated with asthma medication, and uncontrollable symptoms may lead to seeking medical treatment. Previous findings linking short-term $PM_{2.5}$ exposure to asthma exacerbation, particularly from epidemiologic studies of children, comprised one line of evidence informing the determination of a likely to be causal relationship with respiratory effects. Some incoherence was noted in the evidence for children with asthma in that $PM_{2.5}$ concentrations were associated with respiratory symptoms and lung function decrements but inconsistently and imprecisely associated with hospital admissions and ED visits for asthma. However, the main uncertainty was whether $PM_{2.5}$ exposure had an effect independent of correlated copollutants. In the few epidemiologic studies that examined copollutant confounding, $PM_{2.5}$ associations with asthma-related effects did not always persist in models that included O_3, NO_2, CO, or SO_2. Further, in the 2009 PM ISA, coherence between evidence for allergic responses and epidemiologic findings for asthma exacerbation was not assessed for short-term $PM_{2.5}$ exposure. In controlled human exposure and animal toxicological studies, short-term $PM_{2.5}$ exposure induced allergic inflammation, which is part of the pathophysiology for allergic asthma. Allergic asthma is the most common asthmatic phenotype in children, and allergic inflammation could link $PM_{2.5}$ exposure and asthma exacerbation.

In characterizing the current state of the evidence, this section begins by considering the effects of short-term exposure to $PM_{2.5}$ on clinical indicators of asthma exacerbation (i.e., hospital admissions, ED visits, and physician visits for asthma) and then considers respiratory symptoms and asthma medication use in people with asthma. The evaluation follows with a consideration of the effects of short-term exposure to $PM_{2.5}$ on lung function, which may indicate airway obstruction and poorer control of asthma. The last section describes the evidence for subclinical effects such as pulmonary inflammation and oxidative stress resulting from short-term exposure to $PM_{2.5}$.

In addition to examining the relationship between short-term $PM_{2.5}$ exposure and asthma exacerbation, some epidemiologic studies often conduct analyses to assess whether the associations observed are due to chance, confounding, or other biases. As such, this evidence across epidemiologic studies is not discussed within this section, but evaluated in an integrative manner and focuses specifically on those analyses that address policy-relevant issues (Section 5.1.10), and includes evaluations of copollutant confounding (Section 5.1.10.1), model specification (Section 0), lag structure (Section 5.1.10.3), the role of season and temperature on $PM_{2.5}$ associations (Section 5.1.10.4), averaging time of $PM_{2.5}$ concentrations (Section 5.1.10.5), and concentration-response (C-R) and threshold analyses (Section 5.1.10.6). The studies that inform these issues and evaluated within these sections are primarily epidemiologic studies that conducted time-series or case-crossover analyses examining asthma hospital admissions and ED visits.

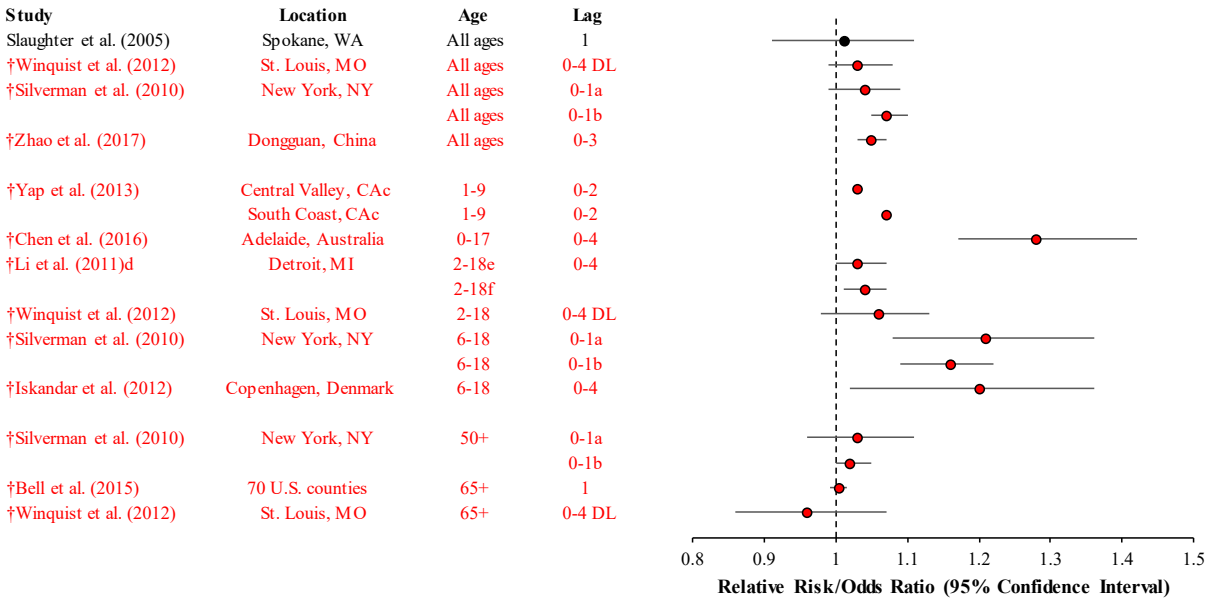
5.1.2.1 Hospital Admissions and Emergency Department (ED) Visits

The 2009 PM ISA reported inconsistent evidence of associations between short-term increases in $PM_{2.5}$ concentration and hospital admissions and ED visits for asthma in children, but generally consistent positive associations in studies focusing on adults and people of all ages combined (U.S. EPA, 2009). However, the evaluation of results from studies conducted in populations of children is complicated by the difficulty in reliably diagnosing asthma in children <5 years of age because young children often have transient wheeze (NAEPP, 2007). The inclusion of children <5 years of age may add some uncertainty to the results of studies focusing on all children, but the few studies that presented results in children older than 5 years did indicate $PM_{2.5}$-associated increases in asthma hospital admissions and ED visits. The examination of potential copollutant confounding was not thoroughly considered by the studies evaluated in the 2009 PM ISA but provided some evidence that $PM_{2.5}$-asthma hospital admission and ED visit associations are robust to the inclusion of gaseous pollutants in copollutant models. Across studies, associations were observed for a range of lags, with evidence that risk estimates for asthma hospital admissions and ED visits increased in magnitude for longer or cumulative lags.

Asthma hospital admissions and ED visit studies are evaluated separately because only a small percentage of asthma ED visits result in a hospital admission. As a result, asthma ED visits may represent less severe outcomes compared to asthma hospital admissions. For each of the studies evaluated in this

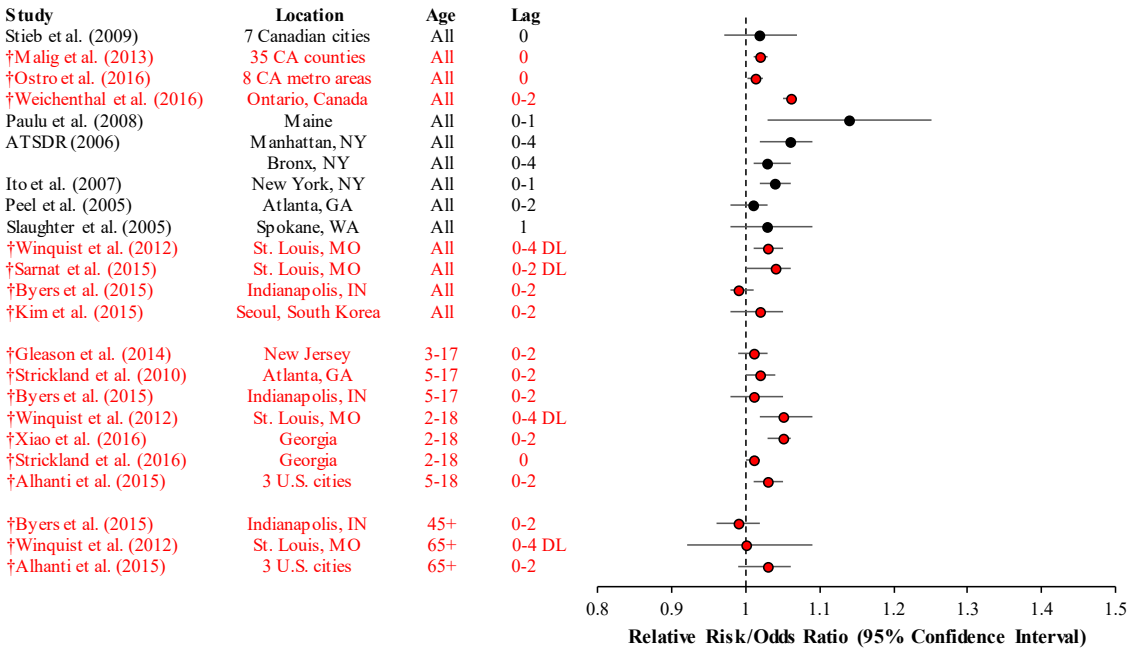
section, Table 5-1 presents the air quality characteristics of each city, or across all cities, the exposure assignment approach used, and information on copollutants examined in each asthma hospital admission and ED visit study. Other recent studies of asthma hospital admissions and ED visits are not the focus of this evaluation because they did not address uncertainties and limitations in the evidence previously identified, and therefore, do not directly inform the discussion of policy-relevant considerations detailed in Section 5.1.10. Additionally, many of these studies were conducted in small single cities, encompassed a short study duration, or had insufficient sample size. The full list of these studies can be found here: (https:/hero.epa.gov/hero/particulate-matter).

Recent studies expand the evidence base from the 2009 PM ISA (U.S. EPA, 2009) with respect to the evaluation of asthma hospital admissions and further reinforce the results reported in studies that examined asthma ED visits. As summarized in Figure 5-2- and Figure 5-3, both studies of hospital admissions and ED visits report evidence of consistent positive associations when examining children and people of all ages, with inconsistent evidence of associations with short-term $PM_{2.5}$ exposure for older adults (i.e., generally >65 years of age). These results are further supported by meta-analyses that include studies reviewed in and published since the 2009 PM ISA (Fan et al., 2015; Zheng et al., 2015). The results from asthma hospital admission and ED visit studies are supported by a study focusing on asthma physician visits in Atlanta, for the initial time period of the study, but this pattern of associations was not observed for the later time period (Sinclair et al., 2010). However, it is important to note that the severity of a $PM_{2.5}$-related asthma exacerbation, personal behavior such as delaying a visit to the doctor for less severe symptoms, and insurance type (i.e., physician visits which often are ascertained for members of a managed care organization) may dictate whether an individual visits the doctor or a hospital, making it difficult to readily compare results between studies focusing on physician visits versus hospital admissions and ED visits.



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA.
a = Intensive Care Unit (ICU) hospital admissions; b = non-ICU hospital admissions; c = values of confidence intervals not reported, but above the null; d = combination of hospital admissions and ED visits; e = time-series model results; f = case-crossover model results. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-2 Summary of associations between short-term $PM_{2.5}$ exposures and asthma hospital admissions for a 10 µg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations.



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. DL = distributed lag. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-3 Summary of associations from studies of short-term $PM_{2.5}$ exposures and asthma emergency department (ED) visits for a 10 μg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations.

Table 5-1 Epidemiologic studies of $PM_{2.5}$ and hospital admissions, emergency department (ED) visits, physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment	Mean Concentration µg/m^{3a}	Upper Percentile Concentrations µg/m^{3a}	Copollutant Examination
Hospital admissions				
†Yap et al. (2013) 12 counties, Central Valley and South Coast, CA 2000−2005 1−9 yr	Average of all monitors in each county	12.8−24.6	NR	Correlation (*r*): NA Copollutant models with: NA
†Bell et al. (2015) 213 U.S. counties 1999−2010 ≥65 yr	Average of all monitors in each county	U.S.: 12.3 Northeast: 12.0 Midwest: 12.9 South: 12.4 West: 11.3	Max U.S.: 20.2 Northeast: 16.4 Midwest: 16.5 South: 16.5 West: 20.2	Correlation (*r*): NA Copollutant models with: NA
†Hebbern and Cakmak (2015) 10 Canadian cities 1994−1997 All ages	Average of all monitors in each city	2.6−21.4	NR	Correlation (*r*): NA Copollutant models with: Pollen
†Silverman and Ito (2010) New York, NY 1999−2006 (warm season only) All ages, 6−18 yr, ≥50 yr	Average of 24 monitors	13[b]	75th: 21 90th: 29	Correlation (*r*): 0.59 O_3 Copollutant models with: O_3
†Liu et al. (2016) Greater Houston area, TX 2008−2013 All ages	Average of four monitors in one county, study area covers nine counties	12.0	90th: 18.5	Correlation (*r*): NA Copollutant models with: NA

Table 5-1 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions, emergency department (ED) visits, physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment	Mean Concentration µg/m^{3a}	Upper Percentile Concentrations µg/m^{3a}	Copollutant Examination
†Kim et al. (2012) Denver, CO 2003−2007 All ages	One monitor	7.9	Max: 59.4	Correlation (*r*): 0.46 EC, 0.54, OC, 0.68 SO_4, 0.82, NO_3 Copollutant models with: NA
†Iskandar et al. (2012) Copenhagen, Denmark 2001−2008 0−18 yr	One monitor	10.3	75th: 11.8	Correlation (*r*): 0.33 NO_2, 0.33 NO_X, 0.85 PM_{10}, 0.26 UFP Copollutant models with: NO_2, NO_X, UFP
†Chen et al. (2016) Adelaide, Australia 2003−2013 0−17 yr	One monitor	7.8	75th: 9.1 Max: 61.2	Correlation (*r*): NA Copollutant models with: NA
†Cheng et al. (2015) Kaohshing, Taiwan 2006−2010 All ages	Six monitors averaged	45.9	75th: 61.9 Max: 144	Correlation (*r*): 0.69 $PM_{10-2.5}$, 0.40 O_3, 0.67 NO_2, 0.69 SO_2 Copollutant models with: O_3, NO_2, CO, SO_2 (but all stratified by temperature)
†Zhao et al. (2016) Dongguan, China 2013−2015 All ages	Five monitors averaged	42.6	75th: 56.8 Max: 192.7	Correlation (*r*): 0.42 O_3, 0.80 NO_2, 0.81 CO, 0.25 SO_2 Copollutant models with: O_3, NO_2, SO_2

Table 5-1 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions, emergency department (ED) visits, physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment	Mean Concentration µg/m^{3a}	Upper Percentile Concentrations µg/m^{3a}	Copollutant Examination
ED visits				
ATSDR (2006) Manhattan and Bronx, NY 1999−2000 All ages	One monitor per borough	24-h avg Manhattan: 16.7 Bronx: 15.0 1-h max Manhattan: 27.6 Bronx: 27.6	NR	Correlation (*r*): Bronx 24-h avg: 0.19 O_3, 0.61 NO_2, 0.45 SO_2, 0.19 pollen, 0.32 mold 1-h max: 0.35 O_3, 0.55 NO_2, 0.28 SO_2 Copollutant models with: O_3, NO_2, SO_2
Ito et al. (2007) New York, NY 1999−2002 All ages	Average of 30 monitors	15.1	75th: 19 95th: 32	Correlation (*r*): NA Copollutant models with: O_3, NO_2, CO, SO_2
Peel et al. (2005) Atlanta, GA 1998−2000 All ages	One monitor	19.2	90th: 32.3	Correlation (*r*): NA Copollutant models with: NA
Stieb et al. (2009) Seven Canadian cities 1992−2003, varies across cities All ages	One monitor to average of seven One monitor Halifax, Ottawa, Vancouver. Three Edmonton. Seven Montreal, Toronto.	Halifax: 9.8 Montreal: 8.6 Toronto: 9.1 Ottawa: 6.7 Edmonton: 8.5 Vancouver: 6.8	75th, Halifax: 11.3 Montreal: 10.9 Toronto: 11.9 Ottawa: 8.7 Edmonton: 10.9 Vancouver: 8.5	No copollutant model *r* = −0.05 to 0.62 O_3, 0.27−0.51 NO_2, 0.01−0.42 CO, 0.01−0.55 SO_2

Table 5-1 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions, emergency department (ED) visits, physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment	Mean Concentration µg/m^{3a}	Upper Percentile Concentrations µg/m^{3a}	Copollutant Examination
Paulu and Smith (2008) Maine, whole state 2000−2003 (warm season only) All ages	Kriging of monitors Estimates for zip code centroid. Number monitors and method validation NR.	8−9[b]	Max across yr: 20 in 2000 to 42 in 2003	Does not persist with: O_3 *r* across yr = 0.76−0.87 O_3
†Alhanti et al. (2016) Three U.S. cities 1993−2009 5−18 yr, ≥65 yr	One monitor in each city	Atlanta: 14.1 St. Louis: 13.6 Dallas: 11.1	NR	Correlation (*r*): 0.57 O_3, 0.39 NO_2 Atlanta; 0.42 O_3, −0.15 NO_2 Dallas; 0.29 O_3, 0.29 NO_2 St. Louis Copollutant models with: NA
†Krall et al. (2016) Four U.S. cities 1999−2010 All ages	One monitor in each city	Atlanta: 15.6 St. Louis: 13.6 Dallas: 10.7 Birmingham: 17.0	NR	Correlation (*r*): NA Copollutant models with: NA
†Malig et al. (2013) 35 California counties 2005−2008 All ages	Nearest monitor within 20 km from population-weighted centroid of each patient's residential zip code	5.2−19.8	NR	Correlation (*r*): NA Copollutant models with: $PM_{10-2.5}$
†Ostro et al. (2016) 2005−2009 Eight California metro areas All ages	Nearest monitor within 20 km from population-weighted centroid of each patient's residential zip code	16.5	NR	Correlation (*r*): NA Copollutant models with: NA

Table 5-1 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions, emergency department (ED) visits, physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment	Mean Concentration µg/m^{3a}	Upper Percentile Concentrations µg/m^{3a}	Copollutant Examination
†Xiao et al. (2016) Georgia 2002−2008 2−18 yr	Combination of CMAQ model estimates and ground-based measurements at 12-km grid cells as detailed in Friberg et al. (2016); 10-fold cross validation, 76%; grid cells averaged over each zip code	13.2	75th: 16.1 Max: 86.4	Correlation (*r*): 0.61 O_3, 0.22 NO_2, 0.26 CO, 0.21 SO_2 Copollutant models with: NA
†Strickland et al. (2015) Georgia 2002−2010 2−18 yr	Satellite aerosol optical depth measurements at 1-km as detailed in Hu et al. (2014); R^2 ranged from 0.71 = 0.85; grid cells averaged over each zip code	12.9[b]	75th: 17.4 99th: 37.4	Correlation (*r*): NA Copollutant models with: NA
†Gleason et al. (2014) New Jersey, whole state 2004−2007 (warm season only) 3−17 yr	Fuse-CMAQ at 12-km grid cells assigned to geocoded address	NR	Max: 47.2	Correlation (*r*): <0.34 pollens, 0.56 O_3 Copollutant models with: Pollen
†Weichenthal et al. (2016) Ontario, Canada (15 cities) 2004−2011 All ages	Nearest monitor to population-weighted zip code centroid or single available monitor	7.1	Max: 56.8	Correlation (*r*): <0.42 NO_2 Copollutant models with: O_3, NO_2, oxidative potential

Table 5-1 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions, emergency department (ED) visits, physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment	Mean Concentration µg/m^{3a}	Upper Percentile Concentrations µg/m^{3a}	Copollutant Examination
†Strickland et al. (2010) 1993−2004 Atlanta, GA 5−17 yr	Population-weighted average across monitors	16.4	NR	Correlation (*r*): Warm season = 0.50 O_3, 0.36 NO_2, 0.32 CO, 0.13 SO_2; cold season = −0.12 O_3, 0.37 NO_2, 0.38 CO, 0.00 SO_2. Copollutant models with: NA
†Sarnat et al. (2015) St. Louis, MO 2001−2003 All ages	One monitor	18.0	NR	Correlation (*r*): 0.25 CO, 0.35 NO_2, 0.08 SO_2, 0.23 O_3 Copollutant models with: NA
†Byers et al. (2015) Indianapolis, IN 2007−2011 All ages, 5−17 yr, ≥45 yr	Average of three monitors	13.4	NR	Correlation (*r*): 0.39 SO_2
†Kim et al. (2015)[c] Seoul, South Korea 2008−2011 All ages	Number of monitors not reported	24.8	75th: 30.8	Correlation (*r*): 0.02 O_3, 0.6 $PM_{10-2.5}$ Copollutant models with: NA

Table 5-1 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions, emergency department (ED) visits, physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment	Mean Concentration µg/m^{3a}	Upper Percentile Concentrations µg/m^{3a}	Copollutant Examination
Physician visits				
†Sinclair et al. (2010) Atlanta, GA 1998−2002 All ages	One monitor	Overall: 17.1 Aug 1998−Aug 2000: 18.4 Sep 2000−Dec 2002: 16.2	NR	Correlation (*r*): Warm season = 0.63 O_3 Copollutant models with: NA
Hospital admissions and ED visits, separately				
Slaughter et al. (2005) Spokane, WA 1995−1999 All ages	One monitor	NR	90: 20.2	Correlation (*r*): 0.62 CO Copollutant models with: NA
†Winquist et al. (2012) St. Louis, MO 2001−2007 All ages, 2−18 yr, ≥65 yr	One monitor	14.4	Max: 56.6	Correlation (*r*): 0.25 O_3 Copollutant models with: NA

Table 5-1 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions, emergency department (ED) visits, physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment	Mean Concentration µg/m^{3a}	Upper Percentile Concentrations µg/m^{3a}	Copollutant Examination
Hospital admissions and ED visits, combined				
†Li et al. (2011) Detroit, MI 2004−2006 2−18 yr	Average of four monitors	15.0	75th: 18.5 Max: 69.0	Correlation (*r*): Across monitors = 0.59, 0.64 NO_2, 0.53, 0.43 SO_2, 0.30, 0.41 CO Copollutant models with: NA

Avg = average, CMAQ = community multiscale air quality model, CO = carbon monoxide, ED = emergency department, max = maximum, NA = not available; NO_2 = nitrogen dioxide, NO_X = sum of NO_2 and nitric oxide, NR = not reported, O_3 = ozone, SO_2 = sulfur dioxide.

[a]All data are for 24-hour average unless otherwise specified

[b]Median concentration.

[c]$PM_{2.5}$ data only available for 1 year (2010).

†Studies published since the 2009 PM ISA.

5.1.2.1.1 Hospital Admissions

Across recent studies, evidence supports an association between short-term $PM_{2.5}$ exposure and asthma hospital admissions, particularly in analyses of children and people of all ages (Figure 5-2). This evidence is supported by studies that examined associations with $PM_{2.5}$ within a state, across multiple cities, or individual cities. In 12 California counties encompassing the south coast and central valley, Yap et al. (2013) focused on examining the influence of socioeconomic status (SES) on hospital admissions for pediatric (children ages 1 to 9 years) respiratory conditions associated with $PM_{2.5}$ exposure (CHAPTER 12). For childhood asthma hospital admissions, the authors reported positive associations across each individual city with varying width of confidence intervals, resulting in relative risks for south coast and central valley combined ranging from 1.03−1.07 at lag 0−2 days. While Yap et al. (2013) reported evidence of positive associations in children, Bell et al. (2015) in a study of 213 U.S. counties focusing on older adults (i.e., ≥65 years of age), 70 of which had asthma data, did not observe an increase in asthma hospital admissions (RR = 1.00 [95% CI: 0.99, 1.01]; lag 1), but the authors only examined single-day lags.

Additional single-city studies conducted in the U.S., Canada, and internationally further examined associations between short-term $PM_{2.5}$ exposure and asthma hospital admissions in different age groups (i.e., people of all ages, children, and older adults). In New York City, Silverman and Ito (2010) focused on asthma hospital admissions consisting of severe episodes that required a stay in the intensive care unit (ICU) and those that did not (non-ICU) across several different age ranges. Due to the focus on both $PM_{2.5}$ and O_3, the study authors limited analyses to the warm season (April−August). The authors examined people of all ages as well as children and adults. An increased risk for total asthma hospital admissions (combined ICU and non-ICU) for children 6−18 years of age was reported for $PM_{2.5}$ (RR = 1.16 [95% CI: 1.10, 1.22]; lag 0−1). An elevated risk due to $PM_{2.5}$ exposure was also evident when examining both ICU and non-ICU admissions for children 6−18 years of age (Figure 5-2). Results similar in magnitude were observed for both children and people of all ages, with associations smaller in magnitude and with wider confidence intervals for ages 50 and older. The results of Silverman and Ito (2010) are consistent with a study conducted by Winquist et al. (2012) in St. Louis, MO that also examined associations across several age ranges. Winquist et al. (2012), reported the strongest evidence of an association when examining people of all ages and children 2−18 years of age, with no evidence of an association for older adults (Figure 5-2). Kim et al. (2012) in a study in Denver, CO examined a longer lag structure, a 14-day distributed lag model, and reported evidence of a positive association between short-term $PM_{2.5}$ exposure and asthma hospital admissions for people of all ages (quantitative results not presented). However, Liu et al. (2016) in a study conducted in the greater Houston area, did not report evidence of an association with $PM_{2.5}$ and unscheduled hospital admissions (quantitative results not presented). It is important to note that the population examined in Liu et al. (2016) consisted of individuals with private insurance, which differs from the other studies evaluated in this section that did

not differentiate amongst insurance coverage when identifying hospital admissions; therefore, the results may not be comparable.

Studies that examined several age ranges tended to indicate stronger associations, in both magnitude and precision, for children. Additional studies focusing only on children provide supporting evidence for associations between short-term $PM_{2.5}$ exposure and asthma hospital admissions. Li et al. (2011) in Detroit, MI; Chen et al. (2016) in Adelaide, Australia; and Iskandar et al. (2012) in Copenhagen, Denmark all reported evidence of positive associations at lag 0−4 days (Figure 5-2).

5.1.2.1.2 Emergency Department (ED) Visits

Similar to hospital admission studies, recent ED visit studies provide evidence of generally consistent positive associations with short-term $PM_{2.5}$ exposures, particularly when examining children and people of all ages (Figure 5-3). However, compared to the hospital admission studies, the magnitude of the association tends to be smaller for ED visits. The evidence supporting an association between short-term $PM_{2.5}$ exposure and asthma ED visits is derived from studies conducted over an entire state, across multiple cities, or in individual cities. Additional studies focusing on exposure-related issues, such as exposure assignment (Sarnat et al., 2013b; Strickland et al., 2011) and air exchange rates (Sarnat et al., 2013a), have also focused on examining the relationship between short-term $PM_{2.5}$ exposure and asthma ED visits. They provide additional supporting evidence, but are characterized in CHAPTER 3 (Section 3.3.2.1 and Section 3.3.2.4.2).

Both Malig et al. (2013) and Ostro et al. (2016) in multilocation studies conducted in California that focused on people of all ages, 35 counties and 8 metropolitan areas, respectively, provided evidence of positive associations at lag 0. Ostro et al. (2016) reported an OR = 1.01 (95% CI: 1.00, 1.02), and Malig et al. (2013) reported an OR = 1.02 (95% CI: 1.01, 1.03). These results are consistent with Weichenthal et al. (2016) in a study that encompassed Ontario, Canada that also reported a positive association with asthma ED visits for people of all ages but encompassed a multiday lag of 0−2 days. Krall et al. (2016) in a study of four U.S. cities (i.e., Atlanta, GA; Birmingham, AL; St. Louis, MO; and Dallas, TX) that primarily focused on $PM_{2.5}$ sources also reported positive associations with asthma/wheeze ED visits in city-specific analyses for people of all ages at lag 3 (quantitative results not presented). Additional evidence from single-city studies conducted in St. Louis, MO (Sarnat et al., 2015; Winquist et al., 2012) and Seoul, South Korea (Kim et al., 2015) report associations similar in magnitude to the multilocation studies, but with wider confidence intervals (Figure 5-3). However, Byers et al. (2015) did not report evidence of an association for asthma hospital admissions for people of all ages in a study conducted in Indianapolis, IN (RR = 0.99 [95% CI: 0.98, 1.01]; lag 0−2).

While a few of the studies that conducted analyses focusing on people of all ages also include analyses focusing on other age ranges including children (Byers et al., 2015; Winquist et al., 2012), several recent studies focus exclusively on the relationship between short-term $PM_{2.5}$ exposure and

asthma ED visits in children. Both Winquist et al. (2012) and Byers et al. (2015) reported associations larger in magnitude in children compared to people of all ages combined in St. Louis, MO (RR = 1.05 [95% CI: 1.02, 1.09]; lag 0−4) and Indianapolis, IN (RR = 1.01 [95% CI: 0.98, 1.05]; lag 0−2), respectively. The results of Winquist et al. (2012) and Byers et al. (2015) are consistent with single-city (Strickland et al., 2010) and whole state (Xiao et al., 2016; Gleason and Fagliano, 2015; Strickland et al., 2015) analyses that focused on pediatric asthma ED visits (Figure 5-3), with ORs and RRs across studies ranging from 1.01−1.05. An additional multicity study encompassing three U.S. cities (i.e., Atlanta, GA, St. Louis, MO; and Dallas, TX), which also examined associations in older adults, provides additional support for the associations observed in other recent studies focusing on children (RR = 1.03 [95% CI: 1.01, 1.05]; lag 0−2) (Alhanti et al., 2016).

Most of studies that examined the association between short-term $PM_{2.5}$ exposure and asthma ED visits focused on analyses for people of all ages and/or children, with a more limited number of studies examining potential $PM_{2.5}$ effects in adults and older adults (Alhanti et al., 2016; Byers et al., 2015; Winquist et al., 2012). Both Byers et al. (2015) in Indianapolis, IN and Winquist et al. (2012) in St. Louis, MO reported evidence of a null association with asthma ED visits in adults 45 and older, and 65 and older, respectively (Figure 5-3). However, Alhanti et al. (2016) in three U.S. cities reported a RR = 1.03 (95% CI: 0.99, 1.06) at lag 0−2. Although Alhanti et al. (2016) included St. Louis, MO in the three U.S. cities examined, when examining city-specific results, the overall association is heavily influenced by Atlanta, GA with the St. Louis, MO result being consistent with that reported in Winquist et al. (2012).

5.1.2.1.3 Summary of Asthma Hospital Admissions and Emergency Department (ED) Visits

Building off the evidence detailed in the 2009 PM ISA (U.S. EPA, 2009), recent epidemiologic studies strengthen the evidence for a relationship between short-term $PM_{2.5}$ exposure and asthma-related hospital admissions and between short-term $PM_{2.5}$ exposure and ED visits in analyses of children and people of all ages. Evidence for a relationship in older adults continues to be inconsistent. The main results of studies detailed within this section are supported by analyses that examined specific policy-relevant issues as detailed in Section 5.1.10. Specifically, analyses of potential copollutant confounding provide evidence that $PM_{2.5}$ associations are relatively unchanged in models with gaseous pollutants and $PM_{10-2.5}$, but the evidence is more limited for $PM_{10-2.5}$ (Section 5.1.10). Although in some instances the results from copollutant models are attenuated, they remain positive overall. The associations observed across studies were found to be robust in sensitivity analyses that examined alternative model specifications to account for temporal trends as well as the potential confounding effects of weather.

Additionally, the overall body of evidence indicating a relationship between short-term $PM_{2.5}$ exposure and asthma hospital admissions and ED visits is supported by studies that conducted analyses to further elucidate this relationship. Across studies that examined whether there was evidence of seasonal

patterns, studies that divided the year into warm and cold season reported associations larger in magnitude for the warmer months. These results are supported by studies that examined all four seasons of the year, but they also indicate that effects may be strongest over more defined periods of the year (i.e., the spring) (Section 5.1.10.4.1). Additionally, examinations of the concentration-response (C-R) relationship provide some evidence for a linear relationship for short-term $PM_{2.5}$ exposure and asthma hospital admissions and ED visits. However, complicating the interpretation of these results is both the lack of thorough empirical evaluations of alternatives to linearity as well as the results from cutpoint analyses that provide some potential indication for nonlinearity in the relationship between short-term $PM_{2.5}$ exposure and asthma hospital admission and ED visits (Section 5.1.10.6).

5.1.2.2 Respiratory Symptoms and Asthma Medication Use in Populations with Asthma

Studies evaluating the effects of short-term $PM_{2.5}$ exposure on respiratory symptoms and asthma medication use consisted solely of epidemiologic studies. Results will be discussed separately for children with asthma and for adults with asthma.

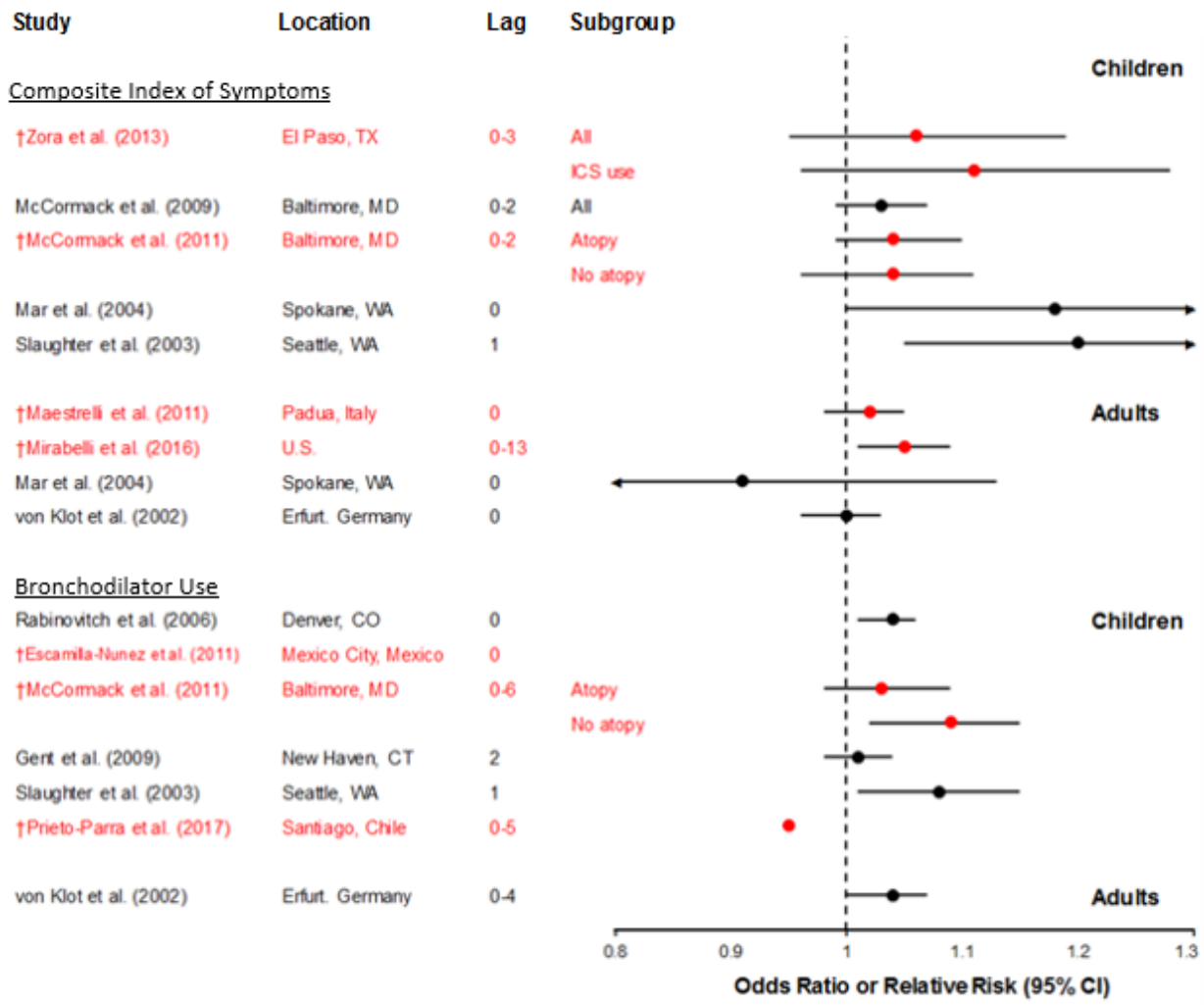
Children

Uncontrollable respiratory symptoms, such as cough, wheeze, sputum production, shortness of breath, and chest tightness, can lead people with asthma to seek medical care. Thus, along with medication use in children, studies examining the relation between $PM_{2.5}$ and increases in asthma symptoms may provide support for the observed increases in asthma hospital admissions and ED visits in children, as discussed in Section 5.1.2.1. A limited number of panel studies reviewed in the 2009 PM ISA (U.S. EPA, 2009) provide evidence of an association between $PM_{2.5}$ and respiratory symptoms (Mar et al., 2004; Gent et al., 2003; Slaughter et al., 2003) and medication use (Gent et al., 2009; Rabinovitch et al., 2006; Slaughter et al., 2003) in children with asthma. In studies that examined copollutant confounding, associations between $PM_{2.5}$ and asthma severity were robust to the inclusion of CO in a copollutant model (Slaughter et al., 2003), while $PM_{2.5}$ associations with persistent cough, chest tightness, and shortness of breath no longer persisted in models adjusting for O_3 (Gent et al., 2003).

A few recent studies provide some additional evidence of an association between $PM_{2.5}$ and a composite index of multiple symptoms (Figure 5-4). In a panel study including 90 schoolchildren with asthma in Santiago, Chile, $PM_{2.5}$ concentrations were associated with increases in coughing and wheezing, as well as a composite index of respiratory symptoms (Prieto-Parra et al., 2017). The observed associations were strongest in magnitude for 7-day average $PM_{2.5}$. Similarly, among children at two schools in El Paso, TX, 5-day average $PM_{2.5}$ concentrations measured outside of the schools were associated with poorer asthma control scores, which reflect symptoms and activity levels (Zora et al., 2013). The two schools included in the study differed in nearby traffic levels but varied similarly in

outdoor $PM_{2.5}$ concentration over time (Section 3.4.3.1). In contrast, students attending schools with varying nearby traffic levels were also examined in the Bronx, NY, though asthma symptoms were not associated with outdoor school or total personal $PM_{2.5}$ concentrations (Spira-Cohen et al., 2011). A low correlation between school and personal $PM_{2.5}$ concentrations ($r = 0.17$) and a reportedly high proportion of time spent indoors (89%), suggests that personal $PM_{2.5}$ exposure was largely influenced by indoor rather than ambient sources. In an additional study related to respiratory symptoms, asthma-related school absence was associated with 19-day average $PM_{2.5}$ concentrations in a U.S. multicity study (O'Connor et al., 2008). Notably, confounding by meteorological factors is difficult to control with long averaging times. Study-specific details, including cohort descriptions and air quality characteristics are highlighted in Table 5-2.

In addition to respiratory symptoms, recent studies of medication use in children add to the limited evidence base, providing some additional evidence of $PM_{2.5}$-associated increases in the use of bronchodilators, which can provide quick relief from asthma symptoms (Figure 5-4). Panel studies of schoolchildren with asthma in Denver, CO (Rabinovitch et al., 2011) and Mexico City (Escamilla-Nuñez et al., 2008) observed associations between $PM_{2.5}$ concentrations and bronchodilator use. Escamilla-Nuñez et al. (2008) reported comparable associations using lag 0 and 5-day average $PM_{2.5}$, while Rabinovitch et al. (2011) observed associations that were stronger in magnitude when estimated using 2-day moving average $PM_{2.5}$ compared to single-day lags. In contrast, $PM_{2.5}$ concentrations were associated with decreased bronchodilator use in a panel study in Santiago, Chile (Prieto-Parra et al., 2017).



Note: †Studies published since the 2009 PM ISA. Studies in black were included in the 2009 PM ISA. Effect estimates are standardized to a 10 μg/m^3 increase in 24-hour average $PM_{2.5}$. CI = confidence interval, ICS = inhaled corticosteroid. Lag times reported in days. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-4 Summary of associations between short-term $PM_{2.5}$ exposures and respiratory symptoms and medication use in populations with asthma.

Table 5-2 Epidemiologic studies of $PM_{2.5}$ and respiratory symptoms and medication use in children with asthma.

Study	Study Population	Exposure Assessment	Concentration (µg/m³)	$PM_{2.5}$ Copollutant Model Results and Correlations
†Spira-Cohen et al. (2011) Bronx, NY 2002−2005	N = 40, ages 10−12 yr 78% with rescue inhaler use Daily diary for 1 mo No information on participation rate 89% time spent indoors	School outdoor and total personal 24-h avg *r* = 0.17 school and personal children walk to school	Mean School: 14.3 Total personal: 24.1	Correlation (*r*): NA Copollutant models with: NA
†Zora et al. (2013) El Paso, TX Mar−Jun 2010	N = 36, ages 6−11 yr 33% ICS use, 47% atopy Weekly measures for 13 weeks 95% follow-up participation	School outdoor 96-h avg Two schools: High and low traffic area *r* = 0.89 between schools, 0.91 between monitors, 0.73−0.86 school and monitor	Mean, max School 1: 13.8, 24.9 School 2: 9.9, 18.5	Correlation (*r*): (School 1, School 2) −0.33, −0.19 NO_2; −0.02, 0.25 benzene; 0.10, 0.33 toluene; 0.47, 0.28 O_3 Copollutant models with: NA
†Rabinovitch et al. (2011); Rabinovitch et al. (2006) Denver, CO 2002−2005	N = 82 (3-yr study), 73 (2-yr study) 65−86% moderate/severe asthma, 82−90% ICS use Daily measures for 4−7 mo No information on participation rate	One monitor 24-h avg, 10-h avg (12−11 a.m.), 1-h max (12−11 a.m.) 4.3 km from school *r* = 0.92 monitor and school	Mean, max for yr 1−3 24-h avg: 6.5−8.2, 20.5−23.7 10-h avg: 7.4−9.1, 22.7−30.2 1-h max: 16.8−22.9, 39−52 (95th)	Correlation (*r*): NA Copollutant models with: NA
†Escamilla-Nuñez et al. (2008) Mexico City, Mexico 2003−2005	N = 147, ages 9−14 yr 43% persistent asthma, 89% atopy Daily diary for mean 22 weeks 94% follow-up participation	One monitor 24-h avg Within 5 km of school or home *r* = 0.77 monitor and school	Mean: 27.8	Correlation (*r*): 0.62 NO_2, 0.54 O_3 Copollutant models with: NA

Table 5-2 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory symptoms and medication use in children with asthma.

Study	Study Population	Exposure Assessment	Concentration (μg/m^3)	$PM_{2.5}$ Copollutant Model Results and Correlations
Prieto-Parra et al. (2017) Santiago, Chile May−Sep 2010−2011	N = 89, ages 6−14 yr 50% mild asthma, 53% ICS use, 64% atopy Daily diary for 3 mo 79% follow-up participation	One monitor Most homes within 3 km	Mean:30	Correlation (*r*): NA Copollutant models with: PM_{10}, NO_2, O_3, SO_2, K, Mo, Pb, S, Se, and V
†Mann et al. (2010) Fresno, Clovis, CA 2000−2005	N = 280, mean (SD) age 8.1 (1.7) 25% moderate/severe asthma, 38% ICS use, 63% atopy Daily diary for 2 weeks, every 3 mo 89% participation from enrolled	One monitor 24-h avg Within 20 km of home	Median: 18.7 75th: 32.0 Max: 137	Correlation (*r*): 0.63 NO_2, −0.45 O_3, −0.23 $PM_{10-2.5}$, 0.76 EC Copollutant models with: $PM_{10-2.5}$
Gent et al. (2009) New Haven, CT 2000−2004	N = 149, ages 4−12 yr 33% moderate/severe asthma Daily diary for mean 313 days No information on participation	One monitor 24-h avg Near highway, 0.9−27 km from homes (mean 10 km)	Mean: 17.0	Correlation (*r*): NA Copollutant models with: NA
Slaughter et al. (2003) Seattle, WA Years NR	N = 133, ages 5−12 yr 100% mild/moderate asthma Daily diary for 28−112 days No information on participation	Three monitors averaged 24-h avg	NR	Correlation (*r*): 0.82 CO Copollutant models with: CO
Mar et al. (2004) Spokane, WA 1997−1999	N = 9, ages 7−12 yr 100% regular medication use Daily diary for mean 580 days No information on participation	One monitor	Means 1997: 11.0 1998: 10.3 1999: 8.1	Correlation (*r*): 0.61 PM_{10}, 0.92 PM_1, 0.28 $PM_{10-2.5}$ Copollutant models with: NA

Avg = average, CO = carbon monoxide, ICS = inhaled corticosteroid use, IQR = interquartile range, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, O_3 = ozone, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 μm; *r* = correlation coefficient; RR = relative risk, SD = standard deviation, SO_2 = sulfur dioxide.

†Studies published since the 2009 PM ISA.

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Recent evidence of associations from studies that measured $PM_{2.5}$ concentrations outside of children's schools, representing exposure where children spend a large part of their day, increases confidence in the associations observed. Additionally, recruitment mostly occurred at schools; thus, the study populations were likely representative of the general population of children with asthma. The representativeness of results is also supported by the high follow-up participation rates (79−95%; Table 5-2). Meanwhile, potential copollutant confounding remains a source of uncertainty given the lack of studies that report copollutant models. In limited copollutant results described in the 2009 PM ISA (U.S. EPA, 2009), $PM_{2.5}$ associations appeared robust to adjustments for CO, but not O_3, despite high copollutant correlation ($r > 0.7$) (Gent et al., 2003; Slaughter et al., 2003). Recent studies show moderate correlations ($0.4 < r < 0.7$) for $PM_{2.5}$ with O_3 and NO_2 (Table 5-2), though only a single study presented copollutant models. The association between $PM_{2.5}$ and asthma control in schoolchildren was attenuated but still positive with adjustment for NO_2, O_3, benzene, or toluene, which were all weakly to moderately correlated ($r < 0.5$) with $PM_{2.5}$ (Zora et al., 2013). Further discussion of copollutant confounding is provided in Section 5.1.10.1.

Adults

Studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) reported inconsistent evidence of an association between $PM_{2.5}$ and respiratory symptoms and medication use in adults with asthma. Recent studies provide limited evidence of association between $PM_{2.5}$ and respiratory symptoms or markers for medication use in adults with asthma (Figure 5-4). A U.S.-wide cross-sectional analysis indicates increases in any asthma symptom with increases in county-average $PM_{2.5}$ concentrations modeled by CMAQ (Mirabelli et al., 2016). Analysis of the concentration-response relationship isolates the association to lower concentrations, ranging from 4.0 to 7.1 $\mu g/m^3$. However, this study is limited by its cross-sectional design, and residual confounding may arise from the 14-day $PM_{2.5}$ averaging time and lack of consideration of confounding by community-level SES. A recent study in Milan, Italy measured levels of the beta-agonist salbutamol in untreated wastewater samples to estimate the daily population-level use of short-acting beta-antagonists (Fattore et al., 2016). Single-day $PM_{2.5}$ lags, ranging from 0 to 10 days, were associated with increases in daily defined doses of short-acting beta-antagonists, with associations that were strongest in magnitude at lags 7 and 8 (RR = 1.07 [95% CI: 1.02, 1.12]). The validity and reliability of wastewater levels of medication as an indicator for medication use is untested, but previous results show increases in self-reported beta-agonist and ICS use with increases in $PM_{2.5}$ concentrations averaged over 5 days (von Klot et al., 2002). Other recent studies of associations between personal exposure to $PM_{2.5}$ and respiratory symptoms, examined in aggregate or individually, are limited by simple correlation analyses on observations (Larsson et al., 2010) or by temporal mismatch between 2-day $PM_{2.5}$ exposure and 4-week symptom interval (Maestrelli et al., 2011).

5.1.2.3 Lung Function Changes in Populations with Asthma

Studies evaluating the effects of short-term $PM_{2.5}$ exposure on lung function consisted solely of epidemiologic studies. Results will be discussed separately for children with asthma and for adults with asthma. Some studies in adults employed scripted exposures to further inform the relationship between short-term $PM_{2.5}$ exposure and lung function. Scripted studies measuring personal ambient $PM_{2.5}$ exposures are designed to minimize uncertainty in the $PM_{2.5}$ exposure metric by always measuring $PM_{2.5}$ at the site of exposure, ensuring exposure to sources of $PM_{2.5}$ and measuring outcomes at well-defined lags after exposure.

Children

Lung function metrics can indicate airway obstruction, which is the defining characteristic of asthma. Further, specific lung function metrics, such as FEV_1, have been shown to have prognostic value for asthma exacerbation (Pijnenburg et al., 2015), such that $PM_{2.5}$-related decrements in lung function may provide support for the observed increases in asthma hospital admissions and ED visits in children, as discussed in Section 5.1.2.1. In the 2009 PM ISA (U.S. EPA, 2009), several panel studies of children with asthma provide generally consistent evidence of an association between short-term $PM_{2.5}$ concentrations and decreased FEV_1. $PM_{2.5}$ exposure in particular microenvironments was also associated with lung function decrements in studies examined in the 2009 PM ISA. In Seattle, decrements in some measures of lung function (PEF, MEF, FEV_1) were associated with $PM_{2.5}$ concentrations (Allen et al., 2008; Trenga et al., 2006). Based on the ratio of personal to ambient sulfur concentrations, total personal $PM_{2.5}$ exposure was partitioned into ambient-generated and nonambient-generated fractions. Only the ambient-generated $PM_{2.5}$ was associated with lung function decrements (FEV_1, PEF, MEF) (Allen et al., 2008). $PM_{2.5}$ concentrations at fixed-site monitors were associated with larger decrements in FEV_1 among children with asthma in Denver, CO after adjusting for an estimate of the ambient-generated portion based on the ratio of personal to ambient sulfur concentrations (Strand et al., 2006). Notably, there was a lack of studies that examined potential confounding by copollutants, raising uncertainties about the independence of the observed associations.

Several recent studies continue to provide evidence of an association between short-term $PM_{2.5}$ exposure and FEV_1 decrements in children with asthma. As in studies of respiratory symptoms in children with asthma (Section 5.1.2.2), lung function studies followed children with asthma in an array of cities in the U.S., Canada, and Asia (Table 5-3) that are similar to the locations of studies that examined asthma hospital admissions and ED visits (Section 5.1.2.1). In Riverside and Whittier, CA, personal $PM_{2.5}$ and monitor $PM_{2.5}$ concentrations were associated with decreased FEV_1 (Delfino et al., 2008). Associations were strongest in magnitude for personal $PM_{2.5}$ exposures, particularly those for 1 and 8-hour max concentrations, suggesting that peak exposures in a certain microenvironment may have increased relevance to lung function. Similarly, among children attending two schools with varying nearby traffic levels in the Bronx, NY, Spira-Cohen et al. (2011) reported decrements in FEV_1 in relation to personal

$PM_{2.5}$ concentrations averaged in the 12 hours prior to spirometry. The authors did not observe a similar association with $PM_{2.5}$ exposure estimated from monitors outside of the schools. In Windsor, Canada, in another panel of schoolchildren with asthma, Dales et al. (2009) observed associations between 24-hour average $PM_{2.5}$ concentrations and nighttime FEV_1 decrements, as well as 12-hour average $PM_{2.5}$ and diurnal FEV_1. $PM_{2.5}$ exposure was estimated from a city monitor, though most panel subjects reportedly lived within 10 km downwind of the monitor. In contrast with evidence of a relationship between FEV_1 and short-term exposure to $PM_{2.5}$, Smargiassi et al. (2014) reported that lung function was not associated with personal $PM_{2.5}$ in a panel study following 72 children with asthma for 10 consecutive days in Montreal, Canada.

Within studies that compared multiple exposure assignment methods, FEV_1 decrements were larger in relation to $PM_{2.5}$ exposure estimated from personal samplers compared to fixed-site monitors (Spira-Cohen et al., 2011; Delfino et al., 2008). This is generally consistent with evidence from the 2009 PM ISA (U.S. EPA, 2009) and potentially indicates reduced exposure measurement error in the personal exposure measures. The errors and uncertainties related to various exposure assignment methods (Section 3.3.5), and the relation between personal and ambient concentrations (Section 3.4.1.3) are discussed in further detail in CHAPTER 3. These results for personal exposure also provide some indication that $PM_{2.5}$ exposure in microenvironments may have an independent effect on lung function. However, uncertainties remain regarding the independent effect of $PM_{2.5}$ given the limited number of studies that examine potential copollutant confounding and the general limitations of copollutant models. A single recent study examined copollutant models, reporting diurnal and nighttime FEV_1 associations with $PM_{2.5}$ that were robust to adjustment for O_3 (Dales et al., 2009). Nighttime FEV_1 associations were also generally unchanged in models including NO_2 or SO_2, while diurnal FEV_1 decrements were attenuated, but still negative. Notably, the correlation between $PM_{2.5}$ and O_3 ($r = 0.26$) was much lower than $PM_{2.5}$-NO_2 ($r = 0.68$) and $PM_{2.5}$-SO_2 ($r = 0.43$) correlations. Further discussion of copollutant confounding is provided in Section 5.1.10.1.

A few recent studies also examine other lung function metrics. In the study of schoolchildren in New York, discussed previously, Spira-Cohen et al. (2011) observed an association between 12-hour average personal $PM_{2.5}$ exposure and PEF decrements. As with the examination of FEV_1, the authors did not observe an association with $PM_{2.5}$ at school-site monitors. In a panel study of children receiving long-term in-hospital care in Yotsukaido, Japan, $PM_{2.5}$ concentrations averaged over the 24 hours prior to spirometry were associated with both morning and evening PEF decrements (Yamazaki et al., 2011). Given the severity of asthma in this population, the results might not be applicable to the general population with asthma. PEF decrements were also associated with 24-hour average $PM_{2.5}$ concentrations in a panel of schoolchildren in Seoul, South Korea (Hong et al., 2010). While the authors examined several single-day lags, ranging from 0 to 4 days, they only observed an association at lag 0. As discussed previously, Smargiassi et al. (2014) reported that personal $PM_{2.5}$ exposure was not related to an array of lung function metrics, including FVC and $FEF_{25–75\%}$.

In summary, recent studies add to the existing evidence linking short-term $PM_{2.5}$ exposure to decrements in FEV_1 in children with asthma. While the previously existing evidence base for $PM_{2.5}$-related decrements in PEF is less consistent than that for FEV_1, a few recent studies provide generally consistent evidence indicating an association. Importantly, uncertainty regarding potential copollutant confounding remains.

Table 5-3 Epidemiologic studies of $PM_{2.5}$ and lung function in populations with asthma.

Study	Study Population	Exposure Assessment	Concentration (μg/m^3)	$PM_{2.5}$ Copollutant Model Results and Correlations
Children				
†Spira-Cohen et al. (2011) Bronx, NY 2002−2005	N = 40, ages 10−12 yr 78% rescue inhaler use Daily supervised measures—1 mo No information on participation rate 89% time spent indoors	School outdoor and total personal 12-h avg (9 a.m.−9 p.m.), 24-h avg *r* = 0.17 school and personal Most children walk to school	Mean School: 14.3 Total personal: 24.1	Correlation (*r*): NA Copollutant models with: NA
†Delfino et al. (2008) Riverside, Whittier, CA Jul−Dec 2003 and 2004	N = 53, ages 9−18 yr 100% mild/moderate persistent asthma, 62% controlled medication use Daily home measures—10 days No information on participation rate	One monitor and total personal 24-h avg, 1-h max, 8-h max Within 16 km of homes in Riverside, 8 km in Whittier. *r* = 0.60 personal-monitor 100% above limit of detection	Mean, max Monitor, 24-h avg: 23.3, 87.2 Total personal 24-h avg: 31.2, 180 1-h max: 90.1, 604 8-h max: 46.2, 241	Correlation (*r*): (personal, ambient) 0.22, 0.51 EC; 0.26, 0.62 OC; 0.38, 0.36 NO_2 Copollutant models with: NO_2
†Smargiassi et al. (2014) Montreal, Canada Oct 2009−Apr 2010	N = 72, ages 8−12 yr 43% ICS use, 68% atopic Daily supervised measures—10 days No information on participation rate	Total personal 24-h avg 12% below limit of detection	Mean: 9.6 75th: 11.7 Max: 100	Correlation (*r*): NA Copollutant models with: NA
†Jacobson et al. (2012) Alta Floresta, Brazil Aug−Dec 2006	N = 56, ages 8−15 yr 5% asthma medication use Daily supervised measures—4 mo 90% follow-up participation	School outdoor 24-h avg, 6-h avg (12−5:30 a.m. to 6−11:30 p.m.), 12-h avg (12−11:30 a.m. to 12−11:30 p.m.)		

Table 5-3 (Continued): Epidemiologic studies of $PM_{2.5}$ and lung function in populations with asthma.

Study	Study Population	Exposure Assessment	Concentration (μg/m³)	$PM_{2.5}$ Copollutant Model Results and Correlations
Allen et al. (2008); Trenga et al. (2006) Seattle, WA 1999−2002	N = 17, ages 6−13 yr Most mild persistent asthma, 65% asthma medication use Daily supervised measures—5-10 days, multiple sessions for some subjects No information on participation rate	Outdoor home, total personal, ambient 24-h avg Ambient estimated from personal to ambient sulfur ratio and outdoor home $PM_{2.5}$.	Mean median, 75th Outdoor home: 11.2, 14.7 Total personal: 11.3, 16.3 Ambient: 6.3, 7.6	Correlation (*r*): (home monitor, ambient monitor) 0.51, 0.56 NO_2; 0.70, 0.77 CO Copollutant models with: NA
Barraza-Villarreal et al. (2008) Mexico City, Mexico 2003−2005	N = 158, ages 6−14 yr 55% mild intermittent asthma, 6% ICS use, 89% atopy Supervised measures every 15 days-mean 22 weeks No information on participation rate	One monitor 8-h moving avg Within 5 km of school or home *r* = 0.77 monitor-school	8-h avg Mean: 28.9 Max: 103	Correlation (*r*): 0.46 O_3, 0.61 NO_2 Copollutant models with: O_3
O'Connor et al. (2008) Boston, MA; Bronx, Manhattan, NY; Chicago, IL; Dallas, TX; Tucson, AZ; Seattle, WA	N = 861, ages 5−12 yr 100% persistent asthma, 100% atopy, 12% ICS use Daily home measures—2 weeks every 2 mo for 2 yr 70% maximum measures obtained	Monitors averaged in city Number NR 24-h avg Within median 2.3 km of home	NR	Correlation (*r*): 0.59 NO_2, 0.37 SO_2, −0.02 O_3, 0.44 CO Copollutant models with: NA
†Dales et al. (2009) Windsor, Canada Oct−Dec 2005	N = 182, ages 9−14 yr 58% medication use Daily home measures—28 days No information on participation rate Mean 1.6 and 2.2 h/day outdoors	Two monitors averaged 24-h avg, 12-h avg (12−8 a.m., 8 a.m.−8 p.m.) 99% within 10 km of monitors	24-h avg Mean: 7.8 75th: 10.0	Correlation (*r*): −0.26 O_3, 0.68 NO_2, 0.43 SO_2 Copollutant models with: NO_2, SO_2, and O_3
†Yamazaki et al. (2011) Yotsukaido, Japan Oct−Dec 2000	N = 17, ages 8−15 yr Children in long-term hospital care 100% severe, 100% medication use, 100% atopy Daily supervised measures—2−3 mo No information on participation rate	One monitor next to hospital 24-h avg, 1-h avg	Mean 6−7 a.m.: 24.0 12−1 p.m.: 26.9 6−7 p.m.: 30.0	Correlation (*r*): (morning, noon, evening, night) −0.44, −0.24, −0.27, −0.40 O_3; 0.54, 0.78, 0.62, 0.56 Copollutant models with: O_3

Table 5-3 (Continued): Epidemiologic studies of $PM_{2.5}$ and lung function in populations with asthma.

Study	Study Population	Exposure Assessment	Concentration (µg/m³)	$PM_{2.5}$ Copollutant Model Results and Correlations
†Hong et al. (2010) Seoul, South Korea May−Jun 2007	N = 18, mean (SD) age 9.3 (0.5) yr No information on asthma severity Daily home measures—1 mo No information on participation rate	Monitors in city, number NR 24-h avg	Mean: 36.2	Correlation (*r*): NA Copollutant models with: NA
Adults				
McCreanor et al. (2007) London, U.K. 2003−2005	N = 60, ages 19−55 yr 100% mild/moderate asthma, 100% AHR, 84% atopy Supervised measures—high and low traffic No information on participation rate	Personal ambient 2-h avg (10:30−12:30 a.m.) Scripted exposure walking on high-traffic road and in park, 3 weeks apart	Median, max High-traffic road: 28.3, 76.1 Park: 11.9, 55.9	Correlation (*r*): 0.62 UFP, 0.60 NO_2, 0.76 C, 0.73 EC Copollutant models with: NO_2
†Mirabelli et al. (2015) Atlanta, GA 2009−2011	N = 18, ages NR. Mean FEV_1: 100% predicted Supervised measures—pre- and post-commute, two exposures 93% completed 2nd commute	Personal in-vehicle 2-h avg (7−9 a.m.) Scripted exposure driving car on highway, median 17/13 weeks apart	Mean (SD) Asthma control > median: 23.8 (11.7) Asthma control < median: 21.5 (11.1)	Correlation (*r*): NA Copollutant models with: NA
†Maestrelli et al. (2011) Padua, Italy Years NR	N = 32, mean (SD) age 40 (7.5) yr 56% severe asthma, 91% atopy Supervised measures, six over 2 yr 76% with ≥ three measures	Total personal 24-h avg	NR	Correlation (*r*): NA Copollutant models with: NA

AHR = airway hyperresponsiveness, avg = average, BTEX = benzene, toluene, ethylbenzene, xylene, CO = carbon monoxide, FEV_1 = forced expiratory volume in 1 second, ICS = inhaled corticosteroid use, IQR = interquartile range, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, O_3 = ozone, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm; *r* = correlation coefficient; RR = relative risk, SD = standard deviation, SO_2 = sulfur dioxide, VOCs = volatile organic compounds.

†Studies published since the 2009 PM ISA.

Adults

A single study evaluated in the 2009 PM ISA (U.S. EPA, 2009) examined the association between short-term exposure to $PM_{2.5}$ and lung function in adults with asthma. In a panel of 60 adults with asthma in London, average $PM_{2.5}$ concentrations measured over a 2-hour outdoor walk was associated with decrements in FEV_1 and $MMEF_{25–75\%}$, but not FVC (McCreanor et al., 2007). Studies published since the completion of the 2009 PM ISA have been limited in number and results are inconsistent. Mirabelli et al. (2015) studied adults with asthma in Atlanta and reported decreased FEV_1 associated with 2-hour average personal $PM_{2.5}$ exposure measured 3 hours prior to spirometry. $PM_{2.5}$ concentrations were measured during scripted commutes through rush hour traffic, resulting in higher exposure levels. The observed associations were stronger in magnitude and more precise in participants with poorly controlled asthma. In contrast, in Padua, Italy, Maestrelli et al. (2011) tested the relationship between FEV_1 and 24-hour average personal $PM_{2.5}$ exposure the day before spirometry and reported no association in adults with asthma. This study was limited by a design that designated six single-day examination visits across a 2-year period, precluding the opportunity to examine alternative exposure lags. Additionally, low variability in personal $PM_{2.5}$ measurements may have contributed to the lack of an observed association.

5.1.2.3.1 Controlled Human Exposure Studies

Individuals with pre-existing airway diseases such as asthma, may suffer increased deleterious health effects from exposure to PM compared with individuals without pre-existing airway disease. Increased susceptibility of a $PM_{2.5}$-related health effect may be associated with specific mechanisms known to underlie the pathology of asthma, namely elevated inflammation and altered immune activity. However, there is little evidence from studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) that exposure to $PM_{2.5}$ results in decrements in lung function in individuals with asthma. Although a study evaluated in the 2009 PM ISA Petrovic et al. (2000) observed that a 2-hour exposure to $PM_{2.5}$ CAPs (92 $\mu g/m^3$) resulted in decreases in thoracic gas volume in healthy volunteers, other measures of lung function (spirometry, diffusing capacity, airway resistance) were unaffected. This general lack of effect of $PM_{2.5}$ exposure on lung function has also been shown in a study investigating the exposure of individuals with asthma to $PM_{2.5}$ CAPs (Gong et al., 2003). A recent study examining the respiratory effects of $PM_{2.5}$ on individuals with asthma has been conducted by (Urch et al., 2010) using a CAP facility for $PM_{2.5}$ located in downtown Toronto, Canada (study details in Table 5-4). Exposure to either $PM_{2.5}$ CAPs alone or in addition to O_3 was not observed to affect any measurement of pulmonary function, breathing parameters (tidal volume, breathing frequency, minute ventilation), or airway responsiveness (PC20), compared to filtered air control exposures. The lack of effect of $PM_{2.5}$ CAPs on respiratory function observed in Urch et al. (2010) is consistent with the results of previous controlled human exposure studies in which worsening of pulmonary function was not observed.

Table 5-4 Study-specific details from a controlled human exposure study of short-term $PM_{2.5}$ exposure and lung function in individuals with asthma.

Study	Study Design	Disease Status; n; Sex	Exposure Details (Concentration; Duration; Comparison Group	Endpoints Measured
Urch et al. (2010)	Blinded randomized block design	Healthy nonsmokers (13) and individuals with asthma (10); n = 23; 11 M, 12 F	$PM_{2.5}$ CAPs only: 64 ± 3 or 140 ± 6 μg/m^3 $PM_{2.5}$ CAPs + O_3: 68 ± 5 or 142 ± 7 μg/m^3 $PM_{2.5}$ + 119 ± 1 ppb O_3 Comparison group for both groups was filtered air; all exposures were for 2 h carried out at rest	Spirometry (pre-, 10-min, and 20-h post-exposure): Flow-volume, DLCO, MV, VT

CAPs = concentrated ambient particles; DLCO = diffusion capacity for CO; MV = minute volume; VT = tidal volume.

5.1.2.3.2 Animal Toxicological Studies

The 2009 ISA for PM (U.S. EPA, 2009) evaluated a limited number of inhalation studies examining pulmonary function in animal models of allergic airway disease, which share phenotypic features with asthma in humans. One study reported increased airway responsiveness to methacholine, as indicated by Penh, following short-term exposure to DE. However, this study did not distinguish between effects due to particles and gases in the mixture. No additional studies have become available since that time. In many animal studies, changes in ventilatory patterns are assessed using whole-body plethysmography, for which measurements are reported as Penh. Some investigators consider Penh solely an indicator of altered ventilatory timing (see Section 5.1.7.4) in the absence of other measurements to confirm changes in airway responsiveness.

5.1.2.3.3 Summary of Lung Function in Populations with Asthma

Overall, panel studies in children with asthma find generally consistent evidence of associations between short-term $PM_{2.5}$ exposure and lung function decrements. However, uncertainty regarding potential copollutant confounding remains. Evidence is more limited and less consistent in panel studies involving adults with asthma. Further, several controlled human exposure studies failed to observe lung function decrements in adults with asthma following short-term $PM_{2.5}$ exposure. No studies have examined this endpoint in animal models of allergic disease, which share many phenotypic features with asthma in humans.

5.1.2.4 Subclinical Effects Underlying Asthma Exacerbation

Studies evaluating the effects of short-term $PM_{2.5}$ exposure on subclinical effects consisted solely of epidemiologic studies. Results are discussed separately for children with asthma and adults with asthma. Some studies in adults employed scripted exposures to further inform this relationship. Scripted studies measuring personal ambient $PM_{2.5}$ exposures are designed to minimize uncertainty in the $PM_{2.5}$ exposure metric by always measuring $PM_{2.5}$ at the site of exposure, ensuring exposure to sources of $PM_{2.5}$ and measuring outcomes at well-defined lags after exposure.

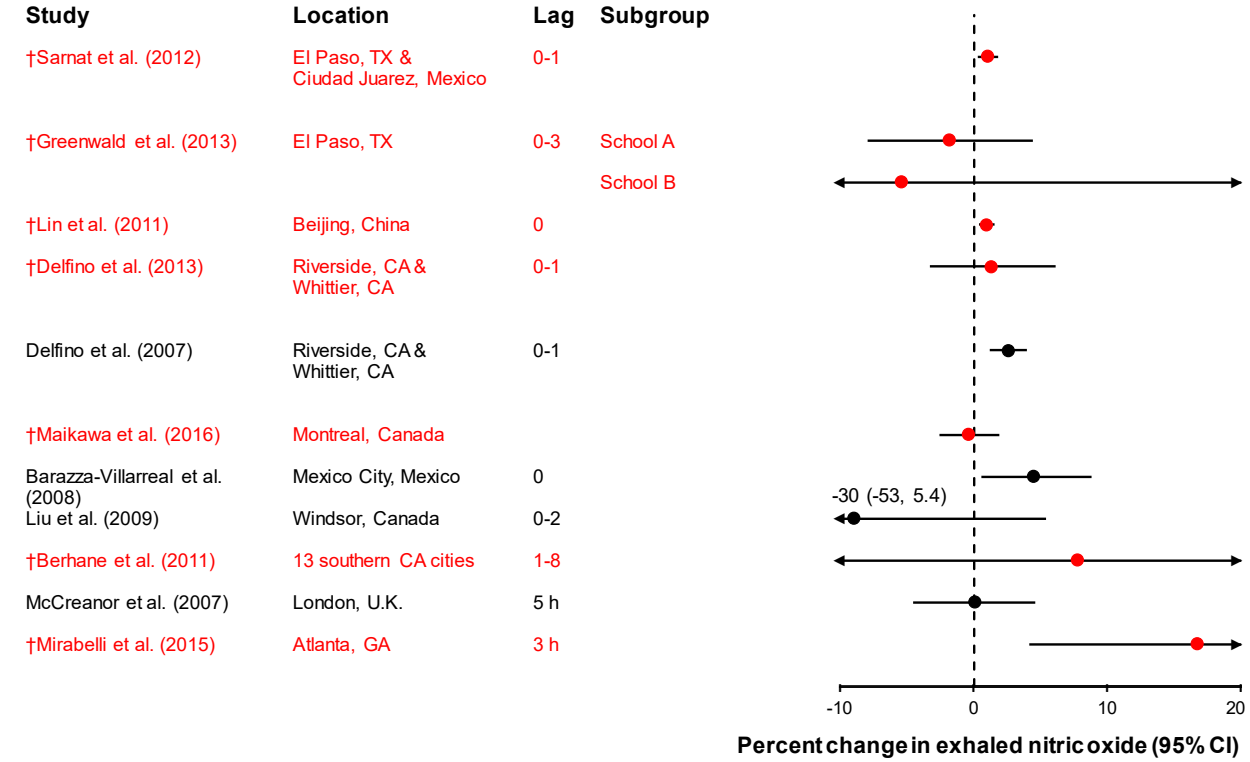
Children

Evidence described in the preceding sections for $PM_{2.5}$-related increases in asthma hospital admissions, asthma ED visits, and respiratory symptoms and lung function in children with asthma indicates a potential link between $PM_{2.5}$ exposure and asthma exacerbation. The 2009 PM ISA (U.S. EPA, 2009) also described generally consistent epidemiologic evidence linking increases in pulmonary inflammation in children with asthma to short-term personal $PM_{2.5}$ exposure and ambient $PM_{2.5}$ concentrations. Most studies examined exhaled nitric oxide (eNO) as an indicator of pulmonary inflammation. The relevance of eNO to asthma exacerbation is well supported. Levels of eNO have been associated with eosinophil counts (Brody et al., 2013), which mediate inflammation in allergic asthma. Further, eNO is higher in people with asthma and increases during acute exacerbation (Soto-Ramos et al., 2013; Kharitonov and Barnes, 2000). In the U.S., associations between short-term $PM_{2.5}$ exposure and eNO were observed in panel studies of children with asthma in southern California (Delfino et al., 2006) and Seattle (Allen et al., 2008; Koenig et al., 2005). In Seattle, total personal $PM_{2.5}$ exposure was partitioned into ambient-generated and nonambient-generated fractions based on the ratio of personal to ambient sulfur concentrations. Only the ambient-generated $PM_{2.5}$ was associated with pulmonary inflammation (Allen et al., 2008). Associations were also observed in most (Liu et al., 2009; Murata et al., 2007; Fischer et al., 2002), but not all (Holguin et al., 2007), studies of children outside of the U.S.

Several recent studies provide less consistent evidence of an association between short-term $PM_{2.5}$ exposure and pulmonary inflammation in children with asthma (Figure 5-5). Study-specific details, including cohort descriptions and air quality characteristics are highlighted in Table 5-5. Among children at four schools in the neighboring cities of El Paso, TX and Ciudad Juarez, Mexico, eNO was associated with 48-hour average outdoor $PM_{2.5}$ (Sarnat et al., 2012). Notably, the observed association was largely driven by results from children in one school (Ciudad Juarez) with the highest mean $PM_{2.5}$ concentrations. While Sarnat et al. (2012) reported a small, imprecise association between 2-day average outdoor $PM_{2.5}$ concentration and eNO in El Paso, a follow-up study of children in the same schools in El Paso observed null associations for 4-day average outdoor $PM_{2.5}$ concentrations (Greenwald et al., 2013). Ambient $PM_{2.5}$ concentrations across the two studies were similar (Table 5-5). A reanalysis of Delfino et al. (2006) confirmed that eNO was not associated with $PM_{2.5}$ concentrations measured at fixed-site monitors within 12 km of subjects' residences in a panel study of children with asthma in southern California (Delfino et

al., 2013). However, Delfino et al. (2006) did report an association with personal $PM_{2.5}$ in the initial study. In contrast to evidence of an association between personal $PM_{2.5}$ exposure an eNO, Maikawa et al. (2016) observed a negative association between previous-day personal $PM_{2.5}$ exposures and eNO in 62 children with asthma in Montreal, Canada.

Other recent studies that used fixed-site monitors to estimate short-term $PM_{2.5}$ concentrations reported more consistent evidence of an association between $PM_{2.5}$ and pulmonary inflammation in children with asthma. Panel studies of children in Beijing, China (Lin et al., 2011) and southern California (Berhane et al., 2011) reported eNO associations with 24-hour average $PM_{2.5}$ concentrations on the same day of examination and 7-day average concentrations prior to examination, respectively. Additionally, a panel study of schoolchildren with asthma in Denver, CO (Rabinovitch et al., 2011) indicated a $PM_{2.5}$ association with increases in urinary leukotriene E4, a cytokine involved in inflammation that is found to increase during asthma exacerbation. Results were similar by asthma severity, but varied across years, with the $PM_{2.5}$-associated increases in urinary leukotriene E4 limited to 2 of the first 3 study years. Only some children overlapped across years, and $PM_{2.5}$ concentrations were slightly higher in Year 3 (Rabinovitch et al., 2011).



CI = confidence interval.

Note: Studies in red with a dagger are recent studies. Studies in black were included in the 2009 PM ISA. Effect estimates are standardized to a 10 μg/m^3 increase in 24-hour average $PM_{2.5}$. Lag times reported in days. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-5 Summary of associations between short-term $PM_{2.5}$ exposures and exhaled nitric oxide in populations with asthma.

Table 5-5 Epidemiologic studies of $PM_{2.5}$ and subclinical effects underlying asthma exacerbation.

Study	Study Population	Exposure Assessment	Concentration (μg/m³)	$PM_{2.5}$ Copollutant Model Results and Correlations
Children				
†Sarnat et al. (2012) El Paso, TX; Ciudad Juarez, Mexico Jan−May 2008	N = 58 (14−15/school), ages 6−12 yr 33% ICS use, 41% hay fever Weekly eNO—16 weeks Mean 14 measures/subject, 787 total No information on participation rate	School outdoor 48-h avg Schools A and B: Low and high traffic Mean distance home—school: 3.2 km *r* = 0.71−0.93 school-school (within city), 0.91 school-monitor, 0.73−0.86 school-monitor	Mean outdoor Ciudad Juarez A: 31 Ciudad Juarez B: 20 El Paso A: 8.8 El Paso B: 15.6	Correlation (*r*): (across schools) 0.00, 0.05, −0.39, −0.28 NO_2 Copollutant models with: O_3 and NO_2
†Greenwald et al. (2013) El Paso, TX Mar−Jun 2010	N = 38, mean age 10 yr 55% ICS use Weekly eNO—13 weeks 536 total measures No information on participation rate	School outdoor 96-h avg School A and B: Low and high traffic *r* = 0.89 school-school, 0.91 monitor-monitor, 0.73−0.86 school-monitor (Zora et al., 2013)	Mean (SD) outdoor School A: 9.9 School B: 13.8	Correlation (*r*): 0.20 NO_2, 0.30 BTEX, 0.44 cleaning product VOCs, 0.37 SO_2 Copollutant models with: NA
†Lin et al. (2011); Zhu (2013) Beijing, China Jun, Sep, Dec 2007 and Jun, Sep 2008	N = 8, ages 9−12 yr Daily eNO—10 days, 5 periods 1,581 total measures No information on participation rate	One monitor, 0.65 km from school 24-h avg *r* = 0.56 school-monitor	Mean across periods 212, 96.0, 144, 183, 46.4 Max overall: 311	Correlation (*r*): 0.30 NO_2 Copollutant models with: NO_2, SO_2, and CO
†Delfino et al. (2013)	N = 45, ages 9−18 yr 100% persistent asthma, 64% ICS use Daily eNO—10 days	One monitor per city 24-h avg Within 12 km of Riverside homes, 5 km of Whittier homes	Mean: 23.2 Max: 87.2	Correlation (*r*): 0.31 NO_2, 0.39 O_3 Copollutant models with: NA

Table 5-5 (Continued): Epidemiologic studies of $PM_{2.5}$ and subclinical effects underlying asthma exacerbation.

Study	Study Population	Exposure Assessment	Concentration (μg/m³)	$PM_{2.5}$ Copollutant Model Results and Correlations
Delfino et al. (2006) Riverside, CA Aug−Dec 2003 Whittier, CA Jul−Nov 2004	Number measures NR No information on participation rate	Total personal, One monitor per city 24-h avg, 1-h max *r* = 0.91 monitor-outdoor home. Riverside, *r* = 0.77 personal-home, 0.64 monitor-personal.	Mean, max Total personal, 24-h avg Riverside: 32.8, 98 Whittier: 36.2, 197 Total personal, 1-h max Riverside: 37.9, 432 Whittier: 93.6, 573 Monitor, 24-h avg Riverside: 36.6, 87 Whittier: 18, 77	Correlation (*r*): (personal, monitor) 0.33, 0.25 NO_2 Copollutant models with: NO_2
†Maikawa et al. (2016) Montreal, Canada Oct 2009−Apr 2010	N = 62, ages 8−12 yr 15% severe asthma, 24% ICS use, 44% atopy Daily eNO—10 days Median three measures/subject	Total personal 24-h avg 60% samples had insufficient mass	Mean: 19.3 Max: 101	Correlation (*r*): 0.00 O_3 Copollutant models with: O_3
Allen et al. (2008); Mar et al. (2005) Seattle, WA 1999−2002	N = 17, ages 6−13 yr Most mild persistent asthma, 65% asthma medication use Daily eNO—5−10 days, multiple periods 6−20 measures/subject, 226 total No information on participation rate	Home outdoor, total personal, ambient 24-h avg Ambient estimated from personal to ambient sulfur ratio and outdoor home $PM_{2.5}$.	Mean/median, 75th Outdoor home: 11.2, 14.7 Total personal: 11.3, 16.3 Ambient: 6.3, 7.6	Correlation (*r*): NA Copollutant models with: NA
†Rabinovitch et al. (2011); Rabinovitch et al. (2006) Denver, CO 2002−2005	N = 82 (3-yr study), 73 (2-yr study) 65−86% moderate/severe asthma, 82−90% ICS use Daily urinary LTE4—up to 8 days, two periods per yr Median 11−13 measures/subject Yr 1−3 No information on participation rate	One monitor 24-h avg, 10-h avg (12−11 a.m.), 1-h max (12−11 a.m.) 4.3 km from school *r* = 0.92 monitor and school	Mean, max for Yr 1−3 24-h avg: 6.5−8.2, 20.5−23.7 10-h avg: 7.4−9.1, 22.7−30.2 1-h max: 16.8−22.9,39−52 (95th)	Correlation (*r*): NA Copollutant models with: NA

Table 5-5 (Continued): Epidemiologic studies of $PM_{2.5}$ and subclinical effects underlying asthma exacerbation.

Study	Study Population	Exposure Assessment	Concentration (µg/m³)	$PM_{2.5}$ Copollutant Model Results and Correlations
Barraza-Villarreal et al. (2008) Mexico City, Mexico 2003−2005	N = 158, ages 6−14 yr 55% mild intermittent asthma, 6% ICS use, 89% atopy eNO, nasal lavage IL—8 every 15 days-mean 22 weeks 702 total measures No information on participation rate	One monitor 8-h avg Within 5 km of school or home *r* = 0.77 monitor-school	Mean: 28.9 Max: 103	Correlation (*r*): 0.46 O_3, 0.61 NO_2 Copollutant models with: O_3
Liu et al. (2009); Liu (2013) Windsor, Canada Oct−Dec 2005	N = 182, ages 9−14 yr 37% ICS use Weekly eNO, TBARS—4 weeks 672 total measures No information on participation rate	Two monitors averaged 24-h avg 99% homes within 10 km	Median (IQR): 6.5 (6.0) 95th: 19.0	Correlation (*r*): −0.41 O_3, 0.71 NO_2, 0.56 SO_2 Copollutant models with: O_3, NO_2, and SO_2
†Berhane et al. (2011) 13 southern California cities 2004−2005	N = 169, ages 6−9 yr One eNO measure, cross-sectional No information on participation rate	One monitor per community 24-h avg	NR	Correlation (*r*): (warm season, cold season) 0.61, −0.05 O_3; 0.47, 0.65 NO_2 Copollutant models with: NA
Adults				
McCreanor et al. (2007) London, U.K. 2003−2005	N = 60, ages 19−55 yr 100% mild/moderate asthma, 100% AHR, 84% atopy 2 eNO measures—high and low traffic No information on participation rate	Personal ambient 2-h avg (10:30−12:30 a.m.) Scripted exposure walking on high-traffic road and in park, 3 weeks apart	Median, max High-traffic road: 28.3, 76.1 Park: 11.9, 55.9	Correlation (*r*): 0.60 NO_2, 0.76 CO Copollutant models with: NO_2
†Mirabelli et al. (2015) Atlanta, GA 2009−2011	N = 18, ages NR. Mean FEV_1: 100% predicted Two measures—pre- and post-commute, Two periods 93% completed 2nd commute	Personal in-vehicle 2-h avg (7−9 a.m.) Scripted exposure driving car on highway, median 17/13 weeks apart	Mean Asthma control > median: 23.8 Asthma control < median: 21.5	Correlation (*r*): NA Copollutant models with: NA

Table 5-5 (Continued): Epidemiologic studies of $PM_{2.5}$ and subclinical effects underlying asthma exacerbation.

Study	Study Population	Exposure Assessment	Concentration (µg/m³)	$PM_{2.5}$ Copollutant Model Results and Correlations
†Maestrelli et al. (2011) Padua, Italy Years NR	N = 32, mean (SD) age 40 (7.5) yr 56% severe asthma, 69% ICS use, 91% atopy Six eNO measures over 2 yr 166 total measures No information on participation rate	Total personal 24-h avg	NR	Correlation (*r*): NA Copollutant models with: NA

AHR = airway hyperresponsiveness, avg = average, BTEX = benzene, toluene, ethylbenzene, xylene, CO = carbon monoxide, eNO = exhaled nitric oxide, FEV_1 = forced expiratory volume in 1 second, ICS = inhaled corticosteroid use, IL-8 = interleukin-8, IQR = interquartile range, LTE4 = leukotriene E4, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, O_3 = ozone, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm; *r* = correlation coefficient; SD = standard deviation, SO_2 = sulfur dioxide, TBARS = thiobarbituric acid reactive substances, VOCs = volatile organic compounds.

†Studies published since the 2009 PM ISA.

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The inconsistency in recent findings, as related to the 2009 PM ISA, is not explained by lower $PM_{2.5}$ concentrations in recent studies (Table 5-5) but may be influenced by location-specific differences in PM sources, study populations, or building infiltration characteristics (Section 3.4). Studies evaluated in the 2009 PM ISA observed associations in locations representing a wide range of $PM_{2.5}$ concentrations. Additionally, a strength of previously reviewed studies of pulmonary inflammation is examination of the hourly lag structure of $PM_{2.5}$ associations. Most (Rabinovitch et al., 2006; Mar et al., 2005) results indicated an increase in inflammation with increases in $PM_{2.5}$ concentrations averaged over the preceding 1 to 11 hours. Associations were also observed with 1-hour or 8-hour max $PM_{2.5}$ that were larger in magnitude than those for 24-hour average $PM_{2.5}$ (Delfino et al., 2006; Rabinovitch et al., 2006). Other results indicate that $PM_{2.5}$ exposure may have a rapid and transient effect on pulmonary inflammation in people with asthma. For Seattle, WA and Riverside and Whittier, CA, distributed lag models show an increase in eNO with the 1-hour average $PM_{2.5}$ concentration up to 5 or 10 hours prior but not with longer lags of 24−48 hours (Delfino et al., 2006; Mar et al., 2005). This may suggest that some recent studies have examined exposure windows that were too long to detect an association, though Berhane et al. (2011) observed eNO associations with cumulative average $PM_{2.5}$ up to 30 days.

Additionally, recent studies of pulmonary inflammation do not establish an independent association with $PM_{2.5}$ exposure. A recent study presents $PM_{2.5}$ associations that are attenuated, but still positive in copollutant models with NO_2, SO_2, or CO (Lin et al., 2011). In a study evaluated in the 2009 PM ISA, personal $PM_{2.5}$ associations with eNO were robust to NO_2 adjustment (Delfino et al., 2006). The result for personal exposure supports an association with $PM_{2.5}$ that is independent of NO_2 exposure based on comparable exposure measurement error and low correlation ($r = 0.30$). However, the limited number of studies examining additional copollutants, in addition to some inconsistency in the observed associations in recent studies, leaves uncertainty as to whether $PM_{2.5}$ exposure leads to an increase in pulmonary inflammation in children with asthma. Further discussion of copollutant confounding is provided in Section 5.1.10.1.

Adults

Studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) provided contrasting evidence of an association between short-term exposure to $PM_{2.5}$ and lung function in adults with asthma. In a panel of 60 adults with asthma in London, average $PM_{2.5}$ concentrations measured over a 2-hour outdoor walk was not associated with eNO measurements taken 3 to 7 hours post-exposure (McCreanor et al., 2007). In contrast, in a panel of older adults in Seattle, $PM_{2.5}$ concentrations measured outside of residences were associated with eNO in subjects with asthma. Recent studies are limited in number and results are also inconsistent (Figure 5-5). Mirabelli et al. (2015) studied adults with asthma in Atlanta and reported increased in eNO associated with 2-hour average personal $PM_{2.5}$ exposure measured 0, 1, 2, and 3 hours prior to spirometry. $PM_{2.5}$ concentrations were measured during scripted commutes through rush hour traffic, resulting in higher exposure levels. The observed associations were stronger in magnitude in

participants with poorly controlled asthma. In contrast, in Padua, Italy, Maestrelli et al. (2011) tested the relationship between eNO and 24-hour average personal $PM_{2.5}$ exposure the day before spirometry and reported negative associations in adults with asthma. This study was limited by a design that designated six single-day examination visits across a 2-year period, precluding the opportunity to examine alternative exposure lags.

5.1.2.4.1 Controlled Human Exposure Studies

There were no studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) that specifically investigated the association between PM2.5 CAPs exposure and subclinical effects underlying asthma exacerbation. Recently, Urch et al. (2010) investigated the respiratory effects of short-term exposure to PM2.5 on individuals with asthma by using a CAP facility for PM2.5 located in downtown Toronto, Canada (study details in Table 5-6) and found little change in sputum total cell counts, neutrophils, or macrophages when compared to pre-exposure levels.

Table 5-6 Study-specific details from a controlled human exposure study of short-term $PM_{2.5}$ exposure and subclinical effects underlying asthma exacerbation.

Study	Study Design	Disease Status; n; Sex	Exposure Details (Concentration; Duration; Comparison Group)	Endpoints Measured
Urch et al. (2010)	Blinded randomized block design	Healthy nonsmokers (13) and individuals with asthma (10); n = 23; 11 M, 12 F	$PM_{2.5}$ CAPs only: 64 ± 3 or 140 ± 6 μg/m^3 $PM_{2.5}$ CAPs + O_3: 68 ± 5 or 142 ± 7 μg/m^3 $PM_{2.5}$ + 119 ± 1 ppb O_3 Comparison group for both groups was filtered air; all exposures were for 2 h carried out at rest	Sputum (pre- and 3- and 20-hour post-exposure): IL-6, IL-8, and IL-10, TNF-α, leukotriene-B, differential cell counts Venous blood (pre-, 10-min, and 3- and 20-h post-exposure): IL-6, TNF-α

CAPs = concentrated ambient particles; IL-6 = Interleukin-6; IL-8 = Interleukin-8; IL-10 = Interleukin-10; O_3 = ozone; TNF-α = tumor necrosis factor α.

5.1.2.4.2 Animal Toxicological Studies

Animal toxicological studies have focused on exacerbation of asthma in the context of allergic airway disease. Allergic airway disease (asthma, rhinitis, etc.) is a type of immune hypersensitivity that is mediated by immunoglobulin E (IgE). Development of allergic airway disease requires sensitization (immunization) that requires, presentation of a foreign antigen by antigen-presenting cells (dendritic cells

and macrophage subsets) to T-lymphocytes, the activation and clonal expansion of B-cells, and finally production of antigen-specific antibody (IgE) that binds to the antigen. Secondary exposure of previously sensitized individuals to the antigen (challenge, or elicitation phase), will activate IgE-mediated pathways that result in eosinophil recruitment, mucus production, and reactive airways.

The 2009 PM ISA (U.S. EPA, 2009) reviewed the evidence that exposure to $PM_{2.5}$ exacerbated allergic responses in laboratory rodents with pre-existing allergic airway disease. Several studies involved multiday exposures of ovalbumin (OVA)-sensitized and challenged Brown Norway rats to $PM_{2.5}$ CAPs. Increased nasal and airway mucosubstances, pulmonary inflammation, and retention of anthropogenic trace elements (La, V, Mn, S) in lung tissue were observed following 4−5 days of exposure to $PM_{2.5}$ CAPs in Detroit, MI (Harkema et al., 2004; Morishita et al., 2004). A 13-day exposure to $PM_{2.5}$ CAPs in Grand Rapids, MI resulted in no changes in BALF cells or gene expression in the whole lung (Heidenfelder et al., 2009). However, enhanced OVA-specific IgE and Muc5AC responses to ovalbumin (OVA) were observed. In addition, $PM_{2.5}$ CAPs exposure resulted in enhanced allergic bronchiolitis and alveolitis, as well as in epithelial hypertrophy and mucus cell metaplasia, which are characteristic of airway epithelial remodeling. Another study showed that enhancement of allergic responses in mice depended on proximity to the PM source following multiday exposure to roadway $PM_{2.5}$ CAPs in Los Angeles (Kleinman et al., 2005). Additionally, a single acute exposure to reaerosolized diesel exhaust particles (DEP) resulted in dose-dependent increases in levels of the Th2 cytokine IL-4 in BALF in allergic mice (Farraj et al., 2006a, b).

Recently, Harkema et al. (2009) extended their field studies in Detroit to determine if $PM_{2.5}$ CAPs inhalation would modify the allergic responses during the process of allergen challenge of sensitized rats. Ovalbumin-sensitized Brown Norway rats that were exposed to Detroit summertime $PM_{2.5}$ CAPs for the same 3 consecutive days of intra-nasal OVA challenge had increased lavaged total protein, secreted mucosubstances (Muc5AC), and numbers of lymphocytes and eosinophils compared to filtered air-exposed, allergic rats ($p < 0.05$). $PM_{2.5}$ CAPs exposure did not increase OVA-specific IgE levels in BALF above that seen in response to OVA alone. Decreases in pulmonary gene expression of TNFα, IL-10, and IFNγ (putative Th1 mediators) were also detected in $PM_{2.5}$ CAPs-exposed, OVA-challenged rats ($p \leq 0.05$). Using the same exposure protocol but in different rats and on different days when $PM_{2.5}$ CAPs concentration was lower; inflammation responses were unaffected by $PM_{2.5}$ CAPs exposure. In addition to having greater $PM_{2.5}$ CAPs concentration the first exposure study consisted of $PM_{2.5}$ that had more iron, sulfate, nitrate, and PAH content than during the second exposure study. Additional study details, for this recent study and a related one, are found in Table 5-7.

Table 5-7 Study-specific details from animal toxicologic studies of subclinical effects underlying asthma exacerbation.

Study/Study Population	Pollutant	Exposure	Endpoints
Harkema et al. (2009) Species: Rat Sex: Male Strain: Brown Norway Age/weight: 10−12 weeks	$PM_{2.5}$ CAPs Detroit, MI (urban residential) Particle size: 0.66−0.79 µm Control: Filtered air	Route: Whole-body inhalation exposure Dose/concentration: Period 1: 596 µg/m³ Period 2: 356 µg/m³ Duration: 8 h/day, 3 days, two exposure periods in July Time to analysis: 24 h All animals sensitized to OVA. $PM_{2.5}$ CAPs inhalation during OVA challenge	Histopathology of nose and lung—light microscopy, airway labelling index BALF cells Gene expression-cytokines and Muc5AC
Wagner et al. (2012) Species: Rat Strain: Brown Norway Sex: Male Age/weight: 10−12 weeks	$PM_{2.5}$ CAPs Urban Grand Rapids, MI Urban Detroit, MI Particle sizes: $PM_{2.5}$ Control: HEPA-filtered control air	Route: Whole-body inhalation Dose/concentration (D) Detroit 542 µg/m³ (GR) Grand Rapids 519 µg/m³ Dose/concentration 8 h × 1 day; begun 30 min after intra-nasal OVA challenge Duration of exposure: 8 h Time to analysis: 16 h post exposure	PM characterization Histopathology—lung BALF cells Lung injury—BALF protein BALF-Muc5AC content

BALF = bronchoalveolar lavage fluid; CAPs = concentrated ambient particles; HEPA = high efficiency particulate absorber; Muc5AC = Mucin 5AC, oligomeric mucus/gel-forming; OVA = ovalbumin.

Morphologic responses to short-term $PM_{2.5}$ CAPs exposure was also examined by (Harkema et al., 2009). Both the nose and the lung were evaluated for histologic changes and epithelial cell proliferation. No additional effect on OVA-induced allergic rhinitis was seen in the animals exposed to $PM_{2.5}$ CAPs. However, exposure to $PM_{2.5}$ CAPs resulted in a greater severity of allergic bronchiolitis and alveolitis in OVA-sensitized and challenged rats. More severe mucus cell metaplasia was found, as evidenced by increased amounts of intra-epithelial mucosubstances in conducting airways ($p \leq 0.05$). Epithelial cell proliferation, as measured by labelling index in the airways, was not altered by $PM_{2.5}$ CAPs exposure. When the same exposure protocol was used but in different rats and on different days when $PM_{2.5}$ CAPs concentration was considerably lower, morphologic responses were unaffected by $PM_{2.5}$ CAPs exposure.

The OVA-allergic Brown Norway rat model was also used to compare the effects of $PM_{2.5}$ CAPs exposure that were derived from two dissimilar urban airsheds in Grand Rapids or Detroit MI (Wagner et

al., 2012). Ovalbumin-sensitized rats were challenged with intra-nasal OVA and 30 minutes later breathed similar concentrations of $PM_{2.5}$ CAPs for 8 hours. Exposure to Detroit $PM_{2.5}$ CAPs, which were characterized by high sulfates and local industrial emissions (high Pb, Zn, and V content), enhanced eosinophilic inflammation ($p < 0.05$), mucus hypersecretion ($p < 0.05$), and mucous cell metaplasia. However, the opposite responses were seen when allergic rats inhaled Grand Rapids $PM_{2.5}$ CAPs, which were dominated by a large spike in morning traffic emissions (NO_2, CO, EC), but had low sulfates throughout the 8-hour exposure. Allergen-induced increases in airway eosinophils ($p < 0.05$), mucus hypersecretion ($p < 0.05$), and mucous cells were reversed in rats exposed to Grand Rapids $PM_{2.5}$ CAPs.

In summary, several studies provide evidence that exposure to $PM_{2.5}$ CAPs and DEP exacerbates allergic responses. In addition, one study found that $PM_{2.5}$ CAPs exposure resulted in an inhibition of allergic responses. These disparate findings may be due to source-related differences in the composition of $PM_{2.5}$ CAP due to different locations where the CAPs were collected.

5.1.2.4.3 Summary of Subclinical Effects Underlying Asthma Exacerbation

Overall, panel studies in children with asthma provide some evidence of associations between short-term $PM_{2.5}$ exposure and inflammatory markers although uncertainty regarding potential copollutant confounding remains. Results were more consistent with shorter lag times. Evidence is mainly negative in panel studies and controlled human exposure studies involving adults with asthma. Further, several studies found that short-term $PM_{2.5}$ exposure led to allergic inflammation and airway remodeling in animal models of allergic disease, which share many phenotypic features with asthma in humans. However, in studies of $PM_{2.5}$ CAPs, the response was dependent on concentration and source profile of the airshed.

5.1.2.5 Summary of Asthma Exacerbations

Recent epidemiologic studies strengthen the evidence for a relationship between short-term $PM_{2.5}$ exposure and asthma exacerbation in children. In particular, recent studies add evidence supporting associations between short-term $PM_{2.5}$ concentration and asthma hospital admissions, ED visits, and physician visits in children. Additional evidence of $PM_{2.5}$-related increases in asthma symptoms, lung function decrements, and pulmonary inflammation is provided by recent panel studies in children with asthma. Findings were not entirely consistent, but overall several well-conducted studies measuring total personal exposure, residential outdoor concentration, and school outdoor $PM_{2.5}$ concentration observed associations with asthma-related effects. Evidence for a relationship between short-term $PM_{2.5}$ exposure and asthma exacerbation in adults continues to be inconsistent.

Evidence from experimental studies provides biological plausibility for associations seen in epidemiologic studies between short-term $PM_{2.5}$ exposure and asthma exacerbation. Although controlled

human exposure studies were inconsistent in showing effects on lung function and pulmonary inflammation in individuals with asthma, animal toxicological studies demonstrated allergic inflammation, enhanced serum IgE, and airway remodeling in animal models of allergic airway disease. These changes may lead to lung function decrements and respiratory symptoms, which were observed in epidemiology studies in relation to $PM_{2.5}$ exposure (Figure 5-1).

Across the indicators of asthma exacerbation, associations continue to be observed with 24-hour average $PM_{2.5}$ concentrations from the same day, from the few preceding days, or averaged over a few days (Section 5.1.10). Evidence does not clearly point to a stronger effect for a particular exposure lag. Recent epidemiologic studies add evidence from copollutant models that show that $PM_{2.5}$ associations are independent of a copollutant among NO_2, CO, and O_3. Based on more limited investigation, there is evidence that $PM_{2.5}$ associations may be modified by these copollutants and aeroallergens. Other copollutants largely are unexamined. While there are some results from copollutant models based on personal exposure measurements that may have less differential exposure measurement error, scarce application of copollutant models limits the ability to analyze potential for confounding. Thus, as in the 2009 ISA for PM (U.S. EPA, 2009), uncertainty remains in distinguishing an independent effect of $PM_{2.5}$ exposure on asthma exacerbation.

5.1.3 Allergy Exacerbation

Animal toxicological studies reviewed in the 2009 PM ISA (U.S. EPA, 2009) provided evidence that $PM_{2.5}$ can facilitate delivery of allergenic material to the airways, promote allergic sensitization, and exacerbate allergic responses. Meanwhile, epidemiologic evidence was limited, with a single study reporting an association between short-term $PM_{2.5}$ concentrations and hospital admissions for allergic rhinitis in children in Turkey (Tecer et al., 2008). Recent evidence that $PM_{2.5}$ exposure enhances allergic inflammation in animal models of allergic airway disease, described in Section 5.1.2.4, not only supports $PM_{2.5}$-related asthma exacerbation but also indicates that $PM_{2.5}$ exposure could affect respiratory responses in people with allergies, but not asthma. Several recent epidemiologic studies add to the evidence base, but do not consistently link short-term $PM_{2.5}$ exposure to allergy exacerbation in children or adults. Recent studies examined an array of outcomes, including allergy symptoms, and lung function changes and pulmonary inflammation in populations with allergies. Notably, lung function can decrease during an allergy exacerbation due to airway obstruction caused by Th2 cytokine mediated inflammation, making lung function and pulmonary inflammation relevant markers of allergy exacerbation.

While Tecer et al. (2008) found evidence of an association between short-term $PM_{2.5}$ concentrations and allergic rhinitis hospitalizations in children, Villeneuve et al. (2006) did not observe an association between short-term $PM_{2.5}$ and physician visits for allergic rhinitis in individuals 65 years of age and older in Toronto. The authors examined single-day lags ranging from 0 to 7 days and reported mostly null associations, with some small positive and negative associations depending on the lag day.

The comparative results of the studies may be indicative of age-related differences in allergic rhinitis sensitivity to $PM_{2.5}$, but differences in study design and location make it difficult to draw conclusions. Other recent studies examined the relationship between short-term exposure to $PM_{2.5}$ and skin allergies, including urticaria (Kousha and Valacchi, 2015) and atopic dermatitis symptoms (Song et al., 2011). Kousha and Valacchi (2015) monitored ED visits for urticaria in relations to short-term $PM_{2.5}$ concentrations in Windsor, Ontario. The authors only analyzed single-day lags, ranging from 0 to 7 days prior to ED visits, and reported associations at lags 1 (OR = 1.07 [95% CI: 0.99, 1. 16]), 2 (1.14 [1.04, 1. 22]), and 3 (1.07 [0.99, 1. 16]), with generally null results at other examined lag times. However, there are uncertainties in the urticaria results, because over 67% of the days included in the study period had less than two reported ED visits. Meanwhile, in a study of schoolchildren with atopic dermatitis in South Korea, $PM_{2.5}$ measured on the school rooftop was not associated with self-reported symptoms of itchy skin (Song et al., 2011).

As mentioned previously, lung function changes and pulmonary inflammation in populations with allergies may serve as markers of allergy exacerbation. In Mexico City, Barraza-Villarreal et al. (2008) examined the association between short-term $PM_{2.5}$ concentrations and several lung function and pulmonary inflammation metrics in schoolchildren with and without asthma. The authors reported that 72% of the 50 subjects without asthma were atopic, leading them to repeat the analysis in a subgroup of atopic children. In the subgroup analysis, $PM_{2.5}$ concentrations were positively associated with FeNO, a measure of airway inflammation, but no quantitative results were presented. The authors presumably did not observe similar associations with the other metrics examined in the main analysis, including IL-8, FEV_1, FVC, and $FEV_{25–75}$.

In summary, recent animal toxicological studies expand the existing evidence base, providing additional support for the biological plausibility of $PM_{2.5}$-related allergy exacerbation. In contrast, a limited number of epidemiologic studies provide inconsistent evidence of an association across multiple endpoints, including a variety of allergic symptoms, and lung function changes and pulmonary inflammation in people with existing allergies.

5.1.4 Chronic Obstructive Pulmonary Disease (COPD) Exacerbation

Chronic obstructive pulmonary disease (COPD) is a lung disease characterized by destruction of alveolar tissue, airway remodeling, and airflow limitation. Reduced airflow is associated with decreased lung function, and clinical symptoms demonstrating exacerbation of COPD include cough, dyspnea, sputum production, and shortness of breath. Severe exacerbation can lead to ED visits or hospital admissions. The epidemiologic studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) provided evidence of consistent positive associations between short-term $PM_{2.5}$ exposure and increases in hospital admissions and ED visits for COPD. Experimental studies evaluated in the 2009 PM ISA and the 2004 PM AQCD (U.S. EPA, 2004) provide biological plausibility for effects seen in epidemiologic studies. A

limited number of controlled human exposure and animal toxicological studies demonstrated changes in lung function-related parameters, as well as lung injury and inflammation. Recent studies of the relationship between short-term $PM_{2.5}$ exposure and COPD exacerbation mainly examine hospital admissions and ED visits and are generally consistent in showing associations with $PM_{2.5}$. A small body of studies expand the evidence base and show associations with respiratory symptoms and pulmonary inflammation in adults with COPD, in some cases with measures of personal $PM_{2.5}$. Results for lung function changes are inconsistent. Thus, there is variable coherence among various endpoints linked to COPD exacerbation.

In addition to examining the relationship between short-term $PM_{2.5}$ exposure and COPD exacerbation, some epidemiologic studies often conduct analyses to assess whether the associations observed are due to chance, confounding, or other biases. As such, this evidence across epidemiologic studies is not discussed within this section, but evaluated in an integrative manner and focuses specifically on those analyses that address policy-relevant issues (Section 5.1.10), and includes evaluations of copollutant confounding (Section 5.1.10.1), model specification (Section 0), lag structure (Section 5.1.10.3), the role of season and temperature on $PM_{2.5}$ associations (Section 5.1.10.4), averaging time of $PM_{2.5}$ concentrations (Section 5.1.10.5), and concentration-response (C-R) and threshold analyses (Section 5.1.10.6). The studies that inform these issues and evaluated within these sections are primarily epidemiologic studies that conducted time-series or case-crossover analyses focusing on COPD hospital admissions and ED visits.

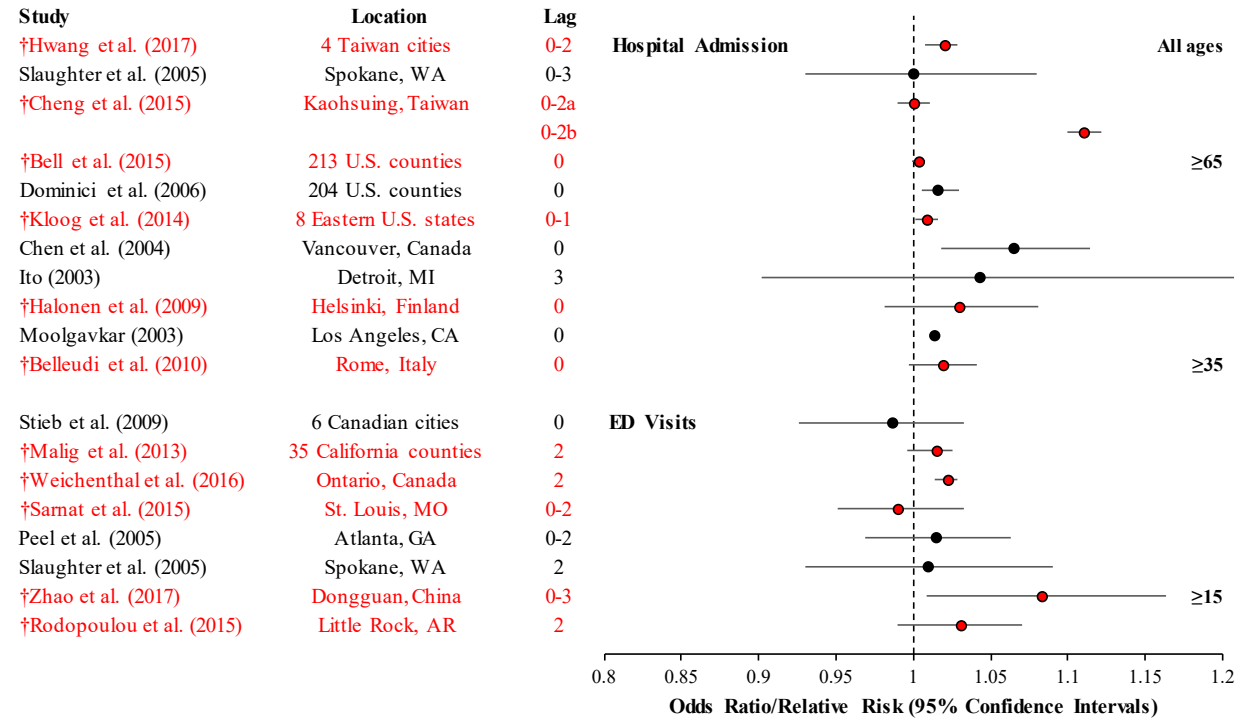
5.1.4.1 Hospital Admissions and Emergency Department (ED) Visits

Associations between short-term exposure to $PM_{2.5}$ and hospital admissions and ED visits for COPD were generally positive among the multicity and single-city studies conducted in the U.S. and Canada and evaluated in the 2009 PM ISA (U.S. EPA, 2009). Multicity studies reviewed in the 2009 PM ISA examining $PM_{2.5}$ and hospital admissions for COPD reported both null [a Canadian study, (Stieb et al., 2009)] and positive [a U.S. study, (Dominici et al., 2006)] associations between COPD hospital admissions and $PM_{2.5}$. The results from multicity studies were supported by single-city studies conducted in the U.S. and Canada that reported positive associations between short-term exposure to $PM_{2.5}$ and hospital admissions and ED visits for COPD.

Recent studies examining associations between short-term $PM_{2.5}$ exposure and COPD hospital admissions and ED visits generally support the positive associations reported in the 2009 PM ISA. These recent studies report positive associations across both multi- and single-city studies, especially for hospital admissions in populations 65 and older (see Figure 5-6, Table 5-8). However, most of the recent studies that examine short-term $PM_{2.5}$ exposure and COPD ED visits consist of single-city studies.

For each of the studies evaluated in this section, Table 5-8 presents the air quality characteristics of each city, or across all cities, the exposure assignment approach used, and information on copollutants

examined in each COPD hospital admission and ED visit study. Other recent studies of COPD hospital admissions and ED visits are not the focus of this evaluation because they did not address uncertainties and limitations in the evidence previously identified, and, therefore, do not directly inform the discussion of policy-relevant considerations detailed in Section 5.1.10. Additionally, many of these studies were conducted in small single cities, encompassed a short study duration, or had insufficient sample size. The full list of these studies can be found here: https://hero.epa.gov/hero/particulate-matter.



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-6 Summary of associations between short-term $PM_{2.5}$ exposures and chronic obstructive pulmonary disease (COPD) hospital admissions and emergency department (ED) visits for a 10 $\mu g/m^3$ increase in 24-hour average $PM_{2.5}$ concentrations.

Table 5-8 Epidemiologic studies of $PM_{2.5}$ and hospital admissions and emergency department (ED) visits for chronic obstructive pulmonary disease.

Study	Exposure Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	$PM_{2.5}$ Copollutant Model Results and Correlations
Hospital admissions				
†Bell et al. (2015) 213 U.S. counties 1999−2010 Older adults ≥65 yr	Monitors in county averaged Number per county NR	U.S.: 12.3 Northeast: 12.0 Midwest: 12.9 South: 12.4 West: 11.3	Max U.S.: 20.2 Northeast: 16.4 Midwest: 16.5 South: 16.5 West: 20.2	Correlations (*r*): NA Copollutant models with: NA
Dominici et al. (2006) 204 U.S. counties †Peng et al. (2009b) 94 U.S. counties 1999−2002 Older adults ≥65 yr	Monitors in county averaged Number per county NR	13.4	75th: 15.2	Correlations (*r*): NA Copollutant models with: NA
†Kloog et al. (2014) New York, New Jersey, Pennsylvania, Maryland, Delaware, Virginia, West Virginia, Washington, DC 2000−2006 Older adults ≥65 yr	Satellite-monitor hybrid model	Urban: 12.8 Rural: 11.5	75th Urban: 16.7 Rural: 14.2 Max Urban: 96.1 Rural: 95.9	Correlations (*r*): NA Copollutant models with: NA
Chen et al. (2004) Vancouver, Canada 1995−1999 Older adults ≥65 yr	NR	7.7	75th: 9.0 Max: 32	Correlations (*r*): NA Copollutant models with: O_3, NO_2, CO, SO_2

Table 5-8 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions and emergency department (ED) visits for chronic obstructive pulmonary disease.

Study	Exposure Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	$PM_{2.5}$ Copollutant Model Results and Correlations
Ito (2003) Detroit, MI 1992−1994 Older adults, age NR	One monitor in Windsor, Ontario	18	75th: 21 95th: 42	Correlations (*r*): NA Copollutant models with: NA
†Halonen et al. (2009a) Helsinki, Finland 1998−2004 Older adults ≥65 yr	Two monitors	Median: 8.8	75th: 11.0 Max: 41.5	Correlation (*r*): 0.43 O_3. Copollutant models with: O_3
Moolgavkar (2003) Los Angeles, CA 1987−1995 All adults	Monitors in city Number of monitors NR	NR	NR	Correlation (*r*): NA Copollutant models with: CO, SO_2, NO_2.
†Kim et al. (2012) Denver, CO 2003−2007 All adults	One monitor	8.0	Max: 59.4	Correlation (*r*): 0.30 O_3, 0.26 NO_2, 0.23 CO, 0.23 SO_2 Copollutant models with: NA
†Liu et al. (2016) Greater Houston area, TX 2008−2013 All adults	Four monitors averaged from one county	12.0	90th: 18.5	Correlations (*r*): NA Copollutant models with: NA
†Cheng et al. (2015) Kaohshing, Taiwan 2006−2010 All adults	Six monitors averaged	Median: 44.3	75th: 61.9 Max: 144	Correlation (*r*): 0.42 O_3, 0.80 NO_2, 0.81 CO, 0.25 SO_2 Copollutant models with: O_3, NO_2, CO, SO_2

Table 5-8 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions and emergency department (ED) visits for chronic obstructive pulmonary disease.

Study	Exposure Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	$PM_{2.5}$ Copollutant Model Results and Correlations
†Zhao et al. (2016) Dongguan, China 2013−2015 All adults	Five monitors averaged	42.6	75th: 56.8 Max: 193	Correlation (*r*): 0.40 O_3, 0.67 NO_2, 0.69 SO_2 Copollutant models with: O_3, SO_2, NO_2
†Belleudi et al. (2010) Rome, Italy 2001−2005	One monitor, 2 km from city center	22.8		Correlation (*r*): 0.84 PM_{10} Copollutant models with: NA
ED visits				
†Weichenthal et al. (2016) 15 cities Ontario, Canada 2004−2011 All ages	Nearest monitor to population-weighted zip code centroid or single available monitor	7.1	Max: 56.8	Correlation (*r*): <0.42 NO_2 Copollutant models with: O_3
†Sarnat et al. (2015) St. Louis, MO (eight Missouri counties, eight Illinois counties) 2001−2003 All adults	One monitor	18.0	75th: 22.7 Max: 48.7	Correlation (*r*): 0.23 O_3, 0.35 NO_2, 0.25 CO, 0.08 SO_2. Copollutant models with: NA
†Krall et al. (2016) Atlanta, GA, 1999−2009 Birmingham, AL, 2004−2010 St. Louis, MO, 2001−2007 Dallas, TX, 2006−2009 All adults	One monitor, each city	Atlanta: 15.6 Birmingham: 17.0 St. Louis: 13.6 Dallas: 10.7	NR	Correlation (*r*): 0.57 O_3, 0.39 NO_2 Atlanta, 0.42 O_3, −0.15 NO_2 Dallas, 0.29 O_3, 0.29 NO_2 St. Louis. Copollutant models with: NA

Table 5-8 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions and emergency department (ED) visits for chronic obstructive pulmonary disease.

Study	Exposure Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	$PM_{2.5}$ Copollutant Model Results and Correlations
Peel et al. (2005) Atlanta, GA 1998−2000 All adults	One monitor	19.2	90th: 32.3	Correlations (*r*): NA Copollutant models with: NA
†Rodopoulou et al. (2015) Little Rock, AR 2002−2012 Adults >15 yr	One monitor	12.4	75th: 15.6	Correlation (*r*): 0.33 O_3 Copollutant models with: O_3
†Malig et al. (2013); †Ostro et al. (2016) 35 or 8 California counties 2005−2008 All adults	Nearest monitor	35 counties: 5.2−19.8 8 counties: 16.5 overall	NR	Correlations (*r*): NA Copollutant models with: NA
Stieb et al. (2009) Halifax, Montreal, Toronto, Ottawa, Edmonton, Vancouver, Canada 1992−2003 across cities All adults	One monitor Halifax, Ottawa, Vancouver; three Edmonton; seven Montreal, Toronto	Halifax: 9.8 Montreal: 8.6 Toronto: 9.1 Ottawa: 6.7 Edmonton: 8.5 Vancouver: 6.8	75th, Halifax: 11.3 Montreal: 10.9 Toronto: 11.9 Ottawa: 8.7 Edmonton: 10.9 Vancouver: 8.5	Correlation (*r*): −0.05 to 0.62 O_3, 0.27−0.51 NO_2, 0.01−0.42 CO, 0.01−0.55 SO_2. Copollutant models with: NA
Hospital admissions and ED visits				
Slaughter et al. (2005) Spokane, WA 1995−1999	One monitor	NR	90th: 20.2	Correlation (*r*): 0.62 CO Copollutant models with: NA

Avg = average, CO = carbon monoxide, IQR = interquartile range, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, O_3 = ozone, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm; *r* = correlation coefficient; R^2 = coefficient of determination, RR = relative risk, SD = standard deviation, SO_2 = sulfur dioxide.

†Studies published since the 2009 PM ISA.

5.1.4.1.1 Hospital Admissions

Several recent multicity studies conducted in the U.S. examined associations between short-term $PM_{2.5}$ exposure and COPD hospital admissions in individuals 65 years and older. In a multicity study conducted in the Mid-Atlantic region of the U.S., Kloog et al. (2014) examined associations between short-term $PM_{2.5}$ exposure and COPD hospital admissions by assigning exposure using a novel prediction model that combined land use regression with surface measurements of $PM_{2.5}$ concentration and satellite aerosol optical depth, which was also employed in a previous study conducted in New England (Kloog et al., 2012). The authors reported a 0.91% (95% CI: 0.18, 1.64) increase in COPD hospital admissions at model lag 0−1 days.

Bell et al. (2015) also examined COPD hospital admissions in adults ages 65 and older in a multicounty time-series analysis conducted in 213 U.S. counties. However, unlike Kloog et al. (2014), where exposures were assigned using model predictions, Bell et al. (2015) assigned exposures through $PM_{2.5}$ data retrieved from ambient monitors in each county. The authors reported a 0.34% (95% CI: −0.05, 0.74) increase in COPD hospital admissions at lag 0, which is smaller in magnitude than the association observed in Kloog et al. (2014), but may reflect the different exposure assignment approaches (Section 3.4.4.1). Consistent with the U.S. multicity studies, Hwang et al. (2017) also reported a positive association of 2% ([95% CI: 0.8, 2.9]; lag 0−2) with COPD hospital admissions in a study of four cities in southwestern Taiwan focusing on people of all ages.

Several recent single-city studies in the U.S. reported inconsistent evidence of an association between short-term exposure to $PM_{2.5}$ and hospital admissions for COPD. Kim et al. (2012) found no evidence of an association with COPD hospital admissions in Denver, Colorado (quantitative results not reported). Several single-city international studies examined the association with COPD hospital admissions and support the evidence reported in the U.S. multicity studies. A single-city study conducted in Rome, Italy focusing on adults aged 35 years and older investigated the association between $PM_{2.5}$ and COPD hospital admissions in a case-crossover analysis (Belleudi et al., 2010). Effects were assessed at several single- (0−6) and multiday lags (0−1, 0−2, 0−5 and 0−6 days). The association for $PM_{2.5}$ at a 0-day lag was positive but with wide confidence intervals (1.88% [95% CI: −0.27, 4.09]). The evidence observed using a shorter distributed lag is consistent with the lag structure of associations observed in the other COPD hospital admission studies, although in many instances the lags examined were selected a priori. In a similar fashion, Halonen et al. (2009a) observed a 3% increase (95% CI: −1.9, 8.1) at lag 0 in a model adjusted for O_3 for hospital admissions in Helsinki, Finland, but with a wide confidence interval due to the low count of hospital admissions compared to other studies. Cheng et al. (2015), examining hospital admissions in a case-crossover study in Kaohsiung, Taiwan, found no association between $PM_{2.5}$ at a 0−2-day lag (RR 1.00, 95% CI: 0.98, 1.03).

5.1.4.1.2 Emergency Department (ED) Visits

Several recent multicity studies conducted in the U.S. examined associations between short-term $PM_{2.5}$ exposure and COPD ED visits. In a multicity study conducted in 35 California counties, Malig et al. (2013) examined the association between short-term $PM_{2.5}$ exposures and respiratory ED visits, including COPD. In a time-stratified case-crossover analysis, the authors examined single-day lags and reported positive associations at lags 1 and 2 days, with the most precise estimate at lag 2 (1.47% [95% CI: 0.40, 2.6]). In a copollutant model with $PM_{10-2.5}$, the $PM_{2.5}$ association was relatively unchanged (1.58% [95% CI: 0.56, 2.62]) [Malig et al. (2013) and supplemental data file available on HERO]. The positive association observed in the multicounty study conducted by Malig et al. (2013) is supported by a study conducted in Little Rock, AR (Rodopoulou et al., 2015) that observed a 3.08% increase (95% CI: −0.98, 7.30) in COPD ED visits at lag 2. Rodopoulou et al. (2015) also examined the $PM_{2.5}$-COPD ED visits association in a copollutant model with O_3 and reported that the association remained positive, but confidence intervals increased in size (2.86% [95% CI: −1.35, 7.24]). A multicity case-crossover study of 15 cities in Ontario, Canada found an increase on the same order (2.2%) with higher precision (95% CI: 1.4, 2.9) than (Rodopoulou et al., 2015) using a 3-day mean lag structure.

In contrast, Sarnat et al. (2015) in a time-series study of $PM_{2.5}$ and cardiorespiratory ED visits in the St. Louis Missouri-Illinois (MO-IL) metropolitan area also reported no evidence of an association with COPD ED visits. The authors used 3-day unconstrained distributed lag models (i.e., lag 0−2) to allow for comparison of relationships among the multiple components and outcomes with potentially different lag structures. There was no evidence of an association between $PM_{2.5}$ and COPD ED visits (RR: 0.99 [95% CI: 0.95, 1.03]).

5.1.4.1.3 Summary of Chronic Obstructive Pulmonary Disease (COPD) Hospital Admissions and Emergency Department (ED) Visits

Consistent with the 2009 PM ISA (U.S. EPA, 2009), several recent studies examined COPD hospital admissions and ED visits and report generally positive associations with $PM_{2.5}$, with more recent multicity studies focusing on hospital admissions for older individuals (i.e., 65 years of age and older). Recent multicity studies conducted in the U.S., as well as single-city studies, that focused on individuals 65 years of age and older reported positive associations between short-term $PM_{2.5}$ exposure and COPD hospital admissions. Associations of short-term $PM_{2.5}$ exposure and ED visits, although generally positive, were less precise due to most studies being conducted in individual cities. The results from the studies evaluated in this section are supported by a recent meta-analysis of 12 studies, some of which were reviewed in the 2009 PM ISA that reported a 3.1% (95% CI: 1.6,4.6) increase in COPD hospital admissions (Li et al., 2015a). As detailed in Section 5.1.10.1, the assessment of potential copollutant confounding in studies of COPD hospital admissions and ED visits was limited, but provided evidence that associations were relatively unchanged in copollutant models. Additionally, although not extensively examined, studies generally provide evidence of larger associations in the cold or winter season compared

to warmer months (Section 5.1.10.4.1). However, it should be noted studies that examined seasonal patterns of associations did not examine potential copollutant confounding by season.

5.1.4.2 Respiratory Symptoms and Medication Use

A single study reviewed in the 2009 PM ISA (U.S. EPA, 2009) examined respiratory symptoms and medication use in adults with COPD and observed inconsistent evidence of an association with $PM_{2.5}$ across three single-day lags (Silkoff et al., 2005). A limited number of recent studies available for review followed populations comprised of adults with moderate or severe COPD. The results were not entirely consistent, though there was some evidence to indicate associations between $PM_{2.5}$ concentrations and increases in respiratory symptoms in adults with COPD. Study-specific details, air quality characteristics, and select results from these studies are highlighted in Table 5-9. Wu et al. (2016) examined the self-reported occurrence of several respiratory symptoms in relation to short-term $PM_{2.5}$ concentrations in a panel study of 23 adults in Beijing. The authors reported associations between most multiday (2−7) average $PM_{2.5}$ concentrations and sore throat, cough, sputum, wheeze, and dyspnea symptoms. Similarly, in a panel of 29 adults in Mexico City, total personal $PM_{2.5}$ exposure was associated with cough and phlegm, though not wheeze (Cortez-Lugo et al., 2015). A notable limitation of the study was high loss to follow-up, with only 4 of the 29 subjects completing all three of the 2-week study phases. In contrast, in a study of adults in Worcester, MA, $PM_{2.5}$ was associated with a decrease in COPD exacerbations, defined as a worsening of respiratory symptoms (Devries et al., 2016). Studies accounted for potential confounding by temperature, season, and time trend and also adjusted for subject characteristics such as COPD severity, race, atopic status, and comorbidity. Few studies examined any copollutants. Associations of $PM_{2.5}$ concentrations with wheeze and dyspnea persisted with adjustment for NO_2 or SO_2 in (Wu et al., 2016). However, correlations for $PM_{2.5}$ with NO_2 and SO_2 were high (r = 0.80, 0.68).

5.1.4.3 Lung Function Changes in Adults with Chronic Obstructive Pulmonary Disease (COPD)

5.1.4.3.1 Epidemiologic Studies

In the 2009 PM ISA (U.S. EPA, 2009), results from a limited number of epidemiologic studies indicated an association between PM and decreased FEV_1 in adults with COPD (Trenga et al., 2006; Ebelt et al., 2005). A few recent studies also evaluated lung function changes in populations with COPD and the results were inconsistent (Table 5-9). Recent studies used trained technicians to measure lung function, but the frequency of measurements varied from daily (Hsu et al., 2011) to less than once per week (Cortez-Lugo et al., 2015). Total personal $PM_{2.5}$ exposure was associated with decreased PEF in adults with COPD in Mexico City, who spent more than 90% of their time indoors (Cortez-Lugo et al.,

2015). As discussed previously, there was high loss to follow-up in this study. Associations were observed with 2-day average exposures lagged 2 or 3 days but not 0 or 1 days. In a small panel study of adults with COPD in New York City, ambient $PM_{2.5}$ concentrations were associated with decreases in PEF at lag 1, but increases in PEF at lag 0 (Hsu et al., 2011). Given the short sampling period (12 days) and relatively small sample size (nine participants), the interpretability of the results is limited.

Table 5-9 Epidemiologic studies of $PM_{2.5}$ and respiratory symptoms, lung function, and pulmonary inflammation in adults with chronic obstructive pulmonary disease.

Study	Study Population	Exposure Assessment Concentration µg/m³	Single Pollutant Effect Estimate 95% CI[a]	$PM_{2.5}$ Copollutant Model Results and Correlations
†Chi et al. (2016) Southwestern Taiwan 2014−2016	N = 19, 68% severe COPD Questionnaire every 2 mo for 1 yr 73% follow-up participation	Home outdoor Three measures for 1-min Mean: 120	Score for $PM_{2.5}$ >35 vs. ≤35 µg/m³ Wheeze: 1.46, $p < 0.01$ Phlegm: −0.22, $p > 0.05$ Dyspnea: 0.84, $p > 0.05$ Activity limitation: −0.84, $p > 0.05$	Correlation (r): NA Copollutant models with: NA
†Cortez-Lugo et al. (2015) Mexico City, Mexico Years NR	N = 29, mean 37% predicted FEV_1 Daily diary for three 12-day periods Recruited from clinic 62% completed two or three sessions 90% time spent indoors	Total personal 2-day avg Mean: 39	Phlegm, lag 2: 1.23 (0.98, 1.54) Cough, lag 2: 1.33 (1.05, 1.69) Nighttime PEF (L/min) Lag 1: 0.16 (−2.3, 2.6) Lag 2: −3.0 (−5.7, −0.3)	Correlation (r): NA Copollutant models with: NA
†Devries et al. (2016) Worcester, MA 2011−2012	N = 168, 68% severe COPD Calls to nurse on symptom onset Recruited from clinic No information on participation rate	Three monitors averaged Mean: 8.6 Max: 37.0	Any symptom, lag 1: 0.54 (0.28, 1.10)	Correlation (r): (seasonal range) 0.41−0.83 NO_2, 0.30−0.79 SO_2 Copollutant models with: NO_2 and SO_2
†Wu et al. (2016) Beijing, China Jan−Apr, Aug−Sep 2014	N = 23, 81% moderate/severe COPD Daily diary for 11−81 days 5−21 weekly eNO measures Recruited from clinic 96% completed one or two test periods	One monitor 1.6−8.8 km from homes 24-h avg Median, 75th Period 1: 96.5, 149 Period 2: 65.5, 92.0	Dyspnea, lag 0−4: 1.20 (1.10, 1.29) Sputum, lag 0−4: 1.06 (1.0, 1.13) Cough, lag 0−4: 1.05 (0.99, 1.14) eNO, lag 0−4: 1.7% (0.6, 2.8)	Correlation (r): 0.80 NO_2, 0.68 SO_2, 0.84 PM_{10} Copollutant models with: NO_2, SO_2, and PM_{10}

Table 5-9 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory symptoms, lung function, and pulmonary inflammation in adults with chronic obstructive pulmonary disease.

Study	Study Population	Exposure Assessment Concentration µg/m³	Single Pollutant Effect Estimate 95% CI[a]	$PM_{2.5}$ Copollutant Model Results and Correlations
Trenga et al. (2006) Seattle, WA 1999−2002	N = 24, mean 56% predicted FEV_1 Daily FEV_1 for 36 sessions, 5−10 days each Supervised spirometry Recruited from clinics, senior centers, retirement homes	Total personal, fixed-site monitor, and home outdoor 24-h avg Medians, 75th Total personal: 11.3, 16 Monitor: 11.2, 16.9 Home outdoor: 9.6, 14.8	Change in FEV_1 (ml), lag 1 Total personal: −19 (−74, 36) Fixed-site monitor: −71 (−118, −23) Home outdoor: −45 (−103, 12)	Correlation (*r*): NA Copollutant models with: NA
Ebelt et al. (2005) Vancouver, Canada 1998	N = 16, light/moderate COPD 5−7 FEV_1 measures, every 1.5 week Supervised spirometry No information on participation rate	Personal exposure, five monitors 24-h avg Ambient exposure estimated from total personal SO_4^{2-}, air infiltration, time-activity Mean, max Total personal: 18.5, 90.9 Ambient exposure: 7.9, 21.3 Monitor: 11.4, 28.7	Change in FEV_1 (ml), lag 0 Total personal: −0.39 (−14, 14) Ambient exposure: −66 (−124, −13) Monitor: −27 (−88, 34)	Correlation (*r*): NA Copollutant models with: NA
†Hsu et al. (2011) New York, NY Nov 2002−Mar 2003	N = 9 Recruited from clinics Daily FEV_1 and PEF for 12 days Supervised spirometry No information on participation rate	One monitor within 4.8 km of home 24-h avg Concentrations NR	New York: Negative association of PEF with $PM_{2.5}$ at monitor at lag 1 but positive association of PEF with $PM_{2.5}$ at monitor at lag 0	Correlation (*r*): NA Copollutant models with: NA

Avg = average, COPD = chronic obstructive pulmonary disease, eNO = exhaled nitric oxide, IQR = interquartile range, FEV_1 = forced expiratory volume in 1 second, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, PEF = peak expiratory flow, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm; *r* = correlation coefficient; R^2 = coefficient of determination, RR = relative risk, SD = standard deviation, SO_2 = sulfur dioxide, SO_4^{2-} = sulfate.

[a]Unless otherwise specified, effect estimates are standardized to a 10 µg/m³ increase in $PM_{2.5}$.

†Studies published since the 2009 PM ISA.

5.1.4.3.2 Controlled Human Exposure Studies

Two studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) provide limited evidence for decreased lung function among subjects with COPD exposed to $PM_{2.5}$ (Gong et al., 2005; Gong et al., 2004). Gong et al. (2004) reported decreases in oxygen saturation among elderly COPD patients, although results were more consistent in elderly subjects without COPD; the authors reported no effects on spirometric measures of lung function. The association between $PM_{2.5}$ and decreased oxygen saturation in COPD patients was confirmed in Gong et al. (2005).

5.1.4.4 Subclinical Effects Underlying Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

5.1.4.4.1 Epidemiologic Studies

A limited number of studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) reported evidence of an association between short-term $PM_{2.5}$ concentrations and pulmonary inflammation in adults with COPD. Studies examined exhaled nitric oxide (eNO) as an indicator of pulmonary inflammation, a key characteristic of COPD. Additionally, there is evidence that eNO increases during acute COPD exacerbation (Perng and Chen, 2017). Small panel studies of older adults in Steubenville, OH (Adamkiewicz et al., 2004) and Seattle, WA, (Jansen et al., 2005) reported increases in eNO associated with 24-hour average $PM_{2.5}$ concentrations measured at a single fixed-site monitor or outside of participants residences, respectively.

Information from the few available recent studies continues to support a relationship between $PM_{2.5}$ and increases in pulmonary inflammation in adults with COPD. Recent studies evaluated panels of older adults with COPD in Shanghai (Chen et al., 2015b) and Beijing, China (Wu et al., 2016). In both studies, $PM_{2.5}$ was measured at a single fixed-site monitor located within 4 km (Chen et al., 2015b) or 1.6−8.8 km (Wu et al., 2016) of subjects' residences, but information on the variability in $PM_{2.5}$ concentrations in the study areas was not reported. Chen et al. (2015b) observed eNO increases consistent with increases in $PM_{2.5}$ concentrations at 7−12-hour, 13−24-hour, 1-, 2-, and 3−7-day lags. Supporting these findings, the authors also reported associations between $PM_{2.5}$ and decreased methylation of the inducible nitric oxide synthase gene promoter that demonstrated the largest decrements at lag 0−6 hour. Lower methylation is associated with increased gene expression of inducible nitric oxide synthase which mediates production of nitric oxide. Wu et al. (2016) did not examine hourly lags but reported associations between eNO and cumulative average $PM_{2.5}$ concentrations ranging from 1 to 7 days. eNO associations were robust to adjustment for NO_2 but attenuated and no longer positive in two-pollutant models including SO_2 (Wu et al., 2016). However, there were high correlations of $PM_{2.5}$ with NO_2 and

SO_2 (r = 0.80, 0.68). While these studies provide additional support to the previously limited evidence of an association between $PM_{2.5}$ exposure and pulmonary inflammation in adults with COPD, uncertainties remain in attributing the observed increases in pulmonary inflammation to $PM_{2.5}$ exposure, similar to findings for other indicators of COPD exacerbation.

5.1.4.4.2 Controlled Human Exposure Studies

In the 2009 PM ISA (U.S. EPA, 2009), a limited number of studies investigated $PM_{2.5}$-induced health effects in adults with COPD. (Gong et al., 2004) and Gong et al. (2005) found a decrease in columnar epithelia cells ($p < 0.01$) following short-term exposure to $PM_{2.5}$. This effect was more pronounced in healthy subjects compared to those with COPD.

5.1.4.4.3 Animal Toxicological Studies

While no additional toxicological studies on the effects of PM on COPD have become available in recent years, the 2004 PM AQCD (U.S. EPA, 2004) reported several studies which examined the effects of multiday exposure to $PM_{2.5}$ CAPs in rats with experimentally induced bronchitis, an animal model of COPD. Changes in tidal volume, BALF injury markers (protein, albumin, and N-acetyl glutaminidase), and numbers of BALF neutrophils and lymphocytes were greater in bronchitic rats compared to nonbronchitic rats exposed to $PM_{2.5}$ CAPs from Boston (Saldiva et al., 2002; Clarke et al., 1999) and Research Triangle Park, NC (Kodavanti et al., 2000).

5.1.4.5 Summary of Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

Recent studies generally support an association between short-term increases in $PM_{2.5}$ concentration and exacerbation of COPD. Recent studies expand on the array of COPD-related outcomes and add coherence for the observations of $PM_{2.5}$-related increases in COPD-related hospital admissions and ED visits. Overall, evidence links short-term $PM_{2.5}$ exposure to COPD hospital admissions and ED visits. These findings are supported by recent observations of $PM_{2.5}$-related pulmonary inflammation; evidence for $PM_{2.5}$-related symptoms and decreases in lung function is less consistent. A strength of these studies is their assessment of personal $PM_{2.5}$ exposures. Overall, copollutant confounding was not adequately examined. Thus, it is unclear the extent to which the results can be attributed specifically to $PM_{2.5}$ exposure. However, experimental studies in individuals with COPD and in an animal model of COPD support an independent effect of short-term $PM_{2.5}$ exposure on exacerbation of COPD. Changes in lung function-related parameters (oxygen saturation and tidal volume), as well as lung injury and inflammation were observed following short-term $PM_{2.5}$ CAPs exposure and provide biological plausibility for the findings of epidemiologic studies (Figure 5-1).

5.1.5 Respiratory Infection

The respiratory tract is protected from exogenous pathogens by lung host defenses that include mucociliary clearance, pathogen detoxification, and clearance by alveolar macrophages, as well as innate and adaptive immunity. Impairment of these defense mechanisms can increase the risk of respiratory infection. The 2009 PM ISA (U.S. EPA, 2009) described evidence supporting $PM_{2.5}$-related respiratory infection but there was uncertainty due to a small evidence base relative to those for other respiratory effects. Previous epidemiologic studies consistently observed associations between $PM_{2.5}$ concentrations and hospital admissions or ED visits for indices aggregating various respiratory infections, particularly in U.S. and European cities. Findings from a limited number of studies also supported associations with pneumonia. In the 2004 PM AQCD and the 2009 PM ISA, controlled human exposure studies were not available to assess coherence, but an animal toxicological study demonstrated increased susceptibility to pneumonia infection and altered macrophage function following exposure to $PM_{2.5}$. Hospital admissions and ED visits comprise most of the epidemiologic evidence of respiratory infections and consistently indicate associations for $PM_{2.5}$ concentrations with multiple respiratory infections grouped together but not individually with pneumonia. Interpretation of the evidence, however, is complicated by the variety of respiratory infection outcomes examined.

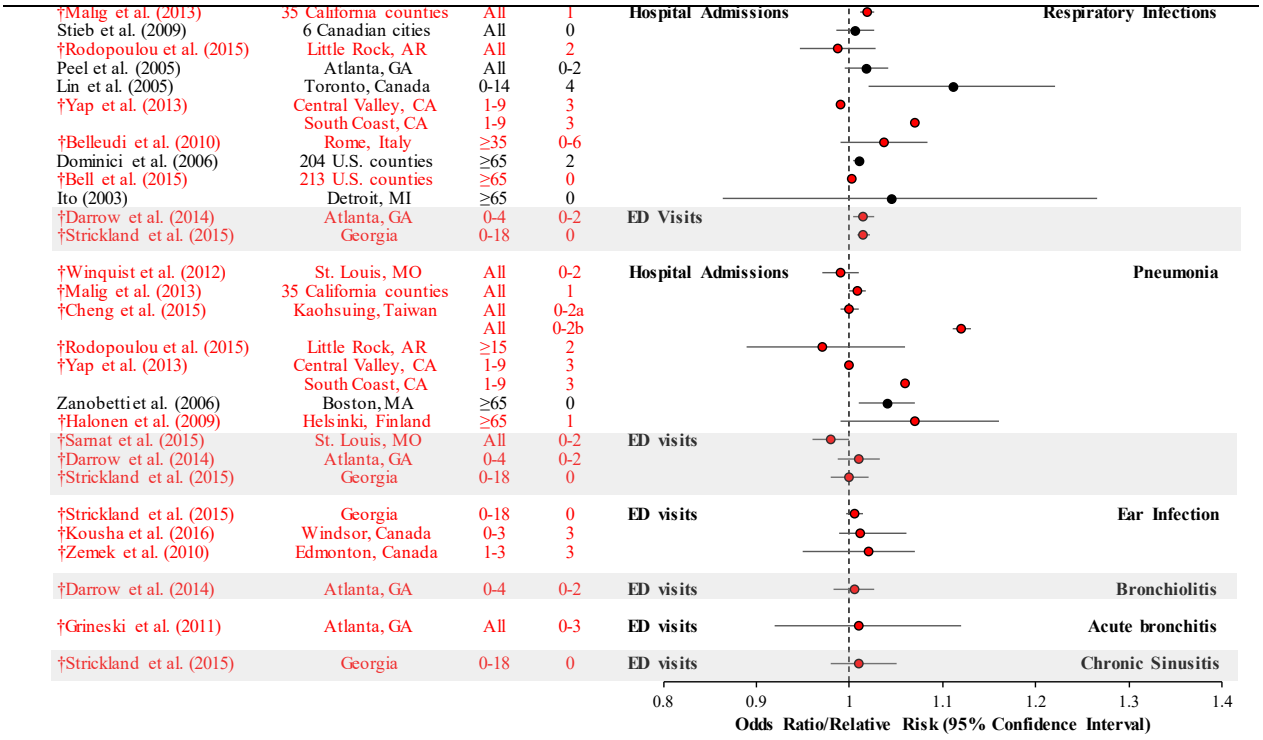
In addition to examining the relationship between short-term $PM_{2.5}$ exposure and respiratory effects, some epidemiologic studies often conduct analyses to assess whether the associations observed are due to chance, confounding, or other biases. As such, this evidence across epidemiologic studies is not discussed within this section, but evaluated in an integrative manner and focuses specifically on those analyses that address policy-relevant issues (Section 5.1.10), and includes evaluations of copollutant confounding (Section 5.1.10.1), model specification (Section 0), lag structure (Section 5.1.10.3), the role of season and temperature on $PM_{2.5}$ associations (Section 5.1.10.4), averaging time of $PM_{2.5}$ concentrations (Section 5.1.10.5), and concentration-response (C-R) and threshold analyses (Section 5.1.10.6). The studies that inform these issues and evaluated within these sections are primarily epidemiologic studies that conducted time-series or case-crossover analyses focusing on respiratory infection hospital admissions and ED visits.

5.1.5.1 Hospital Admissions and Emergency Department (ED) Visits

Associations between short-term $PM_{2.5}$ exposure and hospital admissions and between short-term $PM_{2.5}$ exposure and ED visits for respiratory infections were consistently observed among multicity studies evaluated in the 2009 PM ISA (U.S. EPA, 2009), although the type of respiratory infection examined varied across the studies (i.e., acute bronchitis, bronchiolitis, and pneumonia). Several multicity studies reported associations between short-term $PM_{2.5}$ exposure and pneumonia and acute bronchitis in children. The overall evidence base examining short-term $PM_{2.5}$ exposure and hospital admissions and ED visits for respiratory infections expanded considerably since the 2009 PM ISA. These recent studies

report generally positive associations between $PM_{2.5}$ and hospital admissions and ED visits for pneumonia, ear infections, and all respiratory infections grouped together (see Figure 5-7, Table 5-10). As in the 2009 PM ISA, respiratory infections when combined capture a range of outcomes (pneumonia, ear infections, bronchiolitis, sinusitis), with studies primarily focusing on children.

For each of the studies evaluated in this section, Table 5-10 presents the air quality characteristics of each city, or across all cities, the exposure assignment approach used, and information on copollutants examined in each respiratory infection hospital admission and ED visit study. Other recent studies of respiratory infection hospital admissions and ED visits are not the focus of this evaluation because they did not address uncertainties and limitations in the evidence previously identified, and therefore, do not directly inform the discussion of policy-relevant considerations detailed in Section 5.1.10. Additionally, many of these studies were conducted in small single cities, encompassed a short study duration, or had insufficient sample size. The full list of these studies can be found here: https://hero.epa.gov/hero/particulate-matter.



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-7 Summary of associations between short-term $PM_{2.5}$ exposures and respiratory infection hospital admissions and emergency department (ED) visits for a 10 µg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations.

Table 5-10 Epidemiologic studies of $PM_{2.5}$ and hospital admissions and emergency department (ED) visits for respiratory infection.

Study	Exposure Assessment	Outcome Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	$PM_{2.5}$ Copollutant Model Results and Correlations
Children					
Lin et al. (2005) Toronto, Canada 1998−2001	Four monitors averaged	Hospital admissions URI + LRI	9.6	75th: 12.3 Max: 50.5	Correlation (*r*): 0.56 O_3, 0.48 NO_2, 0.10 CO, 0.47 SO_2 Copollutant models with: NA
†Yap et al. (2013) 12 counties, Central Valley and South Coast, CA 2000−2005	Monitors in county averaged Number per county NR. 73 monitors total in state.	Hospital admissions ARI and pneumonia	12.8 Sacramento to 24.6 Riverside	NR	Correlation (*r*): 0.25 O_3. Copollutant models with: NA
†Darrow et al. (2014) Atlanta, GA 1993−2010	11 monitors combined for each census tract	ED visits URI and pneumonia	14.1	75th: 17.8 95th: 27.4 Max: 75.2	Correlation (*r*): 0.30 O_3, 0.41 NO_2, 0.45 CO Copollutant models with: NA
†Xiao et al. (2016); †Strickland et al. (2015) Georgia, whole state 2002−2008 or 2010	Fuse-CMAQ; satellite-monitor model	ED visits URI, pneumonia, ear infection, chronic sinusitis	Fuse-CMAQ Mean 13.2 Satellite-monitor Median State: 12.9 Large urban: 13.0 Nonurban: 12.9	Fuse-CMAQ 75th: 16.1 Max: 86.4 Satellite-monitor State 75th: 17.4 99th: 37.4	Correlation (*r*): 0.61 O_3, 0.22 NO_2, 0.26 CO, 0.21 SO_2 Copollutant models with: NA
†Zemek et al. (2010) Edmonton, Canada 1999−2002	Three monitors averaged	ED visits Ear infection	8.5	75th: 10.9	Correlation (*r*): NA Copollutant models with: NA

Table 5-10 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions and emergency department (ED) visits for respiratory infection.

Study	Exposure Assessment	Outcome Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	$PM_{2.5}$ Copollutant Model Results and Correlations
†Kousha and Castner (2016) Windsor, Canada 2004−2010	Monitors in city Number N	ED visits Ear infection	4.7	NR	Copollutant correlation (*r*): NA Copollutant models with: NA
Older adults					
Dominici et al. (2006) 204 U.S. counties 1999−2002	Monitors in county averaged Number per county NR	Hospital admissions URI + LRI	13.4	75th: 15.2	Copollutant correlation (*r*): NA Copollutant models with: NA
†Bell et al. (2015) 213 U.S. counties 1999−2010	Monitors in county averaged Number per county NR	Hospital admissions URI + LRI	U.S.: 12.3 Northeast: 12.0 Midwest: 12.9 South: 12.4 West: 11.3	Max U.S.: 20.2 Northeast: 16.4 Midwest: 16.5 South: 16.5 West: 20.2	Copollutant correlation (*r*): NA Copollutant models with: NA
Ito (2003) Detroit, MI 1992−1994	One monitor Sited in Windsor, Ontario	Hospital admissions Type of infection NR	18	75th: 21 95th: 42	Copollutant correlation (*r*): NA Copollutant models with: NA
Zanobetti and Schwartz (2006) Boston, MA 1995−1999	One monitor Data missing for 1998	Hospital admissions Pneumonia	Median: 11.1	75th: 16.1 95th: 26.3	Correlation (*r*): 0.20 O_3, 0.55, NO_2, 0.52 CO Copollutant models with: NA
†Halonen et al. (2009b) Helsinki, Finland 1998−2004		Hospital admissions Pneumonia	Median: 9.5	75th: 11.7 Max: 69.5	Correlation (*r*) = 0.39 NO_2, 0.30 CO Copollutant models with: NO_2, CO
All adults					

Table 5-10 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions and emergency department (ED) visits for respiratory infection.

Study	Exposure Assessment	Outcome Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	$PM_{2.5}$ Copollutant Model Results and Correlations
†Halonen et al. (2009a) Helsinki, Finland 1998−2004	Two monitors	Hospital admissions Pneumonia	Median: 8.8	75th: 11.0 Max: 41.5	Correlation (*r*): 0.43 O_3. Copollutant models with: O_3
†Rodopoulou et al. (2015) Little Rock, AR 2002−2012	One monitor	ED visits ARI and pneumonia	12.4	75th: 15.6	Correlation (*r*): 0.33 O_3 Copollutant models with: O_3
†Liu et al. (2016) Greater Houston area, TX 2008−2013 Mostly adults (92%)	Four monitors averaged	Hospital admissions Pneumonia	12.0	90th: 18.5	Copollutant correlation (*r*): NA Copollutant models with: NA
†Belleudi et al. (2010) Rome, Italy 2001−2005	One monitor	Hospital admissions LRI	22.8	75th: 27.8	Correlation (*r*): 0.84 PM_{10} Copollutant models with: NA
†Sarnat et al. (2015) St. Louis, MO (eight Missouri counties, eight Illinois counties) 2001−2003 All adults	One monitor	ED visits Pneumonia	18.0	75th: 22.7 Max: 48.7	Correlation (*r*): 0.23 O_3, 0.35 NO_2, 0.25 CO, 0.08 SO_2 Copollutant models with: NA
All ages					
†Krall et al. (2016) Atlanta, GA, 1999−2009 Birmingham, AL, 2004−2010 St. Louis, MO, 2001−2007 Dallas, TX, 2006−2009	One monitor in each city	ED visits URI and pneumonia	Atlanta: 15.6 Birmingham: 17.0 St. Louis: 13.6 Dallas: 10.7	NR	Correlation (*r*): 0.57 O_3, 0.39 NO_2 Atlanta, 0.42 O_3, −0.15 NO_2 Dallas, 0.29 O_3, 0.29 NO_2 St. Louis. Copollutant models with: NA

Table 5-10 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions and emergency department (ED) visits for respiratory infection.

Study	Exposure Assessment	Outcome Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	$PM_{2.5}$ Copollutant Model Results and Correlations
Peel et al. (2005) Atlanta, GA 1998−2000	One monitor	ED visits URI and pneumonia	19.2	90th: 32.3	Copollutant correlation (*r*): NA Copollutant models with: NA
†Malig et al. (2013) 35 California counties, 2005−2008 †Ostro et al. (2016) Eight California counties, 2005−2008	Nearest monitor Monitor within 25 or 20 km of population-weighted zip code centroid	ED visits ARI and pneumonia	35 counties: 5.2 to 19.8 8 counties: 16.5 overall	NR	Copollutant correlation (*r*): NA Copollutant models with: NA
Stieb et al. (2009) Halifax, Montreal, Toronto, Ottawa, Edmonton, Vancouver, Canada 1992−2003 across cities	One monitor	ED visits URI + LRI	6.7−9.8	75th 8.7−11.9	Correlation (*r*): −0.05 to 0.62 O_3, 0.27−0.51 NO_2, 0.01−0.42 CO, 0.01−0.55 SO_2. Copollutant models with: NA
Host et al. (2008) Paris, Le Havre, Toulouse, Rouen, Marseille, Lille, France, 2000−2003	Seven monitors	Hospital admissions URI + LRI	13.8−18.8	95th 26.3−33.0	Copollutant correlation (*r*): NA Copollutant models with: NA
†Winquist et al. (2012) St. Louis, MO 2001−2007	One monitor	Hospital admissions and ED visits Pneumonia	14.4	Max: 56.6	Correlation (*r*): 0.25 O_3 Copollutant models with: NA
†Kim et al. (2012) Denver, CO 2003−2007	One monitor	ED visits Pneumonia	8.0	Max: 59.4	Correlation (*r*): 0.30 O_3, 0.26 NO_2, 0.23 CO, 0.23 SO_2 Copollutant models with: NA
†Cheng et al. (2015) Kaohsiung, Taiwan 2006−2010	Six monitors averaged	Hospital admissions Pneumonia	Median: 44.3	75th: 61.9 Max: 144	Correlation (*r*): 0.42 O_3, 0.80 NO_2, 0.81 CO, 0.25 SO_2 Copollutant models with: O_3, NO_2, CO, SO_2

Table 5-10 (Continued): Epidemiologic studies of $PM_{2.5}$ and hospital admissions and emergency department (ED) visits for respiratory infection.

Study	Exposure Assessment	Outcome Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	$PM_{2.5}$ Copollutant Model Results and Correlations
†Grineski et al. (2011) El Paso, TX 2000−2003	Two monitors averaged	Hospital admissions Acute bronchitis	12.8	75th: 15.6 95th: 26.6 Max: 119.1	Copollutant correlation (*r*): NA Copollutant models with: NA
†Winquist et al. (2012) St. Louis, MO 2001−2007	Two monitors averaged	Hospital admissions and ED visits	14.4	Max: 56.6	Correlation (*r*): 0.25 O_3 Copollutant models with: NA
†Sinclair et al. (2010) Atlanta, GA 1998−2002	One monitor	Outpatient visits for acute respiratory illness	17.1	NR	Copollutant correlation (*r*): NA Copollutant models with: NA

ARI = acute respiratory infection, avg = average, CMAQ = community multiscale air quality, CO = carbon monoxide, ED = emergency department, IDW = inverse distance weighted, IQR = interquartile range, LRI = lower respiratory infection, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, O_3 = ozone, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, *r* = correlation coefficient, R^2 = coefficient of determination, SD = standard deviation, SO_2 = sulfur dioxide, URI = upper respiratory infection.

†Studies published since the 2009 PM ISA.

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5.1.5.1.1 Hospital Admissions

Studies examined the association between short-term $PM_{2.5}$ exposure and hospital admissions for a variety of respiratory infections. Several recent multicity studies conducted in the U.S. examined associations between short-term $PM_{2.5}$ exposure and hospital admissions for respiratory infections in children age 1 to 9 years (Yap et al., 2013) and in individuals 65 years of age and older (Bell et al., 2015). Yap et al. (2013) evaluated pediatric (children ages 1 to 9 years) hospital admissions for respiratory conditions associated with $PM_{2.5}$ exposures in 12 California counties. For acute respiratory infections, including pneumonia, relative risks (RR) ranged from 1.03 to 1.07 in Los Angeles, Riverside, San Bernardino, and San Diego counties at lags 0−2 days. The association for combined respiratory infection hospital admissions was significantly higher in the south coast than the central valley (RR 1.07 vs. 0.99); confidence intervals were not reported. In addition to this evidence for pediatric infections, in a multicounty time-series analysis of adults conducted in 213 U.S. counties Bell et al. (2015) reported a 0.21% (95% CI: −0.07, 0.49) increase in combined respiratory tract infection hospital admissions among adults aged 65 and older at lag 0.

In addition to the multicity studies presented above, several single-city studies were conducted in the U.S. and internationally that examined respiratory infection hospital admissions. Grineski et al. (2011) primarily focused on examining the effect of dust and low wind events on asthma and acute bronchitis hospital admissions in El Paso, TX. The authors reported imprecise associations with $PM_{2.5}$ and acute bronchitis hospital admissions across both single and multiday lags with an OR = 1.01 (95% CI: 0.92, 1.12) at lag 0−3 days. By contrast, in Denver, CO, Kim et al. (2012) reported no association between $PM_{2.5}$ and pneumonia hospital admissions at any lag when examining a distributed lag model of 0−14 days (quantitative results not presented). Winquist et al. (2012) conducted a study in the St. Louis-MO metropolitan area to evaluate the impact of the type of health care visit on the association with short-term air pollution exposures, including $PM_{2.5}$. This study compared four visit types including ED visits, hospital admissions, hospital admissions that came through the ED, and nonelective hospital admissions. The authors found that compared with ED visits patients, hospital admission patients tended to be older, had evidence of greater severity for some outcomes, and had a different mix of specific outcomes. For pneumonia, associations with $PM_{2.5}$ were positive only among the 2−18-year-old group for ED visits, nonelective hospital admissions, and hospital admissions through ED types of visits. The only positive association was observed for hospital admissions through ED visits (0.43% [95% CI: −0.56, 0.68] at lag 0−4 days. In Rome, Italy, Belleudi et al. (2010) reported evidence of an association between $PM_{2.5}$ and lower respiratory tract infection hospital admissions among adults aged 35 years and older (3.62% [95% CI: −0.96, 8.42]; lag 0−6 DL).

5.1.5.1.2 Emergency Department (ED) Visits

Several recent multicity studies conducted in the U.S. examined associations between short-term $PM_{2.5}$ exposure and respiratory infection-related ED visits. In a multicity study conducted in 35 California counties, Malig et al. (2013) examined the association between short-term $PM_{2.5}$ exposures and ED visits, including pneumonia and acute respiratory infections. Using a time-stratified case-crossover analysis, the authors reported positive associations at 1-day lags between short-term $PM_{2.5}$ and acute respiratory infections (1.9% [95% CI: 1.1, 2.7]) and pneumonia (0.86% [95% CI: −0.06, 1.8]) ED visits in single pollutant models.

The evidence for associations with ED visits from single-city studies also expanded considerably since the 2009 PM ISA (U.S. EPA, 2009). Winquist et al. (2012) observed a positive association for hospital admissions through ED visits, can be compared to a more recent study conducted in the same St. Louis Missouri-Illinois (MO-IL) metropolitan area. However, unlike Winquist et al. (2012), Sarnat et al. (2015) found no evidence of an associations between $PM_{2.5}$ and pneumonia ED visits (RR = 0.98 [95% CI: 0.96, 1.00]) at lag 0−2 days.

Several studies investigated the associations between $PM_{2.5}$ and ED visits related to several respiratory infections in Atlanta, GA. Darrow et al. (2014) conducted an 18-year (1993−2010) study examining the association between $PM_{2.5}$ and pediatric (ages 0−4) ED visits for respiratory infections, including bronchitis and bronchiolitis, pneumonia, and upper respiratory infection (URI). Daily concentrations of ambient air pollution from several networks of ambient monitors were combined using population-weighting. Pneumonia ED visits were positively associated with $PM_{2.5}$ (for children aged 0−4 years, RR = 1.01 [95% CI: 0.99, 1.03]). $PM_{2.5}$ at lag 0−2 days was not associated with an increase in ED visits for bronchiolitis and bronchitis, although some of the point estimates in the children aged 1−4 years were positive, but uncertain for URI and pneumonia. In the same location, Strickland et al. (2015) examined children ages 0−18 years old between 2002−2010 in a case-crossover study using predicted daily $PM_{2.5}$ concentrations from a two-stage spatiotemporal model with geographical weighting. The authors found that the association with ED visits for bronchitis and upper respiratory infection increased slightly at lag 0-day (OR: 1.010 [95% CI: 0.994, 1.027], and OR: 1.015 [95% CI: 1.008, 1.022]). In contrast, the association for pneumonia-related ED visits were essentially null at both a 0-day lag (OR: 0.999 [95% CI: 0.979, 1.019]) and a 1-day lag (OR: 1.001 [95% CI: 0.981, 1.022]).

In contrast to the results of Winquist et al. (2012), other single-city studies such as Darrow et al. (2014), Strickland et al. (2015), and Rodopoulou et al. (2015) found no associations for respiratory infection ED visits. For example, in Little Rock, AR, Rodopoulou et al. (2015) found an association of −1.34% (95% CI: −5.31, 2.79) amongst all age groups using a 2-day lag. The association slightly increased to −0.82% after the inclusion of O_3 in a copollutant model (95% CI: −4.96, 3.50).

5.1.5.2 Outpatient and Physician Visit Studies

A study conducted in Atlanta, GA, Sinclair et al. (2010) examined the association between air pollution and several respiratory-related outpatient visits, including upper and lower respiratory infections. The authors separated the analysis into two consecutive time periods to compare the air pollutant concentrations and relationships for acute respiratory visits for the 25-month time-period examined in a previous study (August 1998−August 2000) and an additional 28-month time-period of available data from the Atlanta Aerosol Research and Inhalation Epidemiology Study (ARIES) (September 2000−December 2002). Across the two-time periods, 24-hour average $PM_{2.5}$ concentrations were lower in the 28-month versus the 25-month time-period (16.2 vs. 18.4 μg/m^3, respectively). A comparison of the two-time periods indicated that associations for $PM_{2.5}$ tended to be larger in the earlier 25-month period compared to the later 28-month period. The highest association with LRI was observed for lag 3−5 in the 25-month time-period (RR: 1.071 [95% CI: 1.003, 1.144]). For URI in the 25-month period, the association was positive at lag 0−2 days (RR: 1.015 [95% CI: 0.990, 1.040]). It should be noted that the severity of a $PM_{2.5}$-related respiratory outcome, personal behavior such as delaying a visit to the doctor for less severe symptoms, and insurance type (i.e., physician visits which often are ascertained for members of a managed care organization) may dictate whether individuals visit the doctor or a hospital, making it difficult to readily compare results between studies focusing on physician visits versus hospital admissions and ED visits.

5.1.5.3 Subclinical Effects Underlying Respiratory Infection

Subclinical effects have been investigated solely in animal toxicological studies. As described in the 2004 PM AQCD (U.S. EPA, 2004), Zelikoff et al. (2003) showed that exposure to $PM_{2.5}$ CAPs in New York City resulted in altered macrophage function in rats. In addition, a greater bacterial burden was found when infection with *S. pneumoniae* was followed 48 hours later by $PM_{2.5}$ CAPs exposure. However, when $PM_{2.5}$ CAPs exposure preceded *S. pneumoniae* infection, it had little effect on bacterial burden. Studies described in the 2009 PM ISA (U.S. EPA, 2009) demonstrated altered susceptibility to infectious agents following exposure to whole motor vehicle exhaust and effects due to metal-enriched particles (i.e., ROFA). Recent studies of respiratory-related infection did not examine the effects of $PM_{2.5}$ CAPs or seek to distinguish between the effect of gaseous and particulate components in a mixture.

5.1.5.4 Summary of Respiratory Infection

The body of evidence for associations between short-term exposure to $PM_{2.5}$ and respiratory infection is comprised mainly of studies of hospital admissions and ED visits. These studies increased in number since the last review. However, because of variability in the type of respiratory infection outcome examined, the overall interpretation of findings is more complicated. Associations reported in single-city

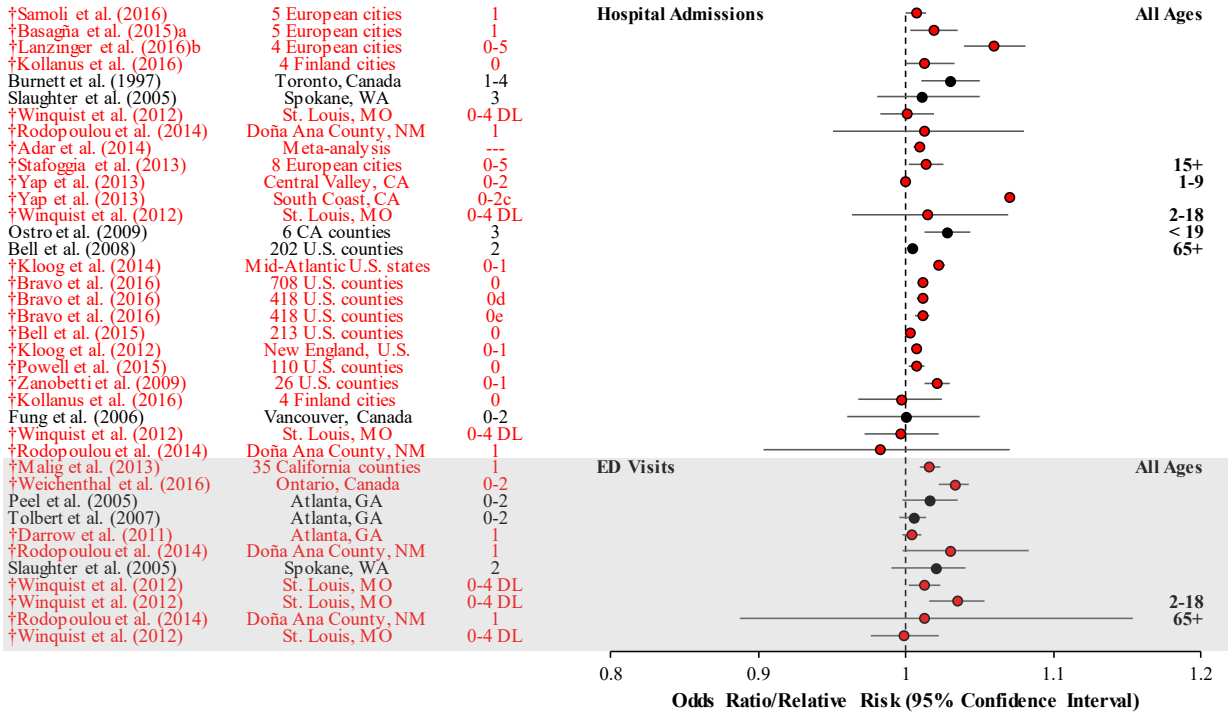
studies were often imprecise, with confidence intervals crossing the null. A few recent single-city studies reported positive associations for acute bronchitis hospital admissions and respiratory tract infection hospital admissions. In several multicity studies, one conducted in the U.S. and one in or Canada, studying $PM_{2.5}$ and hospital admissions for respiratory infections, both reported positive associations. Most single-city studies in the U.S. consistently reported positive associations for pneumonia (adults and children, ages 0−4), but this effect was not observed for bronchiolitis and bronchitis in children ages 0−4. In contrast, a study of acute respiratory infection ED visits reported no evidence of an association with $PM_{2.5}$. However, a single-city U.S. study reported positive associations with outpatient visits for lower and upper respiratory tract infections. Moreover, these studies generally provide inconsistent evidence for seasonal patterns in the strength of association. A single experimental study in animals, demonstrating altered macrophage function and increased susceptibility to pneumonia in response to $PM_{2.5}$ CAPs exposure, supports findings of epidemiologic studies.

5.1.6 Combinations of Respiratory-Related Hospital Admissions and Emergency Department (ED) Visits

In addition to individual respiratory diseases, epidemiologic studies examined respiratory diseases in aggregate where, in some cases, the aggregate represented all respiratory diseases while, in others, a specific combination of respiratory diseases was represented (e.g., COPD, asthma and respiratory infections). In the 2009 PM ISA (U.S. EPA, 2009) there was a small number of studies that examined short-term $PM_{2.5}$ exposure and all respiratory-related diseases in the context of hospital admissions and ED visits. These studies generally encompassed single-city studies and reported evidence of consistent, positive associations when examining effects in children, people of all ages, adults, and older adults (i.e., ≥65 years of age) at lags within the range of 0 to 2 days. However, across these studies the evaluation of potential copollutant confounding was limited to analyses of $PM_{10-2.5}$, with no evaluation of gaseous pollutants. When interpreting these results, it is often difficult to determine if the associations observed indicate that $PM_{2.5}$ may affect the spectrum of respiratory diseases or reflects the evidence supporting associations with specific respiratory diseases, such as asthma.

Studies published since the completion of the 2009 PM ISA (U.S. EPA, 2009) report generally consistent, positive associations across studies of hospital admissions and ED visits for all age ranges, particularly in multicity studies (Figure 5-8). Among studies that examined both combinations of respiratory diseases grouped together and individual respiratory diseases, as detailed in previous sections within this chapter, most observed positive $PM_{2.5}$ associations with asthma (Section 5.1.2), respiratory infection (Section 5.1.5), or both, with results for COPD (Section 5.1.4) being more variable. However, some studies show associations with all three respiratory diseases. For studies that did not observe $PM_{2.5}$-related increases in hospital admissions or ED visits for all respiratory-related diseases, associations were often observed for individual respiratory diseases within the same study, for example asthma [e.g., Yap et al. (2013)]. Similar to the individual respiratory diseases discussed earlier within this

chapter, positive associations with respiratory-related diseases are more consistently observed among children and when examining people of all ages. However, recent studies further expand analyses with older adults, with multicity studies conducted in the U.S. providing evidence of consistent, positive associations between short-term $PM_{2.5}$ exposure and respiratory-related diseases.



DL = distributed lag.

Note: †Studies published since the 2009 PM ISA. Black text: U.S. and Canadian studies included in the 2009 PM ISA. a = five European cities as part of the MED-PARTICLES project; b = only four of the five cities had $PM_{2.5}$ data; c = quantitative data for confidence intervals not reported, but above the null; d = monitoring data result; e = downscaler CMAQ, only counties and days with monitoring data. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-8 Summary of associations from studies of short-term $PM_{2.5}$ exposure and respiratory-related hospital admission and emergency department (ED) visits for a 10 µg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations.

Consistent with earlier sections, the focus of this section is on those studies that address uncertainties and limitations in the evidence for association between short-term $PM_{2.5}$ exposure and respiratory-related hospital admissions and ED visits identified at the completion of the 2009 PM ISA (U.S. EPA, 2009). For each of the studies that evaluated hospital admissions and ED visits for combinations of respiratory-related diseases, Table 5-11 presents the air quality characteristics of each

city, or across all cities, the exposure assignment approach used, and information on copollutants examined. Other recent studies of hospital admissions and ED visits for respiratory-related diseases that did not address uncertainties and limitations in the evidence previously identified are not the focus of this evaluation. Additionally, many of these other studies were conducted in small single cities, encompassed a short study duration, or had insufficient sample size. The full list of these other studies can be found in HERO: https://hero.epa.gov/hero/particulate-matter.

In addition to examining the relationship between short-term $PM_{2.5}$ exposure and respiratory effects, some epidemiologic studies often conduct analyses to assess whether the associations observed are due to chance, confounding, or other biases. As such, this evidence across epidemiologic studies is not discussed within this section, but evaluated in an integrative manner and focuses specifically on those analyses that address policy-relevant issues (Section 5.1.10), and includes evaluations of copollutant confounding (Section 5.1.10.1), model specification (Section 0), lag structure (Section 5.1.10.3), the role of season and temperature on $PM_{2.5}$ associations (Section 5.1.10.4), averaging time of $PM_{2.5}$ concentrations (Section 5.1.10.5), and concentration-response (C-R) and threshold analyses (Section 5.1.10.6). The studies that inform these issues and evaluated within this section consist only of epidemiologic studies that conducted time-series or case-crossover analyses focusing on combinations of respiratory-related ED visits and hospital admissions.

Table 5-11 Epidemiologic studies of $PM_{2.5}$ and respiratory-related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
Hospital admissions					
Bell et al. (2008) 202 U.S. counties 1999−2005 ≥65 yr	Average of all monitors in each county	490−492; 464−466; 480−487	NR	NR	Correlation (*r*): NA Copollutant models with: NA
Bell et al. (2009a) 168 U.S. counties 1999−2005 ≥65 yr	Average of all monitors in each county	490−492; 464−466; 480−487	NR	NR	Correlation (*r*): NA Copollutant models with: NA
Ostro et al. (2009) Six California counties 2000−2003 <19 yr	Average of all monitors in each county	460−519	19.4	NR	Correlation (*r*): NA Copollutant models with: NA
Fung et al. (2006) Vancouver, Canada 1995−1999 ≥65 yr	Average of all monitors	460−519	7.7	Max: 32	Correlation (*r*): −0.03 O_3, 0.36 NO_2, 0.23 CO, 0.42 SO_2 Copollutant models with: NA
Burnett et al. (1997) Toronto, Canada 1992−1994, summers only All ages	One monitor	464−466; 490; 480−486; 491−494, 496	16.8	75th: 23 95th: 40 Max: 66	Correlation (*r*): 0.32 O_3, 0.45 NO_2, 0.42 CO, 0.49 SO_2 Copollutant models with: O_3, CO, NO_2, SO_2

Table 5-11 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
†Powell et al. (2015) 119 U.S. counties 1999–2010 ≥65 yr	Average of all monitors in each county	464–466, 480–487; 490–492	12.1[a]	75: 14.2	Correlation (*r*): NA Copollutant models with: NA
†Bravo et al. (2017) 708 U.S. counties, Eastern 2/3rd of U.S. 2002–2006 ≥65 yr	Average of all monitors within a county County-level population-weighted average of $PM_{2.5}$ concentrations predicted by downscaler CMAQ at census tract centroids Same as (2), but only for counties and days with monitoring data	464–466, 480–487; 490–492	Monitors: 12.5 Downscaler CMAQ: 12.6 Downscaler CMAQ Subset: 12.6	NR	Correlation (*r*): NA Copollutant models with: NA
†Bell et al. (2015) 213 U.S. counties 1999–2010 ≥65 yr	Average of all monitors in each county	464–466, 480–487; 490–492; 493	U.S.: 12.3 Northeast: 12.0 Midwest: 12.9 South: 12.4 West: 11.3	Max U.S.: 20.2 Northeast: 16.4 Midwest: 16.5 South: 16.5 West: 20.2	Correlation (*r*): NA Copollutant models with: NA
†Zanobetti et al. (2009) 26 U.S. counties 2000–2003 ≥65 yr	Average of all monitors in each county	460–519	15.3	NR	Correlation (*r*): NA Copollutant models with: NA
†Bell et al. (2014) Three Connecticut and one Massachusetts counties 2000–2004 ≥65 yr	One monitor in each of three counties, two averaged in one Connecticut county	464–466, 480–487; 490–492	14.0	NR	Correlation (*r*): NA Copollutant models with: NA

Table 5-11 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
†Kloog et al. (2012) New England, U.S. 2000−2006 ≥65 yr	Predicted daily concentrations to 10 km² grid cells based on AOD observation data and 78 monitoring sites code as detailed in Kloog et al. (2011), R^2 = 0.81, then matched to zip codes	460−519	9.6	75th: 11.7 Max: 71.6	Correlation (*r*): NA Copollutant models with: NA
†Kloog et al. (2014)[c] Mid-Atlantic States, U.S. 2000−2006 ≥65 yr	Predicted daily concentrations to 10-km² grid cells based on AOD observation data and 78 monitoring sites code as detailed in Kloog et al. (2011), R^2 = 0.81, then matched to zip codes	460−519	11.9	75th: 14.7 Max: 95.9	Correlation (*r*): NA Copollutant models with: NA
†Yap et al. (2013) 12 counties, Central Valley and South Coast, CA 2000−2005 1−9 yr	Average of all monitors in each county	460−466, 480−486; 493	12.8−24.6	NR	Correlation (*r*): NA Copollutant models with: NA
†Samoli et al. (2016a) Five European cities 2001−2011 All ages	Average of all monitors in each city	466, 480−487; 490−492, 494, 496; 493	7.8−22.7	NR	Correlation (*r*): NA Copollutant models with: NA
†Lanzinger et al. (2016b)[d] Four European cities (UFIREG) 2011−2014 All ages	Average of all monitors in each city	J00−J99	14.9−20.7	Max: 78.8−114.8	Correlation (*r*): 0.55−0.73 NO_2, 0.41−0.61 $PM_{10-2.5}$, 0.25−0.37 UFP, 0.49−0.50 PNC Copollutant models with: NA

Table 5-11 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m^3	Upper Percentile Concentrations µg/m^3	Copollutant Examination
†Basagaña et al. (2015) Five European cities (MED-PARTICLES) 2001−2010 All ages	One monitor in each city	460−519, J00−J99	16.0−27.6	NR	Correlation (*r*): NR Copollutant models with: NR
†Stafoggia et al. (2013) Eight European cities (MED-PARTICLES) 2003−2013 ≥15 yr	Average of all monitors in each city	460−519	17.2−34.4	NR	Correlation (*r*): >0.60 with NO_2 Copollutant models with: O_3, NO_2, $PM_{10-2.5}$
†Jones et al. (2015) New York State 2000−2005 All ages	Fused-CMAQ[b] to 12-km^2 grid cells, geocoded addresses to each grid cell	491, 492, 493, 496	8.0	75th: 11.1 Max: 69.5	Correlation (*r*): −0.34−0.59 O_3 Copollutant models with: NA
†Kim et al. (2012) Denver, CO 2003−2007 All ages	One monitor	480−486; 490−493, 496	7.9	Max: 59.4	Correlation (*r*): 0.68 SO_4^{2-}, 0.82 NO_3^- Copollutant models with: NA
†Kollanus et al. (2016) Helsinki, Finland 2001−2010 All ages	One urban background monitor and one regional background monitor	J00−J99	8.6	75th: 10.8 Max: 54.1	Correlation (*r*): NA Copollutant models with: NA

Table 5-11 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
ED visits					
Peel et al. (2005) Atlanta, GA 1993−2000 All ages	One monitor	460−466, 477; 480−486; 491, 492, 496; 493, 786.09	19.2	90th: 32.3	Correlation (*r*): 0.55−0.68, CO, NO_2 Copollutant models with: NA
Tolbert et al. (2007) Atlanta, GA 1993−2004 All ages	One monitor	460−465, 460.0, 477; 480−486; 491, 492, 496; 493, 786.07, 786.09; 466.1, 466.11, 466.19	17.1	75th: 21.9 90th: 28.8 Max: 65.8	Correlation (*r*): 0.62 O_3, 0.47 NO_2, 0.47 CO, 0.17 SO_2, 0.47 $PM_{10-2.5}$ Copollutant models with: NA
†Malig et al. (2013) 35 California counties 2005−2008 All ages	Nearest monitor within 20 km from population-weighted centroid of each patient's residential zip code	460−519	5.2−19.8	NR	Correlation (*r*): NA Copollutant models with: $PM_{10-2.5}$
†Krall et al. (2016) Four U.S. cities 1999−2010	One monitor in each city	460−465, 466.0, 477; 480−486; 491−493, 496, 786.07	Atlanta: 15.6 St. Louis: 13.6 Dallas: 10.7 Birmingham: 17.0	NR	Correlation (*r*): NA Copollutant models with: NA
†Darrow et al. (2011) Atlanta, GA 1998−2004 All ages	One monitor 24-h avg, 1-h max, commute (7−10 a.m.), daytime (8 a.m.−7 p.m.), nighttime (12−7 a.m.)	460−466, 477; 480−486; 491−493, 496, 786.09	24-h avg: 16 1-h max: 29 Commute: 17 Daytime: 15 Nighttime: 17	75th, Max: 24-h avg: 21, 72 1-h max: 36, 188 Commute: 21, 76 Daytime: 19, 71 Nighttime: 14, 88	Correlation (*r*): 24-h avg: 0.46 O_3, 0.52 NO_2, 0.45 CO. Similar for 1-h max, higher for nighttime, lower for daytime and commute. Copollutant models with: NA

Table 5-11 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
†Weichenthal et al. (2016) Ontario, Canada (15 cities) 2004−2011 All ages	Nearest monitor to population-weighted zip code centroid or single available monitor	J00−J99	7.1	Max: 56.8	Correlation (*r*): <0.42 NO_2 Copollutant models with: O_3, NO_2, oxidative potential
Hospital admissions and ED visits, separately					
Slaughter et al. (2005) Spokane, WA 1995−1999 All ages	One monitor	464−466, 490; 480−487; 491−494, 496	NR	90: 20.2	Correlation (*r*): 0.62 CO; 0.31 $PM_{10-2.5}$ Copollutant models with: NA
†Winquist et al. (2012) St. Louis, MO 2001−2007 All ages	One monitor	460−465, 466.0, 466.1, 466.11, 466.19, 477, 480−486, 491−493, 496, 786.07	14.4	75th: 22.7 Max: 48.7	Correlation (*r*): 0.25 O_3 Copollutant models with: NA
†Rodopoulou et al. (2014) Doña Ana County, NM 2007−2010 ≥18 yr	Three monitors	460−465, 466, 480−486, 490−493, 496	10.9	75th: 13 Max: 55.6	Correlation (*r*): −0.05 O_3 Copollutant models with: NA

CMAQ = Community Multi-Scale Air Quality model; MED-PARTICLES = particles size and composition in Mediterranean countries: Geographical variability and short-term health effects; UFIREG = Ultrafine particles—an evidence-based contribution to the development of regional and European environmental and health policy.

[a]Median concentration.

[b]CMAQ predictions bias corrected using monitored data.

[c]$PM_{2.5}$ concentrations are for lag 0−1 day.

[d]Only four of the five cities had $PM_{2.5}$ data.

†Studies published since the 2009 PM ISA.

5.1.6.1 Hospital Admissions

Recent studies that examined the association between short-term $PM_{2.5}$ exposure and respiratory-related hospital admissions build upon the evidence detailed in the 2009 PM ISA (U.S. EPA, 2009), particularly the examination of effects in older adults (i.e., ≥65 years of age). Multicity studies conducted in Europe (Lanzinger et al., 2016b; Samoli et al., 2016a; Basagaña et al., 2015) and Finland (Kollanus et al., 2016) that examined people of all ages provide evidence of consistent, positive associations that are similar in magnitude to those reported in the U.S. and Canadian studies evaluated in the 2009 ISA (Figure 5-8). The results from analyses of people of all ages are further supported by Stafoggia et al. (2013) in a study of eight southern European cities that reported a 1.36% (95% CI: 0.23, 2.49) increase in hospital admissions at lag 0−5 days, as well as a meta-analysis conducted by Adar et al. (2014) (RR = 1.01 [95% CI: 1.00, 1.02]). However, single-city studies conducted in St. Louis, MO (Winquist et al., 2012) and Doña Ana County, NM (Rodopoulou et al., 2014), do not provide consistent evidence of an association with respiratory-related diseases in all ages analyses.

Studies that examined the relationship between short-term $PM_{2.5}$ exposure and respiratory-related hospital admissions in children are limited in number, but generally report associations that are similar in magnitude to previous studies. An exception is the study conducted by Yap et al. (2013) in 12 California counties focusing on children 1 to 9 years of age where there was no evidence of an association in the central valley counties (RR = 1.0), but a positive association in the south coast counties was seen (RR = 1.07) at lag 0−2 days. Winquist et al. (2012) also reported a positive association for children in St. Louis, MO, but confidence intervals were wide (RR = 1.02 [95% CI: 0.96, 1.07]; lag 0−4 DL).

Most of the recent studies focusing on respiratory-related hospital admissions focus on older adults, and consisted mostly of multicity or entire state analysis conducted in the U.S. These recent multicity studies report evidence of consistent, positive associations, except the study by Kollanus et al. (2016) in four cities in Finland (Figure 5-8). The associations reported across the U.S. for multicity studies are based on a variety of exposure assignment approaches (see Table 5-11), all of which resulted in associations that are similar in magnitude. In a multicounty time-series analysis conducted in 213 U.S. counties from 1999−2010, Bell et al. (2015) observed a 0.25% (95% CI: 0.01, 0.48) increase in all respiratory hospital admissions at lag 0 among adults aged 65 years and older. In a similar study of 110 U.S. counties, Powell et al. (2015) reported results consistent with Bell et al. (2015) (0.67% [95% CI: 0.14, 1.2]; lag 0). Bell et al. (2014), also examined single-day lags, but in four counties in Connecticut and Massachusetts, and reported evidence of positive associations across lags of 0 to 2 days, albeit with wide confidence intervals (quantitative results not presented). Additional evidence of a positive association between short-term $PM_{2.5}$ exposure and respiratory-related hospital admissions is provided by Zanobetti et al. (2009) in an analysis of 26 U.S. counties where a 2.1% (95% CI: 1.2, 3.0) increase in hospital admissions was reported at lag 0−1. The results from the epidemiologic studies that rely on

community-based monitors are supported by a series of studies that used a combination of monitored, modeled, and in some cases satellite-based $PM_{2.5}$ concentrations. In a multicity study conducted in the New England region of the U.S., Kloog et al. (2012) assessed exposure using a novel prediction model that combined land use regression with surface $PM_{2.5}$ measurements from satellite aerosol optical depth. The authors observed a 0.70% (95% CI: 0.35, 1.05) increase in respiratory-related hospital admissions for a 0−1-day lag. In a sensitivity analysis using monitor-based exposure assessment in the time-series analysis, Kloog et al. (2012) reported similar results (1.51% [95% CI: 0.42, 1.65]), but with slightly larger confidence intervals. Kloog et al. (2014) built upon the exposure assessment used in Kloog et al. (2012) in a study conducted in the Mid-Atlantic region of the U.S. The authors reported a 2.2% (95% CI: 1.9, 2.6) increase in respiratory-related hospital admissions at lag 0−1 day. The results of Kloog et al. (2012) and Kloog et al. (2014) are supported by Bravo et al. (2017) in a study of 708 U.S. counties. The authors examined associations between short-term $PM_{2.5}$ exposure and respiratory-related hospital admissions using three different exposure assessment approaches: (1) a population-weighted average of $PM_{2.5}$ concentration computed in 708 U.S. counties using a downscaled CMAQ model (Section 3.3.2.4.3); (2) a population-weighted average of downscaled CMAQ-simulated $PM_{2.5}$ concentrations computed in the 418 U.S. counties that have monitoring data; and (3) $PM_{2.5}$ concentrations from the 418 U.S. counties with fixed-site monitors. Across these three exposure assignment approaches, the authors reported a relatively consistent percent increase in hospital admissions at lag 0: (1) 1.16% (95% CI: 0.88, 1.45); (2) 1.11 (95% CI: 0.66, 1.56); and (3) 1.10% (95% CI: 0.70, 1.50).

5.1.6.2 Emergency Department (ED) Visits

Compared to studies that examined hospital admissions for respiratory-related diseases, fewer studies focused on ED visits, with the majority examining associations with short-term $PM_{2.5}$ exposure in analyses of all ages. Additionally, a recent study examined associations with PM size fractions smaller than 2.5 µm, but larger than UFP (i.e., number concentration [NC] and surface area concentration [SC] for particles 100−300 nm), which also supports the positive associations with respiratory-related ED visits observed for $PM_{2.5}$ (Leitte et al., 2011). Whereas, many hospital admission studies were conducted over multiple cities or entire states, the ED visit studies are mostly limited to individual cities.

Malig et al. (2013), in a study of 35 California counties, reported a 1.6% (95% CI: 0.98, 2.27) increase in respiratory-related ED visits at lag 1. Building on the previous studies conducted in Atlanta, GA (Tolbert et al., 2007; Peel et al., 2005), Darrow et al. (2011) also examined associations between short-term $PM_{2.5}$ exposures and respiratory-related ED visits, reporting an association similar in magnitude to the previous studies (0.4% [95% CI: −0.2, 1.0]; lag 1). Additionally, Krall et al. (2016) in a study of four U.S. cities (i.e., Atlanta, Birmingham, St. Louis, and Dallas) reported positive associations for each city at lag 0 (quantitative results not presented). Single-city studies conducted in Canada and the U.S. report associations that overall are consistently positive and generally similar in magnitude to Malig et al. (2013) (Figure 5-8). Across the studies evaluated, only Winquist et al. (2012) examined associations

with respiratory related ED visits in children (i.e., 2−18 years of age) in St. Louis, MO, and reported an association larger in magnitude (RR = 1.03 [95% CI: 1.02, 1.05]; lag 0−4 DL) compared to that observed when examining people of all ages (RR = 1.01 [95% CI: 1.0, 1.02]; lag 0−4 DL). Of the few studies that examined effects in older adults (Rodopoulou et al., 2014; Winquist et al., 2012), there was no evidence of an association between short-term $PM_{2.5}$ exposure and respiratory-related ED visits.

5.1.6.3 Summary of Respiratory-Related Hospital Admissions and Emergency Department (ED) Visits

Recent epidemiologic studies that examined short-term $PM_{2.5}$ exposure and hospital admissions and ED visits for respiratory-related diseases generally support the results from studies evaluated in the 2009 PM ISA (U.S. EPA, 2009). Across studies, there is evidence of generally consistent, positive associations among children, with a growing body of evidence, primarily from multicity U.S.-based studies of older adults (Figure 5-8). Additional studies focusing on people of all ages, also provide evidence supporting an association with $PM_{2.5}$, with most of the studies conducted in individual cities.

The main results of studies detailed within this section are supported by analyses that examined specific policy-relevant issues as detailed in Section 5.1.10. Compared to the 2009 PM ISA (U.S. EPA, 2009), recent studies provide a more extensive examination of potential copollutant confounding, but overall the assessment is limited to only a few studies. These studies demonstrate that associations between short-term $PM_{2.5}$ exposure and respiratory-related hospital admissions and ED visits are relatively unchanged in models with gaseous pollutants and $PM_{10-2.5}$ (Section 5.1.10.1). In addition to copollutant confounding, several studies examined the influence of alternative model specifications on the $PM_{2.5}$ association with respiratory-related hospital admissions and ED visits and found that associations remained relatively unchanged when accounting for temporal trends and weather covariates using different specifications (Section 0). Analyses that focused on whether there are differences by season provide some evidence that $PM_{2.5}$ associations are larger in magnitude during the warmer months, but some studies reported larger associations during the colder months (Section 5.1.10.4.1). The difference in associations by season could reflect geographic variability that continues to be observed in multicity studies. However, to date it remains unclear what factors contribute to the observed geographic variability in $PM_{2.5}$ associations with respiratory-related diseases (Bell et al., 2009a).

While studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) tended to support $PM_{2.5}$ associations within the first few days after exposure (i.e., lag 0 to 3 days), recent studies support that evidence and provide initial evidence indicating that $PM_{2.5}$ effects may be more prolonged, ranging from 0−5 days (Section 5.1.10.3). To date, there are very few studies that have examined subdaily averaging times of $PM_{2.5}$ concentrations (Section 5.1.10.5). In terms of respiratory-related hospital admissions and ED visits, available evidence indicates that subdaily averaging times do not result in stronger associations with respiratory-related hospital admissions and ED visits compared to a 24-hour averaging time (Section 5.1.10.5). Lastly, recent evaluations of the C-R relationship between short-term $PM_{2.5}$ exposure

and respiratory-related hospital admissions and ED visits provides evidence of a linear relationship, but this assessment is based on rather limited analyses that did not empirically evaluate alternatives to linearity (Section 5.1.10.6).

5.1.7 Respiratory Effects in Healthy Populations

The 2009 PM ISA (U.S. EPA, 2009) did not have a delineated discussion of respiratory effects in healthy populations, but relevant epidemiologic studies provided inconsistent evidence for $PM_{2.5}$-related decreases in lung function and increases in pulmonary inflammation, and no evidence for increases in respiratory symptoms in individuals with no underlying respiratory disease. Controlled human exposure studies evaluated in the 2009 PM ISA provided no evidence for changes in lung function and limited evidence for pulmonary inflammation, while animal toxicological studies more consistently provided evidence for $PM_{2.5}$ exposure-related effects.

To characterize the current state of the evidence, this section focuses on results specific to healthy populations. Some studies employed scripted exposures in an attempt to further inform the relationship between short-term $PM_{2.5}$ exposure and respiratory effects. Scripted studies measuring personal ambient $PM_{2.5}$ exposures are designed to minimize uncertainty in the $PM_{2.5}$ exposure metric by always measuring $PM_{2.5}$ at the site of exposure, ensuring exposure to sources of $PM_{2.5}$ and measuring outcomes at well-defined lags after exposure.

There are recent epidemiologic studies in populations with 13−28% prevalence of asthma, COPD, or atopy, some of which indicate $PM_{2.5}$-associated increases in respiratory effects. However, these studies are not evaluated in this section, as it is not known whether the results apply to the healthy portion of the population or are instead driven solely by an association in individuals with pre-existing respiratory conditions, these studies can be found in HERO (https://hero.epa.gov/hero/particulate-matter). Further, these studies do not provide additional insight on issues such as copollutant confounding, effects at low $PM_{2.5}$ exposure concentrations, or critical exposure periods.

5.1.7.1 Epidemiologic Studies

The 2009 PM ISA (U.S. EPA, 2009) evaluated a limited number of epidemiologic studies that examined respiratory effects in healthy populations. A study of adult school crossing guards in New Jersey observed decreases in lung function associated with 1-hour max $PM_{2.5}$ concentrations (Fan et al., 2008). In contrast, Holguin et al. (2007) did not observe an association between $PM_{2.5}$ and lung function or lung inflammation in a study of school children in Ciudad Juarez, Mexico. Several recent studies are available for evaluation, with most focusing on lung function changes and/or lung inflammation in healthy populations. Study-specific details, including cohort descriptions and air quality characteristics are highlighted in Table 5-2.

Respiratory Symptoms

While respiratory symptoms are frequently studied in populations with pre-existing respiratory conditions, such as asthma or COPD, the outcome is less often examined in healthy populations. As such, only a single recent study is available for review. In a study of school children in Santiago, Chile, 7-day average PM2.5 was associated with increased odds of cough and a composite index of respiratory symptoms (Prieto-Parra et al., 2017). The associations were relatively unchanged in two-pollutant models with PM10, NO2, SO2, or O3. However, copollutant correlations were not reported, limiting the interpretability of the copollutant models.

Lung Function Changes

The majority of recent studies on lung function changes in relation to $PM_{2.5}$ concentrations examined adults during scripted exposures and exposure interventions. Studies examining lung function changes in adults after commuting in cars, buses, or on bicycles, did not observe associations between personal ambient $PM_{2.5}$ exposure and FEV_1 (Mirabelli et al., 2015; Weichenthal et al., 2011; Zuurbier et al., 2011b). In a study of adults commuting 2 hours through Atlanta traffic, Mirabelli et al. (2015) reported $PM_{2.5}$-related decreases in FVC immediately after the commute. The association appeared to be transient, with no association observed 3 hours post-commute.

A number of studies in the U.S. (Mirowsky et al., 2015), Canada (Dales et al., 2013), and Europe (Matt et al., 2016; Kubesch et al., 2015; Steenhof et al., 2013; Strak et al., 2012) used quasi-experimental designs to assign participants to either rest or exercise in different locations with notable pollutant contrasts. Similar to the studies of scripted commutes through traffic, many of these quasi-experimental studies observed null associations between lung function and $PM_{2.5}$ (Kubesch et al., 2015; Mirowsky et al., 2015; Strak et al., 2012). In contrast, Dales et al. (2013) observed decreases in FEV_1 and $FEF_{25-75\%}$ associated with 8-hour average $PM_{2.5}$ concentrations in Sault Ste. Marie, Canada. Associations were observed despite low mean concentrations of 8-hour average $PM_{2.5}$. Additionally, in Barcelona, Spain, Matt et al. (2016) reported that healthy adults experienced decreased FEV_1 associated with 2-hour average $PM_{2.5}$ immediately after exposure. Notably, $PM_{2.5}$ was associated with increased FEV_1 7 hours after exposure, again indicating potentially transient effects. Another study in China implemented an exposure intervention by moving healthy, nonsmoking adults from an industrial town to a less polluted city for 9 days (Hong et al., 2010). Participants experienced increased FEV_1 and PEF associated with decreased 24-hour average $PM_{2.5}$.

Studies of lung function in healthy children were limited in number. School-children in an agricultural area of Brazil experienced decreases in PEF in association with $PM_{2.5}$ concentrations measured outside of school, averaged over the 6, 12, or 24 hours preceding spirometry (Jacobson et al., 2012). In Seoul, South Korea Hong et al. (2010), composite monitor 24-hour average $PM_{2.5}$ was associated with a small, imprecise decrease in PEFR in schoolchildren at lags 0 and 3, but no other lags

up to 4 days. The location of the monitors relative to the school was not specified, so it is not clear to what degree exposure measurement error might have impacted the results (Section 3.4.2.2).

Subclinical Effects

Most recent studies of subclinical respiratory effects in healthy populations examined exhaled nitric oxide (eNO) as an indicator of pulmonary inflammation. Many of the same studies that were evaluated in the previous subsection on lung function also measured eNO. As such, the majority of recent studies similarly examined adults during scripted exposures. Studies of adults during and after commuting in cars, buses, or on bicycles, generally observed associations between personal ambient $PM_{2.5}$ exposure and subclinical respiratory effects (Mirabelli et al., 2015; Weichenthal et al., 2011; Zuurbier et al., 2011b). Mirabelli et al. (2015) observed associations between eNO and $PM_{2.5}$ concentrations during a 2-hour scripted commute through Atlanta traffic. The authors reported $PM_{2.5}$-related increases in eNO levels 0, 1, 2, and 3 hours post-commute. A similar $PM_{2.5}$-related increase in eNO was reported in a group of adults cycling alongside high- and low-traffic roads in Ottawa, Canada (Weichenthal et al., 2011). The observed associations with personal $PM_{2.5}$ concentrations were strongest 2 hours after cycling. Conversely, $PM_{2.5}$ was associated with a decrease in eNO in a study of adults commuting 2 hours by either car, bus, or bike in the Netherlands (Zuurbier et al., 2011b). However, the authors also noted that personal ambient $PM_{2.5}$ was associated with a decrease in Clara cell secretory protein (CC16), a pulmonary biomarker that is often decreased in subjects with lung epithelial damage.

Studies utilizing quasi-experimental designs were less consistent, despite similarly high mean concentrations of $PM_{2.5}$. In New York, $PM_{2.5}$ exposure while walking near high-traffic roads and in a forest was associated with eNO 24 hours after exposure (Mirowsky et al., 2015). However, eNO was not associated with $PM_{2.5}$ in studies where participants were randomized to exercise or rest at locations with air pollution exposure contrasts in Barcelona, Spain (Kubesch et al., 2015) or Utrecht, The Netherlands (Strak et al., 2012). As part of the same project in the Netherlands, Steenhof et al. (2013) reported an association between $PM_{2.5}$ exposure and nasal lavage levels of the pro-inflammatory cytokine, IL-6. The observed association was persistent in two-pollutant models including NO_X, O_3, or SO_2 (Steenhof et al., 2013).

A single study examined subclinical effects in school children. Carlsen et al. (2016) observed a 5.4 ppb (95% CI: −3.1, 13.0 ppb) increase in eNO associated with 2-day average $PM_{2.5}$ at two schools in Umea, Sweden. $PM_{2.5}$ was measured at monitors located within 1.5 km of the two schools. Although copollutant models were not examined, $PM_{2.5}$ was weakly correlated with NO_X and only moderately correlated with O_3.

Table 5-12 Epidemiologic studies of $PM_{2.5}$ and respiratory effects in healthy populations.

Study	Study Population	Exposure Assessment Concentration in µg/m³	Single-Pollutant Association 95% CI	$PM_{2.5}$ Copollutant Model Results and Correlations
Exposure interventions				
†Hao et al. (2017) Shanghai and Shandong, China 2012	N = 42, ages 50−61 yr 9-day relocation from higher to lower air pollution city Outcomes every other day	Total personal 24-h avg Mean (SD) Shanghai: 95.1 Shandong: 187	Per 10 µg/m³ decrease FEV_1: 9.0 (3.6, 14.4) mL PEF: 33.2 (4.8, 61.5) mL/sec	Correlation (*r*): NA Copollutant models with: NO_2
Scripted outdoor exposures				
†Mirabelli et al. (2015) Atlanta, GA 2009−2011	N = 21, ages NR Morning commute on highway Two times each, 75 observations Outcomes 0, 1, 2, 3 h after	Personal in-vehicle 2-h avg (7−9 a.m.) Mean: 28.8	Per 20.9 µg/m³ eNO, 0 h: 2.4% (−3.3, 8.5) FEV_1 percent predicted, 0 h: −0.42% (−2.2, 1.3)	Correlation (*r*): NA Copollutant models with: NA
†Mirowsky et al. (2015) New York, Sterling Forest NY; Nutley, NJ Jun−Sep, 2011−2012	N = 26, ages 18−33 yr Walking on highway bridge, no-truck highway, forest One time each, 70 observations Outcomes 0, 24 h after	Personal ambient 2-h avg Mean, max Bridge: 31, 45 No-truck highway: 21, 50 Forest: 13, 24	Increment NR eNO, 0 h: −0.38% (−1.6, 0.31) eNO, 24 h: 0.87% (−0.09, 1.8)	Correlation (*r*): 0.66 PM_{10}, 0.29 EC, 0.38 BC, 0.4 OC, 0.39 O_3 Copollutant models with: NA
†Dales et al. (2013) Sault Ste Marie, Canada May−Aug 2010	N = 61, mean (SD) age 24 (6) yr Near steel plant, college campus five times each Outcomes 0 h after	Personal ambient 8-h avg Mean (SD) Steel plant: 12.8 College campus: 11.6	Per 9 µg/m³ FEV_1: −0.42% (−0.83, 0) $FEF_{25-75\%}$: −0.92% (−1.7, −0.12)	Correlation (*r*): NA Copollutant models with: NA

Table 5-12 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory effects in healthy populations.

Study	Study Population	Exposure Assessment Concentration in µg/m³	Single-Pollutant Association 95% CI	$PM_{2.5}$ Copollutant Model Results and Correlations
†Weichenthal et al. (2011) Ottawa, Canada May–Sep 2010	N = 42, ages 19–58 yr Cycling on high- and low-traffic road One time each, 118 observations Outcomes 0, 1, 2, 3 h after	Personal ambient 1-h avg Mean, max High-traffic road: 12.2, 34 Low-traffic road: 8.1, 26	Per 8.7 µg/m³ 1-h post-exposure FEV_1: −16 (−90, 58) ml 2-h post-exposure eNO: 1.1 (0.08, 2.2) ppb	Correlation (*r*): (high traffic, low traffic) 0.06, −0.22 UFP; 0.32, 0.24 BC; 0.75, 0.59 CO; −0.30, −0.04 SO_2; 0.31, 0.45 NO_2; 0.58, 0.36 O_3 Copollutant models with: NA
†Strak et al. (2012); †Steenhof et al. (2013) Utrecht, the Netherlands Mar–Oct 2009	N = 31, ages 19–26 yr Free-flowing traffic road, stop-and-go traffic road, urban site, farm, underground train station One time each, with exercise Outcomes 0, 2, 22 h after	Personal ambient 5-h avg Geometric mean, max 39, 167	Per 11.5 µg/m³ FVC: 0.08%, $p > 0.10$ eNO: 0.17%, $p > 0.10$ For outdoor sites only Nasal lavage IL-6: 16%, $p < 0.05$	Correlation (*r*): −0.65 O_3, 0.21 NO_2, 0.31 NO_X Copollutant models with: O_3, SO_2, NO_X
†Zuurbier et al. (2011b); †Zuurbier et al. (2011a) Arnhem, the Netherlands Jun 2007–Jun 2008	N = 34, ages 23–55 yr Commute in car, bus, bike One time each, 352 observations Outcomes 0, 6 h after	Personal ambient 2-h avg Mean, max Diesel bus: 39.1, 324 Diesel car: 58.1, 358 Gas car: 68.1, 403 Bike, high traffic: 49.8, 219 Bike, low traffic: 65.2, 241	Per 68.1 µg/m³, 6 h post-exposure FEV_1: 0.02% (−0.41, 0.45) MMEF: 0.60% (−0.73, 1.9) eNO: −2.5% (−5.9, 1.1) CC16: −1.3% (−6.8, 0.3)	Correlation (*r*): NA Copollutant models with: NO_2
†Matt et al. (2016) Nov 2013–Mar 2014	N = 30, ages 19–57 yr Bridge over high-traffic road, seaside park One time each, with exercise and rest Outcomes 0, 7 h after	Personal ambient 2-h avg Mean, 95th High-traffic: 82, 92 Seaside Park: 39, 48	Per 1 µg/m³, 0-h post-exposure FEV_1: −0.55 (−1.4, 0.31) mL PEF: −0.06 (−0.32, 0.21) L/min Per 1 µg/m³, 7-h post-exposure FEV_1: 0.43 (−0.52, 1.4) mL PEF: 0.15 (−0.05, 0.35) L/min	Correlation (*r*): −0.04 high-traffic, 0.7 seaside park NO_X Copollutant models with: NA

Table 5-12 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory effects in healthy populations.

Study	Study Population	Exposure Assessment Concentration in µg/m³	Single-Pollutant Association 95% CI	$PM_{2.5}$ Copollutant Model Results and Correlations
†Kubesch et al. (2015) Barcelona, Spain Feb–Nov 2011	N = 28, ages 18–60 yr Bridge over high-traffic road, marketplace One time each, with exercise and rest Outcomes 0, 3, 6 h after	Personal ambient 2-h avg Mean, 95th High-traffic: 80.8, 88.6 Marketplace: 30.0, 37.7	Per IQR (NR) FEV_1: 0.00 (−0.02, 0.02) mL $FEF_{25-75\%}$: −0.05 (−0.11, 0) mL eNO: 0.40 (−0.53, 1.3) ppb	Correlation (*r*): 0.91 NO_X Copollutant models with: NA
Fan et al. (2008) Patterson, NJ Feb–May 2005	N = 11, mean (SD) age 61 (14) yr Crossing guards at work Three work shifts, 27 observations Outcomes 0 h after	Personal ambient Mean (SD), max difference from 24-h avg 1-h avg: 35.2, 87 1-h max: 71.3, 278	Increment NR FEV_1, 1-h avg: 20 (−58, 98) mL FEV_1, 1-h max: −130 (−287, 27) mL	Correlation (*r*): NA Copollutant models with: NA
General community exposures				
Holguin et al. (2007) Ciudad Juarez, Mexico 2002–2003	N = 99, ages 6–12 yr Biweekly measures for 4 mo	Outdoor school Children live 0.2–0.7 km 24-h avg Mean: 17.5	No quantitative results	Correlation (*r*): 0.30 NO_2, 0.49 EC Copollutant models with: NA
†Carlsen et al. (2016) Umea, Vasterbotten, Sweden Apr–Jun 2011	N = 95, ages 11–12 yr Two measures/week for 2 mo 973 observations	Monitors within 1.5 km of schools 24-h avg Mean: 5.6 Max: 16.7	Per 10 µg/m³ eNO (ppb) Lag 0: 1.9 (−5.8, 10) Lag 0–1: 5.4 (−3.1, 13)	Correlation (*r*): 0.01 $PM_{10-2.5}$, 0.36 NO_2, 0.42 O_3 Copollutant models with: NA
†Jacobson et al. (2012) Alta Floresta, Brazil Aug–Dec 2006	N = 224, ages 8–15 yr Daily measures for 4 mo	School outdoor 24-h avg, 6-h avg (12–6 a.m.), 12-h avg (12 a.m.–noon) Mean, 90th for 24-h avg 24.4, 44.1	Per 10 µg/m³ PEF (L/min) 24-h avg: −0.38 (−0.63, −0.13) 6-h avg: −0.36 (−0.66, −0.06) 12-h avg: −0.31 (−0.65, 0.02)	Correlation (*r*): NA Copollutant models with: NA

Table 5-12 (Continued): Epidemiologic studies of $PM_{2.5}$ and respiratory effects in healthy populations.

Study	Study Population	Exposure Assessment Concentration in µg/m³	Single-Pollutant Association 95% CI	$PM_{2.5}$ Copollutant Model Results and Correlations
†Prieto-Parra et al. (2017) Santiago, Chile May−Sep 2010−2011	N = 83, ages 6−14 yr Daily measures for 3 mo Mean observations: 100 yr 1, 80 yr 2	One monitor Most children live within 3 km Mean: 30	OR per 10 µg/m³, lag 0−6 Cough: 1.22 (CI NR) Three symptom index: 1.28	Correlation (*r*): NA Copollutant models with: PM_{10}, NO_2, O_3, SO_2, K, Mo, Pb, S, Se, and V
†Hong et al. (2010) Seoul, South Korea May−Jun 2007	N = 92, mean (SD) age 9 (0.5) yr Daily measures for 1 mo	Monitors in city, number NR 24-h avg Mean: 36.2	No quantitative results	Correlation (*r*): NA Copollutant models with: NA

Avg = average, CC16 = club cell protein, CI = confidence interval, CO = carbon monoxide, eNO = exhaled nitric oxide, $FEF_{25-75\%}$ = forced expiratory flow between 25 and 75% of forced vital capacity, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, IQR = interquartile range, max = maximum, NO_2 = nitrogen dioxide, NO_X = sum of NO_2 and nitric oxide, NR = not reported, O_3 = ozone, PEF = peak expiratory flow, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, *r* = correlation coefficient, SD = standard deviation, SO_2 = sulfur dioxide.

†Studies published since the 2009 PM ISA.

5.1.7.2 Controlled Human Exposure Studies

Studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) provided little evidence that exposure to $PM_{2.5}$ results in decrements in lung function in healthy populations. Although Petrovic et al. (2000) observed that a 2-hour exposure to $PM_{2.5}$ (92 $\mu g/m^3$) resulted in decreases in thoracic gas volume, other measures of lung function (spirometry, diffusing capacity, airway resistance) were unaffected. No clear effect of short-term exposure to $PM_{2.5}$ on lung function was demonstrated in several studies investigating the exposure of healthy volunteers to $PM_{2.5}$ CAPs (Gong et al., 2003; Ghio et al., 2000; Gong et al., 2000) or urban traffic particles. In a recent study, Huang et al. (2012) exposed healthy volunteers to $PM_{2.5}$ CAPs collected from Chapel Hill, NC. The authors reported no changes in multiple markers of lung function (including FVC, FEV_1, and $FEF_{25–75}$) or in the marker for diffusion capacity DLCO at 1 and 18 hours post exposure (study details in Table 5-13).

The 2009 PM ISA (U.S. EPA, 2009) provided limited evidence that exposure to $PM_{2.5}$ resulted in subclinical or inflammatory effects in healthy populations. Ghio et al. (2000) reported an increase in airway and alveolar neutrophils following exposure to $PM_{2.5}$ CAPs. A follow-up analysis of Ghio et al. (2000) determined the increase in BALF neutrophils was associated with the Fe, SE, and SO_4^{2-} content of the particulate matter (Y-CT et al., 2003). Recently, the healthy population respiratory response to $PM_{2.5}$ has been further examined by Behbod et al. (2013) and Huang et al. (2012). These studies involved exposure to $PM_{2.5}$ CAPs at either approximately 250 $\mu g/m^3$ (Behbod et al., 2013) or 90 $\mu g/m^3$ for approximately 2 hours (Huang et al., 2012) (additional study details are in Table 5-13). Multiple markers of airway inflammation were measured. Behbod et al. (2013) reported that relative to filtered air, no significant airway (sputum) responses were observed in subjects exposed to Toronto, Ontario $PM_{2.5}$ CAPs. Exposures to relatively lower levels of $PM_{2.5}$ CAPs (approximately 90 $\mu g/m^3$) (Huang et al., 2012) corroborated the effects seen in the higher exposure study (Behbod et al., 2013) in that exposure to Chapel Hill NC $PM_{2.5}$ CAPs had no effect on IL-6, IL-8, or α1-antitrypsin in the bronchoalveolar lavage of exposed healthy subjects, although changes in blood parameters were observed (see Section 6.1.11).

Table 5-13 Study-specific details from controlled human exposure studies of short-term $PM_{2.5}$ exposure and respiratory effects in healthy populations.

Study	Study Design	Disease Status; n; Sex; (Age)	Exposure Details (Concentration; Duration; Comparison Group)	Endpoints Measured
Behbod et al. (2013)	Double-blind, randomized cross-over block design	Healthy nonsmokers; n = 35; 11 M, 12 F (18−60 yr)	234.7 μg/m^3 $PM_{2.5}$ CAPs, Toronto, ON. (IQR: 52.4 μg/m^3) for 130 min (120-min exposure + 10 min to complete tests) at rest. Comparison groups were either (1) filtered air or (2) medical air; a minimum 2-week washout period was used between exposures.	Sputum (pre- and 24-hour post-exposure): Total cell and neutrophil counts
Huang et al. (2012)	Not specifically stated	Healthy nonsmokers; n = 23; 15 M, 8 F (20−36 yr)	89.5 ± 10.7 μg/m^3 $PM_{2.5}$ CAPs or 73.4 ± 9.9 μg/m^3 $PM_{2.5}$ CAPs + 0.5 ppm NO_2 for 2 h, Chapel Hill, NC. During exposure, subjects completed four cycles of 15 min each rest or exercise. Comparison group was clean air.	Lung function BAL (18-h post-exposure): IL-6, IL-8, α1-antitrypsin, LDH, differential leucocyte counts

BAL = bronchoalveolar lavage; CAPs = concentrated ambient particles; IL-6 = interleukin-6; IL-8 = interleukin-8; IQR = interquartile range; LDH = lactate dehydrogenase; NO_2 = nitrogen dioxide.

5.1.7.3 Animal Toxicological Studies

Lung Function

The 2004 PM AQCD (U.S. EPA, 2004)and the 2009 PM ISA (U.S. EPA, 2009) reported several animal toxicological studies that measured pulmonary function following single or multiday exposure to $PM_{2.5}$ CAPs. Decreased breathing frequency (or respiratory rate) was observed in dogs exposed to $PM_{2.5}$ CAPs in Boston by tracheostomy exposure (Godleski et al., 2000). In addition, a strong increase in airway irritation, as indicated by decreases in end inspiratory pause and increases in end expiratory pause, pause, and enhanced pause (Penh) was observed (Nikolov et al., 2008). Increased tidal volume was found in rats exposed to $PM_{2.5}$ CAPs in Boston (Clarke et al., 1999) but not in New York City (Gordon et al., 2000). Increases in inspiratory and expiratory times were not seen in Wistar Kyoto rats exposed to $PM_{2.5}$ CAPs in Research Triangle Park, NC (Kodavanti et al., 2005). Results of these studies, showing changes in

breathing frequency and depth of breathing, indicate that short-term $PM_{2.5}$ exposure stimulated lung irritant responses through the activation of sensory nerves and local reflexes.

Recently, Diaz et al. (2013) evaluated the effects of exposure to $PM_{2.5}$ roadway tunnel particles on pulmonary function in Sprague Dawley rats. A 2-day exposure to tunnel particles with gases removed by a denuder resulted in increased rapid shallow breathing, as indicated by increased frequency and decreased tidal volume, minute volume, inspiratory time, and expiratory time ($p < 0.05$). This breathing pattern, as well as the observed decrease in expiratory flow at 50% (EF_{50}) ($p = 0.01$), provide evidence of an irritative respiratory response. A 2-day exposure to a secondary organic aerosol formed from photochemical oxidation of primary tunnel gases (SOA) resulted in increases in pauses, including Penh ($p \leq 0.05$). A 4-day exposure to SOA decreased several parameters including frequency, tidal volume, minute volume, EF_{50}, and Vi, an indicator of respiratory drive ($p < 0.05$). A 4-day exposure to photochemically aged primary particles plus SOA (P + SOA) produced the largest change in breathing parameters including decreased volumes, flow, respiratory drive, and respiratory effort ($p < 0.05$). This pattern is reflective of rapid shallow breathing and suggests an irritative respiratory response with an additional effect at the thoracic level. Additional study details for this study, and other recent toxicological studies, are found in Table 5-14.

The effect of social stress on pulmonary function was examined in older Sprague Dawley rats exposed to $PM_{2.5}$ CAPs in Boston (Clougherty et al., 2010). In stressed animals, $PM_{2.5}$ CAPs exposure was associated with increased breathing frequency ($p = 0.001$), lower tidal volume ($p = 0.001$), lower PEF ($p = 0.003$), and shorter times ($p < 0.001$), suggesting rapid shallow breathing. In unstressed animals, $PM_{2.5}$ CAPs exposure was associated with increased PIF ($p = 0.03$) and greater MV ($p = 0.05$).

Effects on other pulmonary function parameters have been reported. Amatullah et al. (2012) found that a 4-hour exposure of BALB/c mice to $PM_{2.5}$ CAPs in Toronto increased quasi-static elastance of the lung ($p < 0.05$). Yoshizaki et al. (2017) examined sex-related differences in tracheal hyperreactivity of BALB/c mice due to a multiday exposure to $PM_{2.5}$ CAPs in Sao Paulo, Brazil. Tracheal rings from male mice that were exposed to $PM_{2.5}$ CAPs were hyporesponsive to methacholine, a bronchoconstrictor, compared to tracheal rings from male mice exposed to ambient air ($p < 0.05$). Tracheal rings from diestrus female mice that were exposed to $PM_{2.5}$ CAPs responded similarly to methacholine as tracheal rings from female mice exposed to ambient air. However, tracheal rings from estrus and proestrus female mice were hyperresponsive to methacholine compared with air controls ($p < 0.05$).

Table 5-14 Study-specific details from animal toxicologic studies of short-term $PM_{2.5}$ exposure and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
Amatullah et al. (2012) Species: Mouse Sex: Female Strain: BALB/c Age/weight: 6−8 weeks, 18 g	$PM_{2.5}$ CAPs Toronto Particle size: $PM_{0.15-2.5}$ Control: HEPA filtered air	Route: Nose-only inhalation Dose/concentration: $PM_{0.5-2.5}$ 254 µg/m³ Duration: 4 h Time to analysis: At end of exposure Modifier: Baseline ECG	Pulmonary function BALF Cells
Aztatzi-Aguilar et al. (2015) Species: Rat Sex: Male Strain: Sprague Dawley	$PM_{2.5}$ CAPs Mexico City Particle size: $PM_{2.5}$ Control: Filtered air	Route: Inhalation Dose/concentration: $PM_{2.5}$ 178 µg/m³ Duration: Acute 5 h/day, 3 days Subchronic 5 h/day, 4 days/week, 8 weeks Time to analysis: 24 h	Gene expression and protein levels—lung tissue IL-6, components of the RAS and kallikrein-kinin endocrine system-heme oxygenase-1
Budinger et al. (2011) Species: Mouse Sex: Male Strain: C57BL/6 wild type and IL-6 knockouts Age/weight: 8−12 weeks	$PM_{2.5}$ CAPs Chicago, IL Particle size: $PM_{2.5}$ Control: Filtered ambient air	Route: Whole-body inhalation Dose/concentration: 88.5 ± 13.4 µg/m³ Duration: 8 h/day for 3 days	BALF and lung tissue-protein level and gene expression of inflammatory mediators Plasma—biomarkers of coagulation
Chiarella et al. (2014) Species: Mouse Sex: Male Strain: C57BL/6 wild type and Adrβ knockouts Age/weight: 8−12 weeks	$PM_{2.5}$ CAPs Chicago, IL Particle size: $PM_{2.5}$ Control: Filtered ambient air	Route: Whole-body inhalation Dose/concentration: 109.1 ± 6.1 µg/m³ Duration: 8 h/day for 3 days	BALF and lung tissue—IL-6, norepinephrine Brown adipose tissue—norepinephrine
Clougherty et al. (2010) Species: Rat Sex: Male Age/weight: 12 weeks	$PM_{2.5}$ CAPs Boston Particle size: PM ≤ 2.5 µm Control: Filtered air	Route: Whole-body inhalation Dose/concentration: 374 µg/m³ With large variance Duration: 10 days, 5 h/day Time to analysis: Respiratory data was collected during exposure at 10 min. intervals using Buxco Coexposure: Stress	Pulmonary function • Peak inspiratory flow • Minute volume • Breathing frequency • Inspiratory time • Expiratory time • Expiratory flows • Tidal volume

Table 5-14 (Continued): Study specific details from animal toxicologic studies of short term $PM_{2.5}$ exposure and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
Diaz et al. (2013) Species: Rat Sex: Male Strain: Sprague-Dawley Age/weight: 250−300 g	Roadway tunnel particles (gases removed by denuder) Primary particles (P) Primary particles and secondary aerosol (P-SOA) Secondary organic aerosol (SOA) Particle size: PM < 2.5 µm Control-Filtered air (oxidizable gases, VOC and particles removed)	Route: Whole-body Inhalation Dose/concentration: P-47.5 µg/m^3 P + SOA-50 µg/m^3 SOA- 48.7 µg/m^3 Duration: 2−4 days, 5 h/day Time to analysis: 24 h or 48 h Coexposure: NO: P- 71.2 ppb P + SOA- 2.1 ppb SOA- 27.1 ppb NO_X: P- 92.6 ppb P + SOA- 37.5 ppb SOA- 56.9 ppb	BALF Cells Lung function • Tidal volume • Minute Volume • Expiratory time • Inspiratory time • Expiratory flow at 50% (flow) • Pause • Enhanced pause • End expiratory pause • End inspiratory pause • Peak of inspiratory flow • Inspiratory time
Kim et al. (2016b) Species: Mouse Strain: Balb/c Sex: Male Age/weight: 6−10 weeks	DEP (NIST SRM) Particle size: Not reported	Route: Inhalation Dose/concentration: 2 mg/m^3 Duration: 1 h/day for 5 days Time to analysis: 9 days	Middle ear: Gene expression microarray and pathway analysis
Mauderly et al. (2011) Species: Mouse/Rat Sex: Male and female Strain: Mouse Age/weight: C57BL/6 (10−13 weeks) A/J (5−8 weeks) BALB/c (3 weeks gestation, 4 weeks after birth) Strain: Rat F344 Age/weight: (7−9 weeks)	Simulated coal emissions low, medium, high doses and high dose filtered groups Particle size: Not reported in this publication. Likely PM < 2.5 Control: Clean air	Route: Whole-body Inhalation Dose/concentration: 1,000, 300, 100 µg/m^3 Duration: 6 mo or 1 week, 7 days/week, 6 h/day	BALF Cells/Cytokines (F344 rats) • MIP-2 • Leukocytes
Plummer et al. (2012) Species: Mouse Sex: Male Strain: C57BL/6 Age/weight: 12−14 weeks, 25−30 g	$PM_{2.5}$ CAPs from Fresno, (F, urban) or Westside (W, rural) locations in California, in two seasons (summer, winter) Particle size: $PM_{2.5}$ Control: Ambient air	Route: Whole-body inhalation Dose/concentration: F/Summer 284 µg/m^3, F/Winter 156 µg/m^3, W/Summer 126 µg/m^3, W/Winter 86 µg/m^3 Duration: 6 h/day for 10 days Time to analysis: 48 hr Note: Composition of $PM_{2.5}$ CAPs defined for organic/elemental carbon, nitriate, sulfate, ammonia, chloride	BALF cells Lung tissue Cytokine/Chemokine Histopathology—lung

Table 5-14 (Continued): Study specific details from animal toxicologic studies of short term $PM_{2.5}$ exposure and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
Rohr et al. (2010) Species: Rat Strain: Spontaneously hypertensive (SH) Wistar Kyoto (WKY) Sex: Male Age/weight: 11−12 weeks	$PM_{2.5}$ CAPs residential urban Detroit, MI Particle size: $PM_{2.5}$ Control: HEPA-filtered clean air	Route: Whole-body inhalation Dose/concentration: 507 µg/m^3 Duration of exposure: 8 h, 13 consecutive days Time to analysis: 24 h	BALF cells Lung Injury • BALF protein content
Tyler et al. (2016) Species: Mouse Strain: C67BL/6 Age/weight: 6−8 weeks	DEP, resuspended Particle size: 1.5−3.0 µm ± 1.3−1.6 µm Control: Filtered air	Route: Whole-body inhalation Dose/concentration: 315.3 ± 50.7 µg/m^3 Duration: 6 h	BALF cells and cytokines Particle uptake in bronchial macrophages
Xu et al. (2013) Species: Mouse Strain: C57BL/6 Sex: Male Age/weight: 3 weeks	$PM_{2.5}$ CAPs Columbus, OH Particle size: ≤$PM_{2.5}$ Control: Filtered air	Route: Whole-body inhalation Dose/Concentration: 143.8 µg/m^3 Duration: 6 h/day, 5 days/week, 5, 14, 21 days Time to analysis: Immediately post-exposure	Immunohistochemistry—lung BALF cells—flow cytometry
Yoshizaki et al. (2016) Species: Mouse Sex: Male and female Strain: BALB/c Age/Weight: 21 days	$PM_{2.5}$ CAPs Sao Paulo, Brazil Particle size: $PM_{0.1-2.5}$ µm Control: Ambient air	Route: Whole-body Inhalation Dose/Concentration: Cumulative dose × time $PM_{2.5}$: 594 ± 77 µg/m^3 Duration: Multiday Coexposure: Other ambient pollutants and also PM_{10}	Gene expression and protein levels—nasal epithelium AhR, estrogen receptor, cytochrome P450 enzymes Immunohistochemistry—nasal epithelium mucus profile and mucus content
Yoshizaki et al. (2017) Species: Mouse Sex: Male and female (diestrus, proestrus, and estrus) Strain: BALB/c Age/Weight: 21 days	$PM_{2.5}$ CAPs Sao Paulo, Brazil Particle size: Control: Ambient air	Route: Whole-body Inhalation Dose/Concentration: Cumulative dose × time $PM_{2.5}$: 600 µg/m^3 Duration: Multiday Coexposure: Other ambient pollutants, PM_{10}	Ex vivo tracheal rings—reactivity to methacholine BALF cells and cytokines Lung Immunohistochemistry

Adrβ = beta adrenergic receptor; AhR = aryl hydrocarbon receptor; BALF = bronchoalveolar lavage fluid; CAPs = concentrated ambient particles; DEP = diesel exhaust particles; ECG = electrocardiogram; HEPA = high-efficiency particulate absorber; IL-6 = interleukin-6; MIP-2 = macrophage inflammatory protein-2; NIST SRM = National Institute of Standards and Technology Standard Reference Material; NO = nitric oxide; NO_X = oxides of nitrogen; RAS = renin-angiotensin system; VOC = volatile organic carbon.

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Pulmonary Injury

As described in the 2009 PM ISA (U.S. EPA, 2009), several studies examined pulmonary injury and altered lung barrier/secretory function in response to single or multiday exposure to $PM_{2.5}$ CAPs. While increased BALF protein and lung water content were observed in rats exposed to $PM_{2.5}$ CAPs in Boston (Gurgueira et al., 2002; Clarke et al., 1999), injury indices were not observed in rats exposed to $PM_{2.5}$ CAPs in New York City and Research Triangle Park, NC (Gordon et al., 2000; Kodavanti et al., 2000). Recently, Rohr et al. (2010) exposed Wistar Kyoto rats to residential urban $PM_{2.5}$ CAPs in Detroit, MI for 13 days and found increased BALF protein content ($p < 0.05$). Indices of injury (BALF protein and LDH activity) were not increased by any exposure to San Joaquin Valley $PM_{2.5}$ CAPs despite evidence of inflammation (Plummer et al., 2012). Additional study details are found in Table 5-14.

Pulmonary Oxidative Stress

As described in the 2009 PM ISA (U.S. EPA, 2009), several studies examined oxidative stress in response to $PM_{2.5}$ exposure. Increased lung chemiluminescence, activities of MnSOD and catalase, TBARS, and protein carbonyl content were reported in rats exposed to $PM_{2.5}$ CAPs in Boston (Rhoden et al., 2004; Gurgueira et al., 2002). Pretreatment with the thiol antioxidant N-acetylcysteine blocked PM-mediated oxidative stress in Rhoden et al. (2004). In a recent study, tissue heme oxygenase-1 activity, an index of oxidative stress, was not increased by any exposure to San Joaquin Valley $PM_{2.5}$ CAPs (Plummer et al., 2012) despite evidence of inflammation (Table 5-14).

Pulmonary Inflammation

The 2004 PM AQCD (U.S. EPA, 2004) and 2009 PM ISA (U.S. EPA, 2009) reported several studies that examined the effect of single and multiday exposure to $PM_{2.5}$ on pulmonary inflammation. Exposure to $PM_{2.5}$ CAPS in Boston resulted in increased BALF neutrophils in dogs (exposed by tracheostomy) (Godleski et al., 2000) and increases in BALF neutrophils and lymphocytes in rats (Rhoden et al., 2004; Saldiva et al., 2002; Clarke et al., 1999), while BALF macrophages were decreased (Clarke et al., 1999). Godleski et al. (2002) found concentration-dependent increases in numbers of BALF neutrophils and increases in gene expression of inflammatory mediators following exposure to $PM_{2.5}$ CAPs in Boston. Increases in BALF total cells, neutrophils, and macrophages were also seen in rats exposed to $PM_{2.5}$ CAPs from Fresno, CA (Smith et al., 2003). Exposure of rats to $PM_{2.5}$ CAPs in New York City resulted in increased lavageable cells in one study (Zelikoff et al., 2003) and no increases in inflammatory cells in another (Gordon et al., 2000). Similarly, exposure to $PM_{2.5}$ CAPs in Research Triangle Park, NC had disparate effects in different studies (Kodavanti et al., 2005; Kodavanti et al., 2000). Other studies investigated the effects of exposure to traffic related air pollution, such as whole DE or GE or on-road highway aerosols, on pulmonary inflammation. However, these studies did not distinguish between effects of the gaseous or particulate parts of the mixture.

Similarly, recent studies are not uniform in the observation of inflammation following inhalation exposure to $PM_{2.5}$. Amatullah et al. (2012) found no changes in BALF inflammatory cells immediately following a 4-hour exposure of BALB/c mice to $PM_{2.5}$ CAPs in Toronto (Table 5-14). No increases in BALF inflammatory cells were found in Wistar Kyoto rats exposed for 13 days to $PM_{2.5}$ CAPs in Detroit despite an increase in BALF protein, an index of lung injury (Rohr et al., 2010). In contrast, increases in lung tissue and BALF IL-6 were observed following multiday exposure of C57BL/6 mice to $PM_{2.5}$ CAPs in Chicago (Chiarella et al., 2014; Budinger et al., 2011), and Mexico City (Aztatzi-Aguilar et al., 2015). Budinger et al. (2011) also reported increases in BALF MCP-1 and TNF-α. In IL-6 knock-out mice, short-term $PM_{2.5}$ exposure failed to increase IL-6 levels, while the other two mediators were unaffected. In addition, upregulation of the IL-6 target genes surfactant protein B and tissue factor in lung tissue and thrombin-antithrombin complex in plasma was observed in wild-type, but not in IL-6 knock-out mice. These results demonstrate the involvement of lung IL-6 in mediating systemic increases in thrombin-antithrombin complex, a key mediator of thrombosis. Furthermore, increased numbers of neutrophils in the BALF were found in C57BL/6 mice exposed for 10 days to $PM_{2.5}$ CAPs in California ($p < 0.05$) (Plummer et al., 2012). In this latter study, $PM_{2.5}$ CAPs were collected during two seasons (summer and winter) from an urban (Fresno) and a rural site (Westside) near Fresno. While BALF neutrophils were increased in mice exposed to Westside summer and Westside winter $PM_{2.5}$ CAPs ($p < 0.05$), levels of KC, MCP-1 and IFN-γ were decreased in lung tissue from mice exposed to Fresno summer $PM_{2.5}$ CAPs ($p < 0.05$). This study demonstrates that urban and rural sites within the same airshed and season can have PM with differing ability to produce inflammation.

A time course study of pulmonary inflammation was conducted by Xu et al. (2013) in C57BL/6 mice exposed for 5, 14, and 21 days to $PM_{2.5}$ CAPs in Columbus, OH. No increases in numbers of macrophages or neutrophils were found in BALF. However, immunohistochemically staining of lung tissue showed increases in macrophages (using F4/80 + as the marker) at the three time points ($p < 0.05$), peaking at 5 days. No increases in neutrophils (using NIMPR14 as the marker) were seen in lung tissue. This study is unique in demonstrating early recruitment of macrophages to lung tissue in the absence of neutrophils and is indicative of innate immune system activation.

Other studies examined the effects of source-related $PM_{2.5}$ on pulmonary inflammation. Tyler et al. (2016) exposed C67BL/6 mice to resuspended DEP for 6 hours and found no increase in inflammatory cells or cytokines in the BALF and no increase in particle uptake in bronchial macrophages, despite inflammation in the hippocampus (Section 8.1.3). Diaz et al. (2013) exposed Sprague Dawley rats to three kinds of $PM_{2.5}$—primary particles that were obtained directly from a tunnel with roadway gases removed by a denuder (P), secondary organic aerosol formed from photochemical oxidation of the primary tunnel gases (SOA), and photochemically aged primary particles plus SOA (P + SOA). Lymphocytes in BALF increased following 1-day exposure to P ($p < 0.05$) and 2-day exposure to P + SOA ($p < 0.07$), while neutrophils in BALF increased after 2-day exposure to SOA ($p < 0.01$) and P + SOA ($p < 0.05$). Mauderly et al. (2011) exposed mice and rats for 1 week to simulated coal emissions with and without the addition

of a particle filter. The increase in MIP-2 seen in the BALF of F344 ($p < 0.05$) was prevented by filtration, indicating that the particulate part of the mixture had a role in the pro-inflammatory response.

Two of the aforementioned studies investigated the relationship between pulmonary inflammation and neurohumoral or endocrine pathways. Chiarella et al. (2014) evaluated the role of the SNS in modulating inflammation following exposure to $PM_{2.5}$ using knock-out mice lacking the β_2-adrenergic receptor specifically on macrophages. While wild type C57BL/6 mice exposed for several days to $PM_{2.5}$ CAPs in Chicago had increased IL-6 mRNA and protein in BALF ($p < 0.05$), knock-out mice had a greatly diminished response ($p < 0.05$). This finding implicates agonists of the β_2-adrenergic receptor, i.e., catecholamines, as partly responsible for the effects of $PM_{2.5}$ on IL-6 through the stimulation of β_2-adrenergic receptors on lung macrophages. Supporting evidence was provided by the finding that treatment with an agonist of the β_2-adrenergic receptor enhanced IL-6 levels in the BALF of wild type mice exposed to $PM_{2.5}$ ($p < 0.05$) Additionally, levels of the catecholamine norepinephrine were increased in BALF and brown adipose tissue following $PM_{2.5}$ exposure ($p < 0.05$), indicative of increased sympathetic tone. Taken together, results of this study provide evidence that exposure to $PM_{2.5}$ activated the sympathetic nervous system, which enhanced the release of IL-6 from lung macrophages. Downstream effects of macrophage-derived IL-6 on thrombosis were also examined (see Section 6.1.12).

Aztatzi-Aguilar et al. (2015) evaluated the RAS and kallikrein-kinin endocrine system in the lung in Sprague Dawley rats exposed for several days to $PM_{2.5}$ CAPs in Mexico City. Increased protein expression of IL-6 in lung tissue ($p < 0.05$) was accompanied by increased expression of the angiotensin I receptor gene, reduced angiotensin I receptor protein levels, and increased angiotensin converting enzyme mRNA levels ($p < 0.05$). Protein levels of angiotensin converting enzyme and mRNA levels of angiotensin II receptor mRNA were not impacted. In addition, $PM_{2.5}$ CAPs exposure resulted in increased mRNA levels for kallikrein-1 enzyme ($p < 0.05$). Kallikrein-1 is a serine protease enzyme required to produce kinin peptides, which are necessary to activate bradykinin receptors The RAS mediates vasoconstriction and vascular oxidative stress and inflammation and is counterbalanced by the kallikrein-kinin endocrine system via bradykinin-mediated production of nitric oxide, an important vasodilator. The SNS is known to regulate the endocrine systems. Although not specifically examined in this study, $PM_{2.5}$ exposure-mediated activation of the SNS activation may link $PM_{2.5}$ exposure and the RAS.

Morphology

As described in the 2009 PM ISA (U.S. EPA, 2009), several studies found that exposure to $PM_{2.5}$ CAPs in Boston, MA resulted in mild morphological changes in the lung including hyperplasia of the terminal bronchiolar and alveolar ductal epithelium and pulmonary arteriolar edema (Rhoden et al., 2004; Batalha et al., 2002; Saldiva et al., 2002). Recently, Yoshizaki et al. (2016) evaluated the effects of multiday exposure to Sao Paulo, Brazil $PM_{2.5}$ CAPs on nasal epithelium in male and female BALB/c mice. The influence of estrus cycle in female was also determined. $PM_{2.5}$ CAPs exposure resulted in an

increase in acidic mucus content in males and a decrease in acidic mucus content in females ($p < 0.05$) (Table 5-14). $PM_{2.5}$ CAPs exposure had no effect on neutral mucus content in either male or female mice. In addition, estrus cycle had no effect on mucus content or response to $PM_{2.5}$ CAPs exposure. Upregulation of message and protein levels of estrogen, aryl hydrocarbon receptors, and cytochrome P450 proteins was examined in nasal epithelium. $PM_{2.5}$ CAPs exposure resulted in decreased mRNA levels of estrogen receptor β2 and cytochrome 1b1 in female mice ($p < 0.01$). Female rats in diestrus, but not estrus or proestrus, exhibited decreased mRNA levels of estrogen receptor β2, cytochrome 1b1, and cytochrome 1a2 ($p < 0.05$). Estrogen receptor protein levels were decreased in nasal epithelium and aryl hydrocarbon receptor protein levels were increased in submucosal gland by $PM_{2.5}$ CAPs exposure in female mice ($p < 0.05$). Only female rats in estrus not diestrus or proestrus) exhibited these changes ($p < 0.05$).

Allergic Sensitization

The 2009 PM ISA (U.S. EPA, 2009) described numerous studies demonstrating the adjuvant potential of PM. While most of these studies involved intra-nasal or other noninhalation routes of exposure, one inhalation study demonstrated a strong adjuvant effect of PM (Whitekus et al., 2002). In this study, mice were exposed to resuspended DEP and subsequently challenged with OVA. OVA-specific IgG1 and IgE were enhanced by DEP exposure in the absence of general markers of inflammation. This effect, as well as DEP-mediated lipid peroxidation and protein oxidation, was blocked by pretreatment with the thiol antioxidants N-acetylcysteine and bucillamine. These results indicate that oxidative stress played a role in DEP-mediated allergic sensitization. Recent studies that have become available since the last review, while supportive of the adjuvant potential of $PM_{2.5}$, involve noninhalation routes of exposure (i.e., subcutaneous, intra-peritoneal and oropharyngeal aspiration).

Pathways Related to Otitis Media

Kim et al. (2016b) conducted a transcriptomic analysis in the middle ear following exposure to DEP (Table 5-14). BALB/c mice were exposed to resuspended DEP for several days and gene expression microarray and pathway analysis were performed on tissue collected 9 days later. In the middle ear, numerous genes were upregulated or downregulated because of DEP exposure. Pathway analysis identified several of these genes as potential biomarkers for DEP-related otitis media including cholinergic receptor muscarinic 1, erythropoietin, son of sevenless homolog 1, estrogen receptor 1, cluster of differentiation 4, and interferon α 1.

5.1.7.4 Summary of Respiratory Effects in Healthy Populations

Similar to results described in the 2009 PM ISA (U.S. EPA, 2009), evaluation of the current epidemiologic evidence indicates that short-term $PM_{2.5}$ exposures are inconsistently related to respiratory effects in healthy adults. Where there is supporting evidence, changes tend to be transient and confounding by copollutants is inadequately examined. For general community daily average exposures, there is some consistent epidemiologic evidence for $PM_{2.5}$-related respiratory effects in healthy children, but the evidence is limited in number for any one particular endpoint. In addition to the limited supporting evidence, uncertainties remain as to whether short-term $PM_{2.5}$ exposure leads to overt and persistent respiratory effects in healthy populations or is related to such effects across a wide range of $PM_{2.5}$ concentrations.

Controlled human exposure and animal toxicological studies also examined pulmonary function and inflammation responses to short-term exposure to $PM_{2.5}$ CAPs. While evidence from controlled human exposure studies was inconsistent, animal toxicological studies clearly demonstrated changes in pulmonary function and inflammation. Recent evidence supports the previously observed involvement of lung irritant responses in mediating the changes in respiratory function, such as rapid shallow breathing, seen following exposure to $PM_{2.5}$. BALF cellular infiltrates are commonly found following exposure to $PM_{2.5}$ and appear to primarily involve recruitment of macrophages and neutrophils into the airways. In addition, several studies implicate changes in various cytokines in BALF and lung tissue. Increases in numbers of specific macrophages in lung tissue provides evidence for the activation of innate immunity over several days to several weeks. Pulmonary injury and oxidative stress responses were inconsistent. However, a study evaluated in the 2009 PM ISA demonstrated oxidative stress-mediated allergic sensitization due to inhalation of $PM_{2.5}$. Different regions of the respiratory tract are impacted by short-term $PM_{2.5}$ exposure with morphologic changes observed in the terminal bronchiolar and alveolar regions and changes in mucus profile found in in nasal epithelium. A mechanistic study shows involvement of the SNS in augmenting macrophage-mediated inflammatory effects following exposure to $PM_{2.5}$. In addition, the RAS and kallikrein-kinin endocrine system in the lung were impacted by short-term exposure to $PM_{2.5}$.

Variability in results observed in controlled human exposure and animal toxicological studies could be due to the time points assessed (too long after exposure), the nature of the exposures (dose, particle composition), the sensitivity of the model (species, strain, age, predisposing factors) and the sensitivity of the measurements used. When $PM_{2.5}$ CAPs are used, the composition of the PM, which is related to source and season, could add to this variability. Finally, whether the exposure was a single time or repeated could have a large effect. Repeated exposures, even those less than 30 days, may trigger adaptive physiologic and cellular responses that are not present for very short term single exposure studies, such as single acute exposures.

5.1.8 Respiratory Effects in Populations with Cardiovascular Disease

Given the prevalence of cardiovascular disease in the general population and the inter-relationships between the cardiovascular and respiratory systems, numerous animal toxicological studies have been conducted in animal models of cardiovascular disease. Many of these studies were evaluated in the 2004 PM AQCD and the 2009 PM ISA (U.S. EPA, 2009). Pulmonary function responses were examined following single and multiday exposure of hypertensive rats to $PM_{2.5}$ CAPs from New York, Research Triangle Park, NC, Taiwan, and Boston, MA (Kodavanti et al., 2005; Lei et al., 2004; Nadziejko et al., 2002; Godleski et al., 2000). Alterations in tidal volume and breathing frequency were found, indicating the involvement of lung irritant receptors and the triggering of local reflexes in the response to short-term $PM_{2.5}$ exposure. Multiday exposure of SH rats to $PM_{2.5}$ CAPs in the Netherlands altered levels of BALF CC16 in a concentration-dependent manner (Kooter et al., 2006). CC16 is a secretory product of nonciliated bronchiolar Club cells and is a marker of injury and thought to contribute to the control of inflammation. However, there was no evidence of pulmonary injury (as assessed by BALF LDH levels) in this study or another study involving $PM_{2.5}$ CAPs in Research Triangle Park, NC (Kodavanti et al., 2005). Kooter et al. (2006) also found that a multiday exposure of SH rats to $PM_{2.5}$ CAPs in the Netherlands increased levels of heme oxygenase-1, an indicator of oxidative stress. Several studies in hypertensive rats evaluated pulmonary inflammation following exposure to $PM_{2.5}$ CAPs. While some studies found increased numbers of inflammatory cells in BALF (and even a correlation between $PM_{2.5}$ CAPs concentrations and numbers of neutrophils) (Cassee et al., 2005; Lei et al., 2004), others did not (Kooter et al., 2006; Kodavanti et al., 2005). Campen et al. (2006) found a concentration-dependent effect on inflammation in $PM_{2.5}$ exposed-ApoE knockout mice, a model of atherosclerosis.

A few recent studies add to this evidence base (Table 5-15). Rohr et al. (2010) exposed SH rats to $PM_{2.5}$ CAPs in Detroit and found no evidence of lung injury as assessed by BALF protein levels. Farraj et al. (2015) studied the effect of a 4-hour exposure of SH rats to $PM_{2.5}$ CAPs in two seasons, summer and winter, in Research Triangle Park, NC. Activities of LDH, glutathione S transferase, and CuZn SOD, indicators of injury and oxidative stress, were decreased by exposure to summer $PM_{2.5}$ CAPs but not winter $PM_{2.5}$ CAPs ($p \leq 0.05$). $PM_{2.5}$ CAPs concentration was higher in summer than in winter, but metal exposure concentrations were roughly equivalent. Concomitant exposure to 200 ppb O_3 appeared to have little additional effect on these parameters. No effects on inflammation were found by Rohr et al. (2010) or Farraj et al. (2015). Furthermore, Tyler et al. (2016) conducted an inhalation exposure of ApoE knockout mice to resuspended DEP and found no increase in inflammatory cells or cytokines in the BALF and no increase in particle uptake in bronchial macrophages, despite inflammatory effects in the hippocampus (Section 8.1.3). Overall, short-term $PM_{2.5}$ exposure results in pulmonary effects in some studies but not others. The most consistent evidence is for changes in pulmonary function.

Table 5-15 Study-specific details from animal toxicological studies of short-term $PM_{2.5}$ exposure and respiratory effects in models of cardiovascular disease.

Study/Study Population	Pollutant	Exposure	Endpoints
Farraj et al. (2015) Species: Rat Sex: Male Strain: SH Age/Weight: 12 weeks	$PM_{2.5}$ CAPs Research Triangle Park, NC Particle size: 324 nm summer, 125 nm winter Control: Filtered air	Route: Whole-body inhalation Dose/Concentration: 85-170 µg/m^3 Duration: 4 h Time to analysis: 24 hr Modifier: Telemeter implanted, summer and winter	Lung Injury—BALF LDH activity Inflammation—BALF cells BALF antioxidant enzymes—GST and CuZn SOD
Rohr et al. (2010) Species: Rat Strain: Spontaneously hypertensive (SH) Wistar Kyoto (WKY) Sex: Male Age/Weight: 11−12 weeks	$PM_{2.5}$ CAPs residential urban Detroit, MI Particle sizes: $PM_{2.5}$	Route: Whole-body inhalation Dose/Concentration: 507 µg/m^3 Duration of exposure: 8 h, 13 consecutive days Time to analysis: 24 h	BALF cells Lung Injury • BALF protein content
Tyler et al. (2016) Species: Mouse Strain: ApoE knockout Age/Weight: 6−8 weeks	DEP, resuspended Particle size: 1.5−3.0 µm ± 1.3−1.6 µm Control: Filtered air	Route: Whole-body inhalation Dose/Concentration: 300 µg/m^3 Duration: 6 h	BALF cells and cytokines Particle uptake in bronchial macrophages

ApoE = Apolipoprotein E; BALF = bronchoalveolar lavage fluid; CAPs = concentrated ambient particles; CuZn SOD = copper, zinc superoxide dismutase; GST = glutathione S transferase; LDH = lactate dehydrogenase; SH = spontaneously hypertensive.

5.1.9 Respiratory Mortality

Studies that examine the association between short-term $PM_{2.5}$ exposure and cause-specific mortality outcomes, such as respiratory mortality, provide additional evidence for $PM_{2.5}$-related respiratory effects, specifically whether there is evidence of an overall continuum of effects. The multicity epidemiologic studies evaluated in the 2009 PM ISA provided evidence of consistent positive associations, ranging from 1.0−2.2% for a 10 µg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations, between short-term $PM_{2.5}$ exposure and respiratory mortality (U.S. EPA, 2009). However, compared to associations between short-term $PM_{2.5}$ exposure and cardiovascular and total (nonaccidental) mortality, confidence intervals were larger due to respiratory mortality comprising a smaller percentage of all mortalities. Across studies, the $PM_{2.5}$ effect on respiratory mortality was observed to be immediate with associations occurring in the range of lag 0 to 2 day(s). A limitation within the evidence was that multicity studies did not extensively examine potential copollutant confounding, but evidence from

single-city studies suggested that the $PM_{2.5}$-respiratory mortality relationship was not confounded by gaseous copollutants. Additionally, there was limited coherence across epidemiologic and controlled human exposure studies, which complicated the interpretation of the associations observed for short-term $PM_{2.5}$ exposure and respiratory mortality.

Recent multicity epidemiologic studies along with meta-analyses provide additional evidence of generally consistent positive associations between short-term $PM_{2.5}$ exposure and respiratory mortality (Figure 11-2). In addition to providing evidence that supports the rather immediate timing of respiratory mortality effects (i.e., lag 0 to 1 days), some recent studies also provide initial evidence that respiratory mortality effects due to short-term $PM_{2.5}$ exposure may be more prolonged (i.e., lags >2 days). Unlike the studies evaluated in the 2009 PM ISA (U.S. EPA, 2009), some recent studies have also further evaluated the $PM_{2.5}$-respiratory mortality relationship by examining cause-specific respiratory mortality outcomes (i.e., COPD, pneumonia, and LRTI) (Samoli et al., 2014; Janssen et al., 2013). Overall, the results reported in the studies that examine cause-specific respiratory mortality outcomes are generally consistent with the results for all respiratory mortality, but the smaller number of mortality events observed results in unstable estimates with larger uncertainty.

Evidence to further characterize the $PM_{2.5}$-respiratory mortality relationship is also provided by recent epidemiologic studies. Overall, these studies continue to support a relationship between $PM_{2.5}$ and respiratory mortality and provide additional evidence that: gaseous pollutants do not confound the $PM_{2.5}$-respiratory mortality relationship; $PM_{2.5}$ effects on respiratory mortality may not be limited to the first few days after exposure; the magnitude of the association tends to be largest during warmer months; and there is inconsistent evidence that temperature extremes modify associations between short-term $PM_{2.5}$ exposure and respiratory mortality (see Section 5.1.10).

5.1.10 Policy-Relevant Considerations

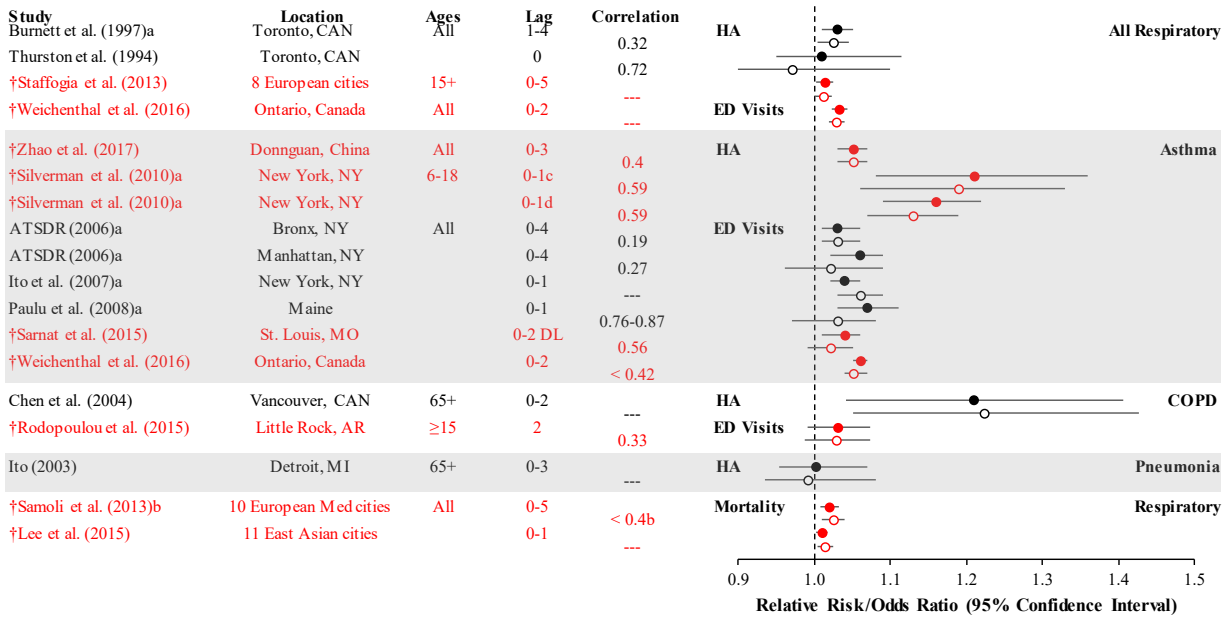
Epidemiologic studies that examined short-term $PM_{2.5}$ exposure and respiratory-related effects often conduct additional analyses to assess whether the associations observed are due to chance, confounding, or other biases. Within this section, evidence is evaluated across epidemiologic studies to further assess the association between short-term $PM_{2.5}$ exposure and respiratory-related effects, focusing specifically on those analyses that address policy-relevant issues: copollutant confounding (Section 5.1.10.1), model specification (Section 0), lag structure (Section 5.1.10.3), the role of season and temperature on $PM_{2.5}$ associations (Section 5.1.10.4), averaging time of $PM_{2.5}$ concentrations (Section 5.1.10.5), and concentration-response (C-R) and threshold analyses (Section 5.1.10.6). The studies that inform these issues are primarily epidemiologic studies that conducted time-series or case-crossover analyses focusing on respiratory-related ED visits and hospital admissions and respiratory mortality. Studies examining additional endpoints, such as subclinical markers of a PM-related respiratory

effect (e.g., lung function, inflammation, etc.), may also examine some of these issues, but are not the focus of this evaluation.

5.1.10.1 Examination of Potential Copollutant Confounding

The potential confounding effect of copollutants is a previously identified source of uncertainty in the examination of the relationship between short-term $PM_{2.5}$ exposure and respiratory effects, and thus requires careful consideration particularly with respect to whether the magnitude and direction of $PM_{2.5}$ risk estimates change in copollutant models. Compared to the evidence available at the completion of the 2009 PM ISA, many recent studies conducted analyses that inform whether the relationship between short-term $PM_{2.5}$ exposures and respiratory-related effects, specifically hospital admissions, ED visits, and respiratory mortality, may be confounded by copollutants. Recent studies have examined the potential for copollutant confounding by evaluating copollutant models that include O_3 (Figure 5-9), NO_2, (Figure 5-10), SO_2 (Figure 5-11), CO (Figure 5-12) and $PM_{10–2.5}$ (Figure 5-13). These recent studies address a previously identified data gap by informing the extent to which effects associated with exposure to $PM_{2.5}$ are independent of coexposures to correlated copollutants. Generally, these studies provide evidence that the association between short-term $PM_{2.5}$ exposures and respiratory health outcomes is robust to the inclusion of copollutants in a statistical model. This evidence provides support for an independent association between $PM_{2.5}$ concentrations and respiratory-related effects.

Building off studies evaluated in the 2009 PM ISA, recent studies that examined the potential confounding effects of O_3 on associations between short-term $PM_{2.5}$ exposure and respiratory-related outcomes continue to report correlations between O_3 and $PM_{2.5}$ ranging from low (<0.4) to high (>0.7). Across the respiratory-related outcomes examined, where positive associations with $PM_{2.5}$ were reported in single-pollutant models, associations were often attenuated in copollutant models, but remained positive. The most extensive evaluation of potential copollutant confounding was for studies focusing on asthma hospital admissions and ED visits, where recent studies report results that are consistent with those observed in studies evaluated in the 2009 PM ISA (Figure 5-9). Additionally, recent evidence provides additional support for positive $PM_{2.5}$ associations with hospital admissions and ED visits for all respiratory diseases as well as initial evidence indicating that $PM_{2.5}$ associations with respiratory mortality are relatively unchanged in copollutant models with O_3. While panel studies infrequently reported results from copollutant models, adverse associations reported across several endpoints were generally persistent, although in some cases attenuated, in copollutant models with O_3. Individual panel study results from copollutant models with O_3 are discussed within the relevant endpoint sections (Section 5.1.2.2, Section 0, and Section 5.1.7.1).

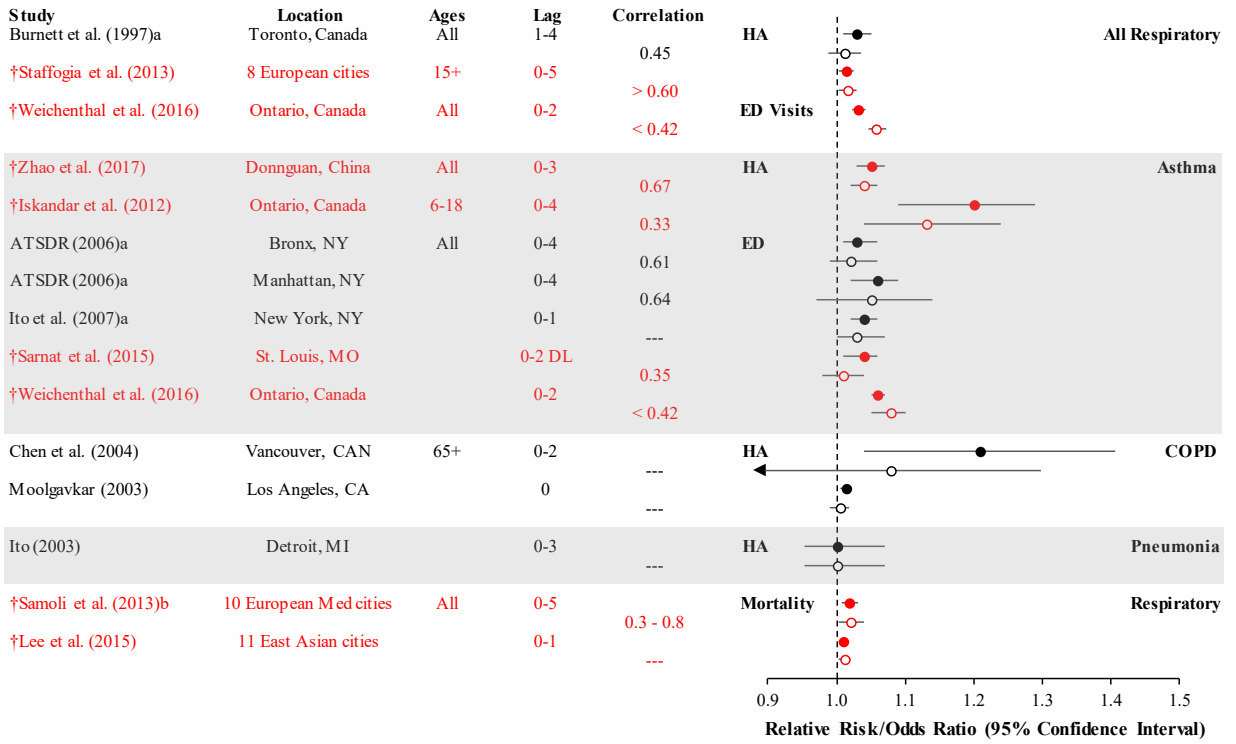


DL = distributed lag model.

Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. a = copollutant analyses for warm season only; b = copollutant analysis only conducted for lag 0−5 days; c = Intensive Care Unit (ICU) admissions; [d] = non-ICU admissions. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-9 Summary of associations for short-term $PM_{2.5}$ exposure and respiratory-related outcomes from copollutant models with ozone (O_3) for a 10 µg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations.

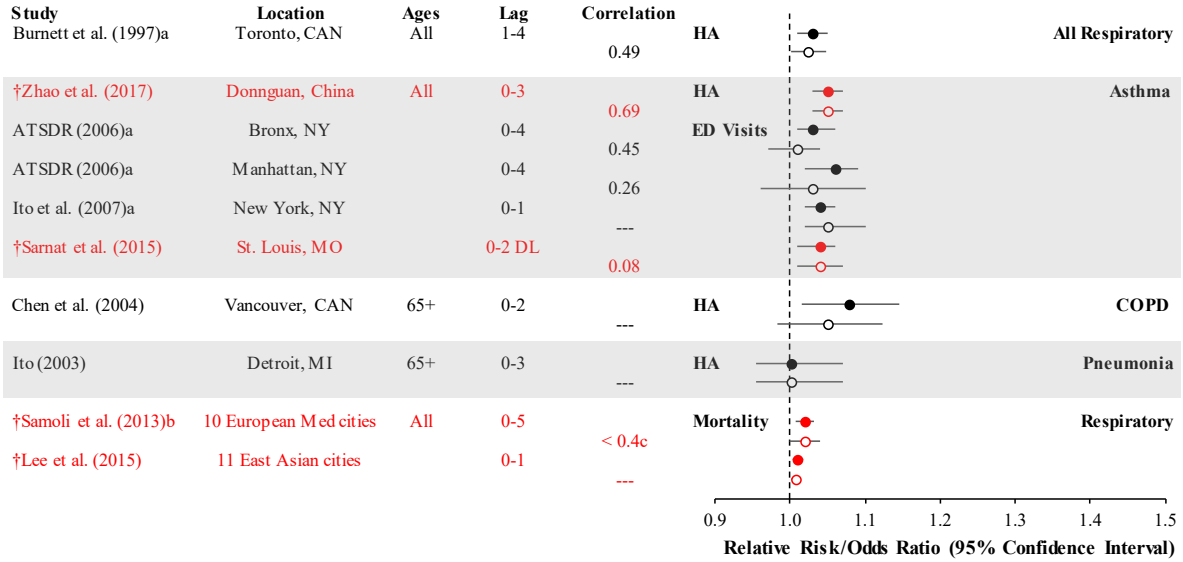
Across studies, $PM_{2.5}$ associations with respiratory-related outcomes remain positive, although in some cases attenuated, in copollutant models with NO_2. Generally, $PM_{2.5}$ was reported to be low to moderately correlated with NO_2 ($r < 0.7$). Similar to the evaluation of copollutant models with O_3, most of the evidence with respect to potential copollutant confounding by NO_2 is from studies examining asthma hospital admissions and ED visits with recent studies supporting the results from studies evaluated in the 2009 PM ISA. Recent studies also build on the initial evidence reported in the 2009 PM ISA that $PM_{2.5}$ associations are robust to control for NO_2 in studies examining hospital admissions and ED visits for all respiratory diseases and provide initial evidence that $PM_{2.5}$ associations with respiratory mortality are also robust (Figure 5-10). While panel studies infrequently reported results from copollutant models, adverse associations reported across several endpoints were persistent, although in some cases attenuated, in copollutant models with NO_2. Individual panel study results from copollutant models with NO_2 are discussed within the relevant endpoint sections (Section 5.1.2.2, Section 0, Section 5.1.2.4, Section 5.1.4.2, Section 5.1.4.4, and Section 5.1.7.1).



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA.
a = copollutant analyses for warm season only; b = copollutant analysis only conducted for lag 0−5 days. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-10 Summary of associations for short-term $PM_{2.5}$ exposure and respiratory-related outcomes from copollutant models with NO_2 for a 10 µg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations.

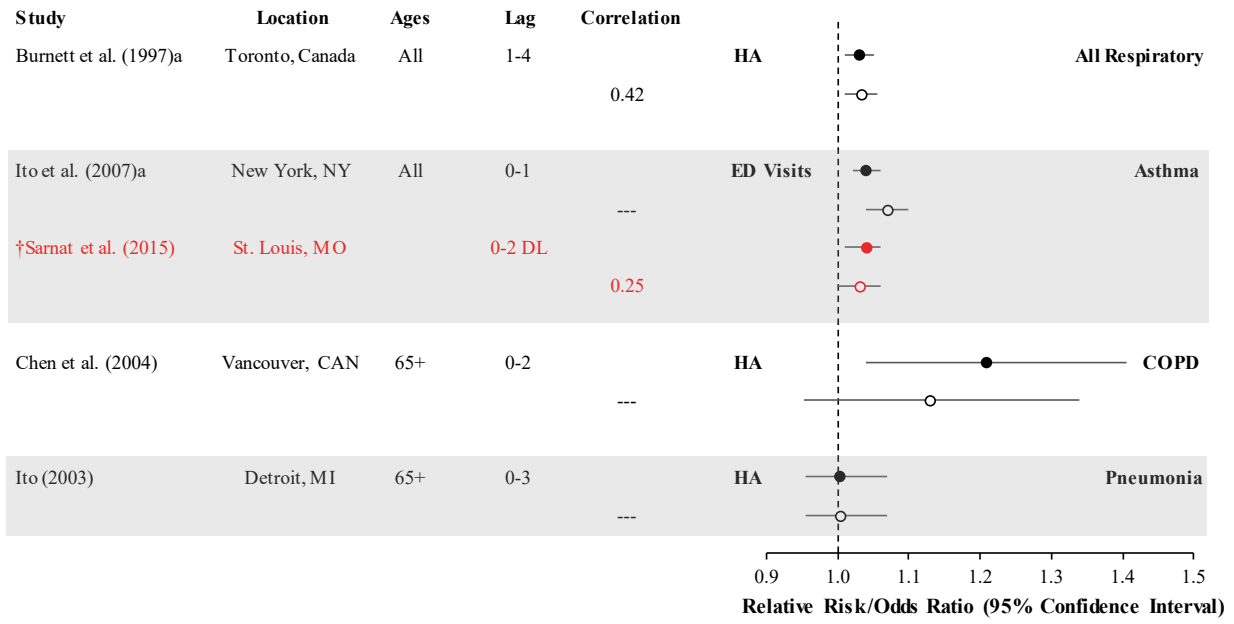
The examination of potential copollutant confounding by SO_2 on the relationship between short-term $PM_{2.5}$ exposure and respiratory-related outcomes is similar to that observed for O_3 and NO_2, with most of the evidence from studies examining asthma hospital admissions and ED visits (Figure 5-11). Across studies, correlations between $PM_{2.5}$ and SO_2 were primarily <0.5. Most of the studies that examined copollutant models with SO_2 were evaluated in the 2009 PM ISA, but recent studies add to the evidence base for asthma hospital admissions and ED visits further demonstrating that associations are relatively unchanged in copollutant models with SO_2, while also providing new evidence for respiratory mortality. While panel studies infrequently reported results from copollutant models, adverse associations reported across several endpoints were generally persistent, although in some cases attenuated, in copollutant models with SO_2. Individual panel study results from copollutant models with SO_2 are discussed within the relevant endpoint sections (Section 0, Section 5.1.2.4, Section 5.1.4.2, Section 5.1.4.4, and Section 5.1.7.1).



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. a = copollutant analyses for warm season only; b = copollutant analysis only conducted for lag 0−5 days; c = correlations were <0.4 in all cities except Milan and Turin where it was ~0.6. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-11 Summary of associations for short-term $PM_{2.5}$ exposure and respiratory-related outcomes from copollutant models with sulfur dioxide (SO_2) for a 10 µg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations.

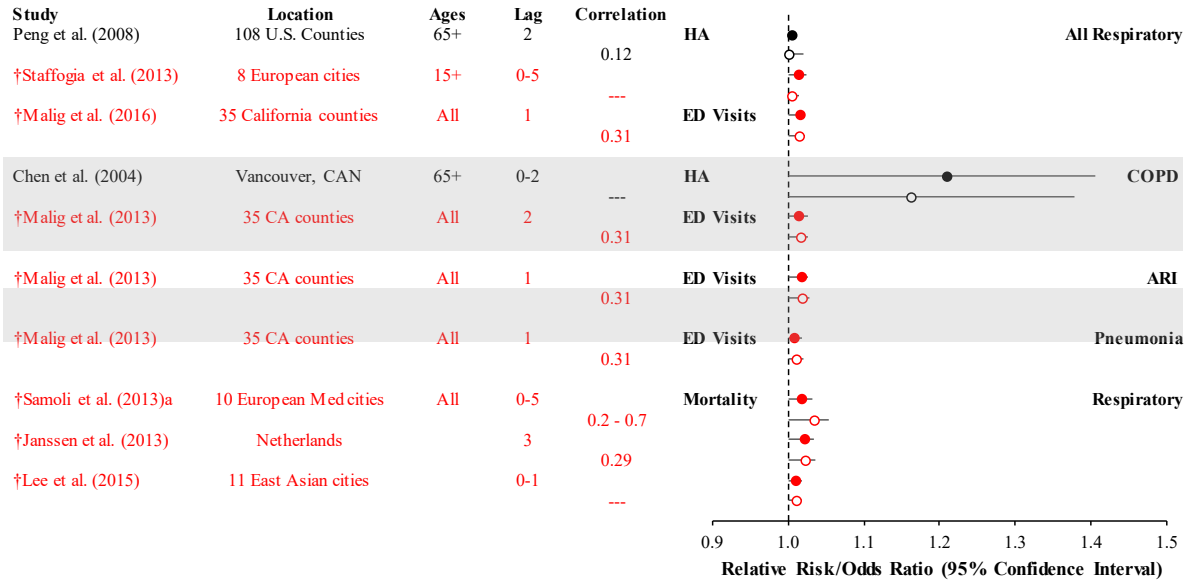
Compared to O_3, NO_2, and SO_2 the assessment of potential copollutant confounding by CO has not been extensively examined in recent studies (Figure 5-12). However, across the studies evaluated in the 2009 PM ISA, along with the recent study conducted by Sarnat et al. (2015) examining asthma ED visits, evidence indicates that in studies that observed positive associations with $PM_{2.5}$, the association was relatively unchanged in copollutant models with CO.



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA.
a = copollutant analyses for warm season only. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-12 Summary of associations for short-term $PM_{2.5}$ exposure and respiratory-related outcomes from copollutant models with carbon monoxide (CO) for a 10 µg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations.

Recent studies also greatly expand upon the examination of potential copollutant confounding by $PM_{10-2.5}$ (Figure 5-13). Across the studies evaluated, correlations between $PM_{2.5}$ and $PM_{10-2.5}$ were primarily low ($r < 0.4$). $PM_{2.5}$ associations for all respiratory-related outcomes are generally unchanged in models that adjust for $PM_{10-2.5}$. However, an uncertainty across studies that examined either single- or copollutant models that include $PM_{10-2.5}$ is the variety of methods employed to estimate $PM_{10-2.5}$ concentrations and the potential measurement error associated with each method (Section 2.5.1.2.3 and Section 3.3.1.1).



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA.
a = copollutant analysis only conducted for lag 0−5. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-13 Summary of associations for short-term $PM_{2.5}$ exposure and respiratory-related outcomes from copollutant models with $PM_{10-2.5}$ for a 10 μg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations.

In conclusion, since the 2009 PM ISA, there has been growth in the number of studies that examined potential confounding of the relationship between short-term $PM_{2.5}$ exposure and respiratory-related outcomes by copollutants. These recent studies provide additional evidence supporting that $PM_{2.5}$ associations are relatively unchanged, although in some instances attenuated as well as increased, in copollutant models with gaseous and particle pollutants.

5.1.10.1.1 $PM_{2.5}$ within the Multipollutant Mixture

Although copollutant models are important in assessing potential copollutant confounding, it is well known that collinearity between pollutants can result in unstable estimates and that air masses are not limited to just two pollutants (Dominici et al., 2010). Therefore, in addition to copollutant models, studies that examine multipollutant exposures can provide additional information on the role of $PM_{2.5}$ within the complex air pollution mixture.

Analyses of pollutant mixtures, which use an array of statistical methods and pollutant combinations, for respiratory-related effects have focused on asthma ED visits. These studies indicate

increases in asthma ED visits when ambient concentrations of $PM_{2.5}$ and a copollutant(s) are simultaneously high, but do not clearly show a larger increase than with $PM_{2.5}$ alone. In analyses conducted in Atlanta (Winquist et al., 2014a) and then subsequently for the entire state of Georgia (Xiao et al., 2016), $PM_{2.5}$ was a priori grouped with the other criteria pollutants (i.e., O_3, CO, NO_2, and SO_2) to examine their joint effect on pediatric asthma ED visits. In both studies, $PM_{2.5}$ was associated with pediatric asthma ED visits in single-pollutant models. However, in Xiao et al. (2016) joint effect models were relatively similar to the single-pollutant model, but in Winquist et al. (2014a) the joint effect model results were much larger (quantitative results only presented for warm season, no interaction model) (Table 5-16). Instead of defining air pollution mixtures a priori, other analyses examined whether there were groups of days with similar pollution profiles, specifically days representative of high and low air pollution exposures based on quartiles of $PM_{2.5}$, NO_2, CO, and O_3 concentrations using a classification and regression tree (C&RT) approach. This approach was used to examine associations between high and low air pollution days and asthma in Atlanta, GA; St. Louis, MO; and Dallas, TX. In Atlanta, GA. Gass et al. (2014) reported that RRs with $PM_{2.5}$ were largest in magnitude for days when $PM_{2.5}$ concentrations were in the highest quartile, while NO_2 was in the lowest two quartiles, as well as days when both NO_2 and $PM_{2.5}$ were in higher quartiles. Gass et al. (2015) expanded the analysis of Gass et al. (2014) to include Atlanta, GA; St. Louis, MO; and Dallas, TX. The authors observed that pollution profiles varied across cities resulting in the overall quartiles of pollutant concentrations for a particular mixture sometimes differing from the distribution of concentrations within an individual city. For example, $PM_{2.5}$ concentrations were in the 4th quartile for one city, but the overall mixture across cities showed that $PM_{2.5}$ concentrations were in the 1st quartile. Gass et al. (2015) reported evidence of mixtures with high $PM_{2.5}$ concentrations having the association largest in magnitude, but associations were similar in magnitude in instances when $PM_{2.5}$ concentrations were in the lowest quartile. While the other multipollutant studies focused on examining combinations of pollutants at different parts of the individual pollutant concentration distribution, Toti et al. (2016) in Houston, TX focused on pollutant concentrations on same and successive days that are in the 4th quartile of each pollutant concentration distribution. Across the different combinations, as well as those that included $PM_{2.5}$, the authors reported ORs that were relatively similar in magnitude. In contrast with U.S. cities, the association between asthma ED visits and an air quality health index (AQHI), which combines $PM_{2.5}$, NO_2, and O_3 based on mortality risk, in Windsor, ON, appears to be influenced by either $PM_{2.5}$ or O_3, depending on the lag (Szyszkowicz and Kousha, 2014). The OR for the AQHI was similar to that of O_3 at lag 0 and that of $PM_{2.5}$ at lags 4 and 5 (Table 5-16). Whereas the previous studies evaluated focused on multipollutant mixtures, Weichenthal et al. (2016) examined whether there was evidence of effect modification of the $PM_{2.5}$-asthma ED visit association in 15 Ontario cities. The authors observed that the $PM_{2.5}$ association increased with increasing city-level oxidative potential of $PM_{2.5}$, NO_2, and O_3 combined (Weichenthal et al., 2016).

In summary, the studies that examined multipollutant mixtures that include $PM_{2.5}$ indicate that mixtures encompassing days with high $PM_{2.5}$ concentrations are often those mixtures with the highest risk estimates. Additionally, when comparing single-pollutant $PM_{2.5}$ results with those based on mixtures, the

risk estimate associated with the mixture is relatively similar and, in some cases, larger than that observed for $PM_{2.5}$.

Table 5-16 Combined influence of $PM_{2.5}$ and copollutants on emergency department (ED) visits for asthma.

Study	$PM_{2.5}$ Single-Pollutant OR RR 95% CI	Combined OR or RR (95% CI)
†Xiao et al. (2016) Georgia, 2002−2008	Per 6.9 μg/m^3 1.03 (1.02, 1.04); lag 0−2	Joint Effect Model, Criteria Pollutants Combination (O_3, CO, NO_2, SO_2, and $PM_{2.5}$); lag 0−2 per IQR increase in each pollutant No interactions: 1.03 (1.01, 1.05) Interactions: 1.06 (1.02, 1.09)
†Winquist et al. (2014a) Atlanta, GA, 1998−2004	Per 9.2 μg/m^3, warm season 1.04 (1.02, 1.07)	Joint Effect Model, Criteria Pollutant Combination (O_3, CO, NO_2, SO_2, and $PM_{2.5}$) Warm season, no interactions: 1.13 (1.06, 1.21)
†Gass et al. (2014) Atlanta, GA, 1999−2009	NR	C&RT to group days by $PM_{2.5}$, NO_2, O_3 and CO quartiles Q1 $PM_{2.5}$, NO_2, CO, and O_3: 1.0 (reference) Q4 $PM_{2.5}$, Q1−4 O_3, Q1 or 2 NO_2, Q1−4 CO: 1.10 (1.05, 1.16) Q4 $PM_{2.5}$, Q1−3 O_3, Q3 NO_2, Q1−4 CO: 1.08 (1.01, 1.15) Q1 $PM_{2.5}$, Q1−4 O_3, Q3 or 4 NO_2, Q1−4 CO: 1.08 (1.03, 1.14)
†Gass et al. (2015) Atlanta, GA, 1999−2009 St. Louis, MO, 2001−2007 Dallas, TX, 2006−2008	NR	C&RT to group days by $PM_{2.5}$, NO_2 and O_3 quartiles Q1 $PM_{2.5}$, NO_2, and O_3: 1.0 (reference) Q4 $PM_{2.5}$, Q3 O_3, Q1 or 2 NO_2: 1.07 (1.03, 1.12) Q1 $PM_{2.5}$, Q3 O_3, Q3 or 4 NO_2: 1.04 (0.99, 1.08) Q1−4 $PM_{2.5}$, Q4 O_3, Q3 NO_2: 1.05 (1.01, 1.09)
†Toti et al. (2016) Houston, TX, 2006−2012	NR	Association rule mining to estimate ORs for all $PM_{2.5}$, O_3, NO_2, SO_2, CO and lag 0 to 4-day combinations and identify unique, statistically significant ORs. Q1−3 of each pollutant in combination: 1.0 (reference) Q4 $PM_{2.5}$ lag 0 and Q4 O_3 lag 0: 1.20 (1.02, 1.41) Q4 $PM_{2.5}$ lag 0, Q4 NO_2 lag 0 and Q4 O_3 lag 2: 1.33 (1.00, 1.65)
†Szyszkowicz and Kousha (2014) Windsor, ON, Canada 2004−2010	Per IQR (not reported) increase Lag 0: 1.02 (0.97, 1.06) Lag 3: 1.03 (0.99, 1.08) Lag 4: 1.05 (1.01, 1.09)	AQHI combining $PM_{2.5}$, O_3 and NO_2 (per 1 unit) Lag 0: 1.03 (0.99, 1.07) Lag 3: 1.02 (0.98, 1.06) Lag 4: 1.04 (1.01, 1.08)

Table 5-16 (Continued): Combined influence of $PM_{2.5}$ and copollutants on emergency department (ED) visits for asthma.

Study	$PM_{2.5}$ Single-Pollutant OR RR 95% CI	Combined OR or RR (95% CI)
†Weichenthal et al. (2016) 15 cities Ontario, Canada 2004−2011	Lag 0−2 avg, per 10 μg/m^3 1.06 (1.05, 1.07)	Effect modification by oxidative potential of $PM_{2.5}$, NO_2 and O_3 Q1: 1.02 (0.99, 1.04) Q2: 1.06 (1.00, 1.13) Q3: 1.08 (0.97, 1.19) Q4: 1.10 (1.05, 1.15)

AQHI = air quality health index, C&RT = classification and regression tree, CO = carbon monoxide, NO_2 = nitrogen dioxide, O_3 = ozone, OR = odds ratio, RR = relative risk, SO_2 = sulfur dioxide.
†Studies published since the 2009 PM ISA.

5.1.10.2 Model Specification

An underlying uncertainty in the interpretation of epidemiologic study results is the difference in the magnitude and precision, and sometimes direction, of risk estimates across studies. It has remained difficult to elucidate why there are differences in risk estimates, but it is often thought to reflect the different statistical models used in each study. However, it has also been hypothesized that other factors may also be contributing to these observed differences such as differences in $PM_{2.5}$ composition or demographics between study locations (e.g., Section 11.6.3).

Recent epidemiologic studies have conducted sensitivity analyses to assess whether $PM_{2.5}$ associations with respiratory-related outcomes are dependent on the statistical model employed, in an attempt to reduce potential biases in observed associations. Such sensitivity analyses assess the influence of alternative model specifications, such as increasing degrees of freedom (df) to account for temporal trends, or the inclusion of alternative weather covariates. Collectively, recent studies that examined model specification provide evidence that $PM_{2.5}$ associations are generally robust to increasing the df per year to account for temporal trends, but in some cases attenuation of the association was observed when these additional df were included. Additionally, studies reported that $PM_{2.5}$ associations are relatively unchanged regardless of the weather covariates included in statistical models (i.e., different weather variables or lag days and df specified for the weather variables). Collectively, these studies reduce the uncertainty associated with the differences in the magnitude and direction of risk estimates in epidemiologic studies potentially resulting from the different statistical models employed across studies.

Several studies examined different approaches to control for seasonality or temporal trends by either increasing or decreasing the df/year used in studies of short-term $PM_{2.5}$ exposure and respiratory-related effects. $PM_{2.5}$-associated increases in asthma hospital admissions and ED visits were consistently observed when different df/year were used to account for temporal trends. For example, studies conducted in several U.S. cities reported that $PM_{2.5}$ associations remained robust to alternative

degrees of freedom (2−28 df/year) for temporal trends (Alhanti et al., 2016; Sarnat et al., 2015; Kim et al., 2012; Silverman and Ito, 2010). When examining all respiratory-related hospital admissions and ED visits, an examination of the control for temporal trends was limited to a few studies, all of which were conducted in Europe, (Stafoggia et al., 2013), in eight European cities, and (Lanzinger et al., 2016b), in the UFIREG project. Stafoggia et al. (2013) provided evidence that uniformly applying the same df/year across all cities could underestimate the $PM_{2.5}$ association. This was reflected by comparing results for models where 8 df/year was applied to each city or the df/year applied to each city was selected by minimizing the absolute value of the sum of the partial autocorrelation functions (PACF) to the base model, which employed a three-way interaction between year, month, and day of week to account for temporal trends. The authors reported that using 8 df/year attenuated the association while the PACF approach, which resulted in df/year ranging from 3−9 for each city, resulted in relatively unchanged $PM_{2.5}$ risk estimates. However, Lanzinger et al. (2016b) reported that $PM_{2.5}$ associations were relatively unchanged in models employing 3, 4, or 6 df/year to account for temporal trends.

In addition to conducting sensitivity analyses that examine control for temporal trends, some studies also assessed whether associations between short-term $PM_{2.5}$ exposure and respiratory-related hospital admissions and ED visits were sensitive to alternative weather covariates. Altering the lags (e.g., 0, 2-day average) for temperature and humidity in New Jersey (Gleason et al., 2014), or adjusting for maximum temperature in Atlanta, GA and St. Louis, MO (Alhanti et al., 2016) resulted in $PM_{2.5}$ associations that were relatively unchanged. Stafoggia et al. (2013) also examined the influence of including a longer temperature lag (i.e., 0−6 days) in the model to account for the potential prolonged effects of temperature on respiratory diseases. Replacing the 0−1-day lag temperature covariate with a 0−6-day lag term resulted in a relatively similar effect (lag 0−1: 1.36% [95% CI: 0.23, 2.49]; lag 0−6: 1.48% [95% CI: 0.29, 2.69]).

While most studies examined the influence of model specification on $PM_{2.5}$ associations with respiratory-related effects by focusing specifically on the inclusion of alternative weather covariates in statistical models, a few studies conducted analyses to examine whether there was evidence of model misspecification and potential residual confounding. In studies conducted in Atlanta, GA (Strickland et al., 2010) and St. Louis, MO (Sarnat et al., 2015), model misspecification was evaluated by examining associations with $PM_{2.5}$ concentrations on the day after an asthma ED visit (lag −1 day). In both studies the results of the base model are relatively similar to those reported for lag −1 day (i.e., (Strickland et al., 2010), warm season: RR = 1.05 [95% CI: 1.02, 1.08], lag 0−2, RR = 1.03 [95% CI: 1.00, 1.05], lag −1; (Sarnat et al., 2015), all-year: RR = 1.04 [95% CI: 1.01, 1.06], lag 0−2, RR = 1.02 [95% CI: 0.99, 1.04], lag −1). The smaller association, closer to the null in both studies, indicates that potential confounders of the relationship between short-term $PM_{2.5}$ exposure and asthma ED visits were adequately accounted for in the statistical model.

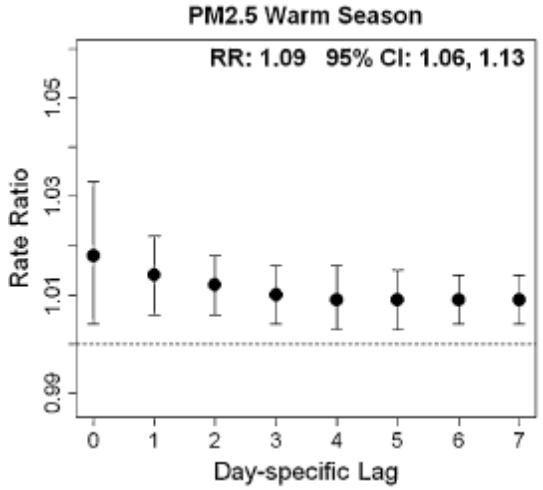
Across studies that examined alternative model specifications, replacing covariates used in the base model to account for the confounding effects of weather did not result in measurable changes in

$PM_{2.5}$ associations for respiratory-related effects. Additionally, there was little evidence that increasing the df/year to account for temporal trends influenced $PM_{2.5}$ associations; however, initial evidence indicates that applying the same df/year across individual cities in a multicity study may contribute to underestimating $PM_{2.5}$ risk estimates.

5.1.10.3 Lag Structure

An examination of associations between short-term $PM_{2.5}$ exposure and respiratory-related effects across different lag days can inform whether $PM_{2.5}$ elicits an immediate, delayed, or prolonged effect on health. As detailed throughout this chapter, evidence from studies that examine respiratory-related hospital admissions and ED visits indicates positive associations across single-day as well as multiday lags ranging from 0 to 4 days. However, to date many studies have not systematically evaluated different lags to examine the timing of effects, specifically whether there is evidence of an immediate (lag 0−1), delayed (lag 2−5), or prolonged (lag 0−5) $PM_{2.5}$ effect. An examination of lag structure in recent studies focusing on asthma, COPD, respiratory infections, and all respiratory-related hospital admissions and ED visits indicates that the strongest association in terms of magnitude and precision is generally within a few days after exposure for each of these outcomes, but there is some evidence demonstrating the potential for a prolonged $PM_{2.5}$ effect.

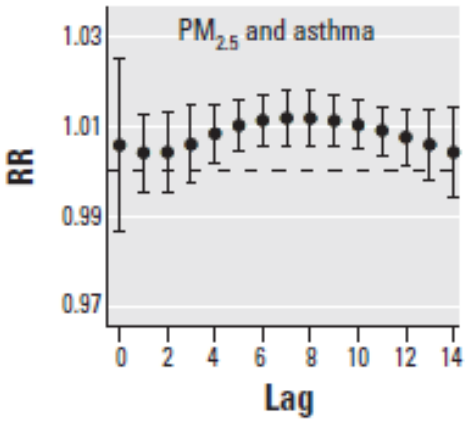
Among children in Atlanta, GA (Strickland et al., 2010) and individuals of all ages in Denver, CO (Kim et al., 2012), the pattern of associations for $PM_{2.5}$-asthma ED visits varied. In Strickland et al. (2010), lag 0 was reported to have the association largest in magnitude, but positive associations persisted across single-day lags of 1 to 7 days (Figure 5-14).



Source: Permission pending, Strickland et al. (2010).

Figure 5-14 Rate ratio and 95% confidence intervals for individual lag days from a constrained cubic polynomial distributed lag model examining associations between short-term $PM_{2.5}$ exposure and pediatric asthma emergency department (ED) visits in Atlanta, GA.

In contrast to the relatively immediate effect observed in Strickland et al. (2010), Kim et al. (2012) reported positive associations across the full range of lags examined (0−14), with the strongest associations, in terms of magnitude and precision, observed at lags 4 to 12 days, indicating a potential delayed response to short-term $PM_{2.5}$ exposure (Figure 5-15). When examining a distributed lag model of 0 to 7 days in Adelaide, Australia, Chen et al. (2016) observed an inconsistent pattern of associations with the strongest associations for asthma hospital admissions occurring at lags 2 and 4 days. When comparing results from multiday averages and distributed lag models, risk estimates were found to be larger in magnitude for the distributed lag model in Atlanta, GA (Strickland et al., 2010) (lag 0−2: RR = 1.05 [95% CI: 1.02, 1.08]; lag 0−7 DL: RR = 1.10 [95% CI: 1.07, 1.14]), but a similar magnitude of an association was observed at shorter and longer distributed lag models in St. Louis, MO (Sarnat et al., 2015) (lag 0−2: 1.04 [95% CI: 1.01, 1.06]; lag 0−4 DL: RR = 1.04 [95% CI: 1.01, 1.08]).



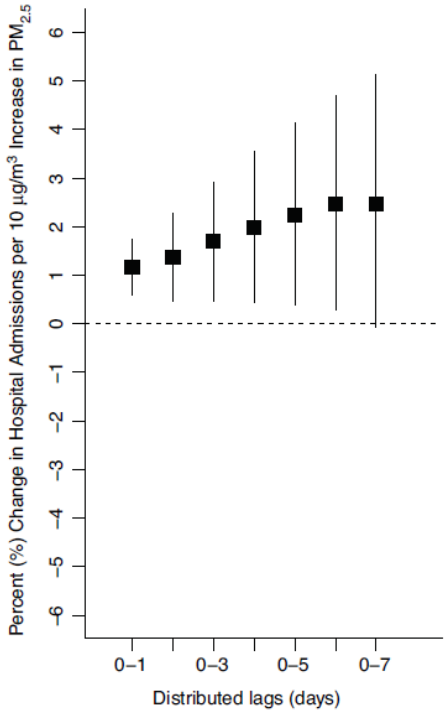
Source: Permission pending, Kim et al. (2012).

Figure 5-15 Relative risk and 95% confidence intervals for individual lag days from a constrained distributed lag model examining associations between short-term $PM_{2.5}$ exposure and asthma hospital admissions in Denver, CO.

Compared to asthma, the assessment of associations across different lags was limited for COPD and respiratory infection. Belleudi et al. (2010) examined both single-day and multiday lags (0 to 6 days, 0−1, 0−2, 0−5, and 0−6) for both COPD and lower respiratory tract infections. For COPD, the authors reported positive associations across a few single-day lags with the strongest association in terms of magnitude and precision observed at lag 0 (1.88% [95% CI: −0.27, 4.09]) and 2 (1.76 [95% CI: −0.18, 3.73]), with no evidence of an association for any of the multiday lags examined. However, for lower respiratory tract infections, positive associations were observed across single-day lags ranging from 1 to 5 days, but the magnitude of the association varied with the largest magnitude at lags 2 (2.82%) and 3 (3.04%). The multiple single-day lags reporting positive associations was further reflected when examining multiday averages, which provide evidence of a prolonged effect of short-term $PM_{2.5}$ exposure on lower respiratory tract infection (lag 0−5: (3.71 [95% CI: −0.57, 8.17]); lag 0−6: (3.62 [95% CI: −0.96, 8.42]).

Associations across different lags were further evaluated in recent studies focusing on all respiratory-related hospital admissions and ED visits. Overall, consistent, positive associations are reported across a range of single-day lags in multiple multicity studies (Bravo et al., 2017; Lanzinger et al., 2016b; Samoli et al., 2016a; Jones et al., 2015; Stafoggia et al., 2013). Some recent studies examined associations over a range of single-day lags through either a traditional single-day lag model or a distributed lag model. For example, Samoli et al. (2016a) and Jones et al. (2015) examined a series of single-day lags and reported positive association that were similar in magnitude across each individual lag, but confidence intervals were wide. In contrast to Samoli et al. (2016a) and Jones et al. (2015), Kim et al. (2012) did not report evidence of an association between short-term $PM_{2.5}$ exposure and

respiratory-related hospital admissions when examining the individual lag days of a 0 to 14 day constrained distributed lag model. However, the results for combinations of respiratory-related diseases differ from those observed for asthma hospital admissions in Kim et al. (2012) where, as previously mentioned, positive associations were observed at lags 4 to 12 days. In single-day lags of 0 to 2 days Bravo et al. (2017) reported a 0.79% increase (95% CI: 0.62, 0.97) at lag 0 in hospital admissions, but no evidence of an association at lags 1 or 2. However, when examining a distributed lag model of 0−7 days, the magnitude of the association increased as lag days increased, but confidence intervals did as well, providing some evidence of a potential prolonged $PM_{2.5}$ effect (Figure 5-16).



Source: Permission pending, Bravo et al. (2017).

Figure 5-16 Percent increase in respiratory-related hospital admissions for a distributed lag model up to 0−7 days for a 10 µg/m³ increase in 24-hour average $PM_{2.5}$ concentrations across 708 U.S. counties.

The results of Bravo et al. (2017) are consistent with both Lanzinger et al. (2016b) and Stafoggia et al. (2013) where positive associations were observed across each of the lags examined with the association with the largest magnitude observed for lag 0−5 in both studies. [(Lanzinger et al., 2016b): 2.8%, lag 0−1; 5.1%, lag 2−5; and 6.0%, lag 0−5; (Stafoggia et al., 2013): 0.49, lag 0−1; 1.1%, lag 2−5; and 1.4%, lag 0−5].

The assessment of associations across different lag structures for short-term $PM_{2.5}$ exposure and respiratory morbidity is further informed by analyses focusing on respiratory mortality. Multicity epidemiologic studies that examined cause-specific mortality in the 2009 PM ISA observed immediate effects with consistent positive associations for respiratory mortality at lags ranging from 0 to 2 days; however, these lags were selected a priori. Lippmann et al. (2013b), within the NPACT study, and Janssen et al. (2013), in a study conducted in the Netherlands, examined $PM_{2.5}$-respiratory mortality associations at single-day lags ranging from 0 to 3 days. While Lippmann et al. (2013b) reported the strongest association at lag 1, Janssen et al. (2013) reported evidence of associations larger in magnitude and with greater precision up to 3 days. Stafoggia et al. (2017), examining single-day lags ranging from 0 to 10 days, provide evidence that potentially supports the pattern of associations observed in both Lippmann et al. (2013b) and Janssen et al. (2013). The authors reported evidence of an immediate effect at lag 1, but also evidence of positive associations similar in magnitude at lags 3, 6, and 7 (quantitative results not presented). However, confidence intervals were wide, complicating the comparison of results across studies.

An examination of multiday lags by Lee et al. (2015) found a similar magnitude of an association across lags ranging from 0−1 to 0−4 days, which is consistent with the results of the studies examining single-day lags. However, Samoli et al. (2013), when examining lags indicative of immediate, delayed, and prolonged effects, reported evidence of an immediate $PM_{2.5}$ effect on respiratory mortality (0.72% [95% CI: −0.11, 1.6]; lag 0−1) that was larger in magnitude at longer lags (lag 2−5: 1.6% [95% CI: 0.62, 2.7]; lag 0−5: 1.9% [95% CI: 0.7, 3.1]). These results were further confirmed when examining single-day lags in a polynomial distributed lag model of 0−7 days, where associations were relatively consistent in magnitude from 0 to 2 days and then steadily increased out to 7 days.

Across the respiratory-related hospital admission and ED visit and mortality studies evaluated that conducted systematic evaluations of $PM_{2.5}$ associations across a range of lags, recent studies further support studies evaluated in the 2009 PM ISA that provided evidence of associations at lags ranging from 0−5 days. Studies of respiratory morbidity, specifically asthma and all respiratory-related hospital admissions and ED visits, along with more limited evidence from studies of COPD and respiratory infection, support that longer $PM_{2.5}$ exposures (i.e., 0−5-day lags) are associated with respiratory-related effects. Studies of respiratory mortality tended to support more immediate $PM_{2.5}$ effects (i.e., lags of 0 to 2 days), but initial evidence of stronger associations, in terms of magnitude and precision, at lags of 0−5 days is consistent with the pattern of associations observed in the hospital admission and ED visit studies.

5.1.10.4 The Role of Season and Temperature on $PM_{2.5}$ Associations

The examination of seasonal differences in $PM_{2.5}$ associations within studies that focus on respiratory-related hospital admissions and ED visits, as well as respiratory mortality, can provide

information that could be used to assess whether specific sources that vary by season are contributing to the $PM_{2.5}$ associations observed in all-year analyses. Additional studies that examine potential modification of $PM_{2.5}$ associations by temperature can further elucidate the impact of season on observed associations. Studies evaluated in the 2009 PM ISA, demonstrated seasonal variability in $PM_{2.5}$ associations with respiratory-related effects with some studies reporting associations in warmer months while others in colder months, which is further supported by recent studies. Fewer recent studies have examined potential modification of $PM_{2.5}$ associations by temperature.

5.1.10.4.1 Season

Recent studies have further examined the role of season on the relationship between short-term $PM_{2.5}$ exposure and respiratory-related effects, with the most extensive analyses focusing on asthma and all respiratory-related hospital admissions and ED visits. In studies of respiratory-related hospital admissions and ED visits, most often the warm season was defined as April−September, particularly for most northern U.S. cities, but in some cases the warm months encompassed May−October, such as for Atlanta, GA. $PM_{2.5}$-associated increases in asthma ED visits were observed in New Jersey in studies restricted to the warm season (Gleason and Fagliano, 2015; Gleason et al., 2014). Seasonal differences in associations are also supported by Malig et al. (2013) in a study of 35 California counties and asthma ED visits, which reported associations larger in magnitude in the warm compared to the cold season, as well as Stafoggia et al. (2013), in a study of eight European cities, which examined whether associations between short-term $PM_{2.5}$ exposure and all respiratory-related hospital admissions in the warm season were larger in magnitude than those observed in the all-year analysis. When restricting the analysis to the warm season (April−September), Stafoggia et al. (2013) reported a larger percent increase in respiratory-related hospital admissions (4.49% [95% CI: 1.72, 7.35]; lag 0−5) compared to the all-year analysis (1.36% [95% CI: 0.23, 2.49]; lag 0−5).

An examination of associations between short-term $PM_{2.5}$ exposure and asthma hospital admissions and ED visits in the cold season in U.S. locations were null except in New York, NY (Silverman and Ito, 2010; Ito et al., 2007). Additionally, (Rodopoulou et al., 2014) in a study examining all respiratory disease and acute respiratory infection ED visits in New Mexico, (Belleudi et al., 2010) in a study conducted in Rome, Italy focusing on respiratory infection ED visits, and (Lanzinger et al., 2016b) in a study of four European cities focusing on all respiratory-related hospital admissions reported evidence of associations larger in magnitude in the cold versus the warm season. The pattern of seasonal associations was also found to differ between two Australian cities, with an association larger in magnitude in the warm season in Sydney (Jalaludin et al., 2008) and in the cold season in Adelaide (Chen et al., 2016).

Additional studies conducted more refined analyses, focusing on all four seasons, to examine potential seasonal differences in $PM_{2.5}$ associations with respiratory-related hospital admissions and ED visits. For studies of asthma hospital admission and ED visit, an examination of $PM_{2.5}$ associations by the

four seasons is limited to Detroit, MI and Seoul, South Korea, but are consistent with each other in showing associations only in the spring (i.e., March−May) (Li et al., 2011 Kim, 2015, 3012210). However, studies focusing on all respiratory-related hospital admissions and ED visits reported a slightly different pattern of associations. Zanobetti et al. (2009), in a study of 26 U.S. counties reported the largest association in the spring (4.34% [95% CI: 2.19, 6.54]; lag 0−1) with the percent increase in respiratory-related hospital admissions ranging from 1.26−1.79% in the other seasons. Jones et al. (2015), in a study of New York state observed a slightly different pattern of associations across the seasons than Zanobetti et al. (2009). Focusing on lag 1, the authors reported associations largest in magnitude in the summer and fall with little evidence of an association in the winter and spring. Bell et al. (2015), in a study of 213 U.S. counties observed stronger associations with respiratory tract infection hospital admissions in spring (0.80% [95% CI: 0.02, 1.58]) and winter (0.40% [95% CI: −0.29, 1.10]), compared to the fall and spring where no evidence of an association was reported. The results from studies examining all four seasons support the results from studies that reported stronger associations during the warm season, but also provide some evidence that the greatest risk of $PM_{2.5}$-related respiratory effects may span into months traditionally defined as representing the cold season.

While studies in the 2009 PM ISA focusing on respiratory morbidity conducted seasonal analyses, studies focusing on mortality were limited to total (nonaccidental) mortality. These studies generally reported larger associations in warmer months (see Section 11.1.6.1) but resulted in uncertainty as to whether the same pattern of associations exists for cause-specific mortality, including respiratory mortality.

Recent multicity studies conducted in the U.S. (Dai et al., 2014; Lippmann et al., 2013a), Europe (Pascal et al., 2014; Samoli et al., 2013), and Asia (Lee et al., 2015) examined whether there was evidence of seasonal differences in the $PM_{2.5}$-respiratory mortality relationship. Within the NPACT study (Lippmann et al., 2013a), the examination of seasonal $PM_{2.5}$ associations resulted in a pattern of associations consistent with what was observed for total mortality (i.e., associations larger in magnitude during the warm season). However, compared to the all-year analysis, there was evidence of positive associations in the warm season across all lags examined with associations similar in magnitude (~0.5% increase) at lags 0, 1, and 3 days. There was also evidence of a positive association with respiratory mortality during the cold season, but only at lag 1 (0.40% [95% CI: −0.34, 1.1]). Dai et al. (2014), in a study of 75 U.S. cities reported results that were generally consistent with Lippmann et al. (2013a), but examined associations across all four seasons. Across seasons, the $PM_{2.5}$-respiratory mortality association was largest in magnitude during the spring (4.0% [95% CI: 2.9, 5.2]; lag 0−1), with positive, but smaller associations across the other seasons ranging from 0.58−1.1%.

Additional studies conducted in Europe report results consistent with those studies conducted in the U.S. In the MED-PARTICLES project, Samoli et al. (2013) examined short-term $PM_{2.5}$ exposure and respiratory mortality at lag 0−5 days and reported associations larger in magnitude in the warm season (6.5% [95% CI: 2.6, 10.5]) compared to the cold (1.7% [95% CI: 0.27, 3.2]). In France, Pascal et al.

(2014) reported similar results, but in an analysis of all four seasons. Associations between short-term $PM_{2.5}$ exposure and respiratory mortality were only positive during the spring and summer seasons, but confidence intervals were wide (quantitative results not presented).

Although the studies that examined U.S. and European cities provide consistent evidence of $PM_{2.5}$-respiratory mortality associations being larger in magnitude during warmer months (i.e., spring and summer), a study conducted in 11 east Asian cities observed a different pattern of associations. Lee et al. (2015) reported that $PM_{2.5}$ associations with respiratory mortality were larger in the cold season (1.3% [95% CI: 0.38, 2.2]) compared to the warm (0.63% [95% CI: −0.21, 1.5]). It is unclear why these results differ from the other studies, but mean $PM_{2.5}$ concentrations and mean temperature tended to be higher across the cities in Lee et al. (2015) compared to the cities in the other studies evaluated in this section.

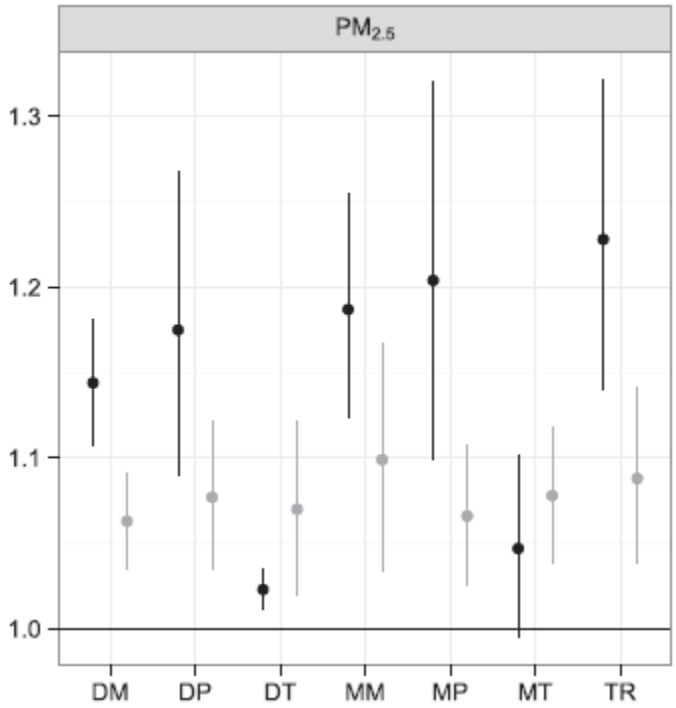
Across the multicity studies that examined seasonal associations, compared to studies of respiratory morbidity, results indicate that associations between short-term $PM_{2.5}$ exposure and respiratory mortality tend to be larger in magnitude during warmer parts of the year (i.e., spring and summer), specifically in locations where mean $PM_{2.5}$ concentrations and temperature are more like those observed in the U.S. These results are supported by studies that conducted more refined examinations of seasonal associations by each of the four seasons and observed associations larger in magnitude in the spring and summer.

In addition to traditional analyses that examine whether $PM_{2.5}$-respiratory-related hospital admission and ED visit associations vary by season; other studies have examined whether specific weather patterns influence associations. Hebbern and Cakmak (2015), in a study conducted in 10 Canadian cities, examined the association between short-term $PM_{2.5}$ exposure and asthma hospital admissions and whether the association was modified by specific synoptic weather patterns. Individual days were grouped into synoptic weather types based on temperature, humidity, and other factors. $PM_{2.5}$ associations with asthma hospital admissions were reported to be largest in magnitude for days classified as moist polar and transitional types and lowest in magnitude for dry tropical and moist tropical days, but interestingly these latter categories had higher $PM_{2.5}$ concentrations. However, when adjusting for aeroallergens, Hebbern and Cakmak (2015) observed that the difference in associations between weather types were absent.

Aeroallergens

While seasonal analyses can inform whether $PM_{2.5}$-asthma hospital admission and ED visit associations are influenced by weather, another factor tangentially related that has a strong seasonal component is aeroallergens. As detailed above, Hebbern and Cakmak (2015) reported that $PM_{2.5}$-asthma hospital admissions varied by synoptic weather pattern, but not when controlling for aeroallergens. However, in the models that controlled for aeroallergens, the RRs across all weather types, although attenuated, remained positive and were relatively similar, ranging from approximately 1.05−1.1

(Figure 5-17). Instead of controlling for the potential confounding effects of aeroallergens, Gleason et al. (2014), in a study conducted in New Jersey, examined whether the $PM_{2.5}$-asthma ED visit association varied across $PM_{2.5}$ quintiles depending on high and low levels of tree, grass, weed, and ragweed pollen. The authors observed no evidence of effect modification across the quintiles for high and low tree and grass pollen levels, and across all quintiles and levels of ragweed except for the combination of high ragweed and the highest quintile of $PM_{2.5}$ concentrations. However, when examining high ragweed pollen levels, as $PM_{2.5}$ concentrations increased there was evidence of effect modification (Table 5-17).



Note: Black circles represent before and grey circles represent after adjustment for aeroallergens.
DM = dry moderate; DP = dry polar; DT = dry tropical; MM = moist moderate; MP = moist polar; MT = moist tropical; TR = transitional weather types.
Source: Permission pending, Hebbern and Cakmak (2015).

Figure 5-17 Pooled relative risks across 10 Canadian cities by synoptic weather category.

Table 5-17 Odds ratios for quintile analyses in Gleason et al. (2014) from single-pollutant $PM_{2.5}$ analyses and analyses examining effect modification by high weed pollen days.

Study	$PM_{2.5}$ Analysis OR (95% CI)	Effect Modification Analysis OR (95% CI)
†Gleason et al. (2014) New Jersey, whole state 2004–2007	Lag 0: 0.53–6.1 μg/m³: 1.0 (reference) 6.1–8.5 μg/m³: 1.0 (0.95, 1.06) 8.5–11.4 μg/m³: 0.99 (0.94, 1.04) 11.4–16.8 μg/m³: 1.01 (0.96, 1.06) >16.9 μg/m³: 1.05 (0.99, 1.11)	Effect modification of $PM_{2.5}$ associations by high weed pollen levels (lag 0–2) by $PM_{2.5}$ quintiles (lag 0): 0.53–6.1 μg/m³: 1.0 (reference) 6.1–8.5 μg/m³: 1.57 (1.14, 2.17) 8.5–11.4 μg/m³: 1.53 (1.11, 2.12) 11.4–16.8 μg/m³: 2.32 (1.61, 3.34) >16.9 μg/m³: 2.51 (1.73, 3.64)

OR = odds ratio.
†Study published since the 2009 PM ISA.

5.1.10.4.2 Temperature

Instead of conducting traditional seasonal analyses, some recent studies examined whether there was evidence that higher temperatures modified the relationship between short-term $PM_{2.5}$ exposure and asthma hospital admissions and respiratory mortality. Cheng et al. (2015) examined whether specific temperatures modified the $PM_{2.5}$-asthma hospital admission association in Kaohsiung, Taiwan. The authors reported that $PM_{2.5}$ associations were larger in magnitude when analyses were restricted to days with lower temperatures, 13–25°C (RR = 1.10 [95% CI: 1.06, 1.13]) compared to days with higher temperatures (i.e., >25°C: RR = 1.02 [95% CI: 0.98, 1.06]).

Pascal et al. (2014) examined the impact of temperature on the $PM_{2.5}$-respiratory mortality relationship across nine French cities by comparing associations on warm and nonwarm days where warm days were defined as those days where the mean temperature exceed the 97.5th percentile of the mean temperature distribution. Pascal et al. (2014) reported no evidence of an interaction between $PM_{2.5}$ and warm days on respiratory mortality.

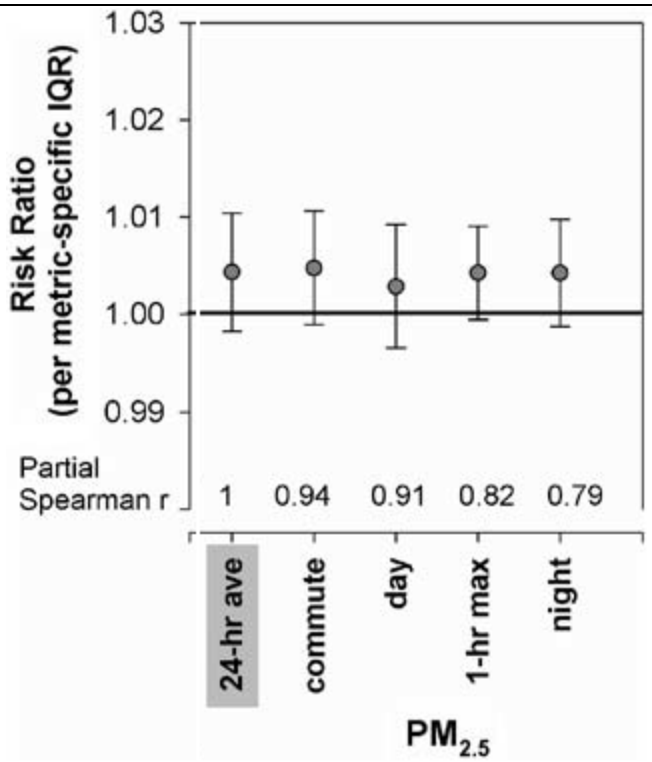
Additional studies conducted in Asia, although at higher mean $PM_{2.5}$ concentrations (i.e., in many cases >20 μg/m³), also examined whether high temperatures modify the $PM_{2.5}$-respiratory mortality relationship. Li et al. (2015b) examined whether same-day temperature, either higher (>23.5°C) or lower temperatures (<2.6°C), modifies the $PM_{2.5}$-respiratory mortality relationship at lag 0 and 1. At lag 0, there was evidence of an association larger in magnitude at high temperatures (1.7% [95% CI: 0.92, 3.3]) compared to medium (0.76% [95% CI: −0.04, 2.0]), with no evidence of an association at low temperatures. However, at lag 1, the strongest evidence of an association was only for the medium

temperatures (0.80% [95% CI: −0.15, 1.8]). Sun et al. (2015) provides evidence contradictory to the results of Li et al. (2015b). At lag 0−1 days, the authors observed positive associations at high (≥25ºC) and medium temperatures, ranging from 0.26−0.39%, but the magnitude of the association was much smaller than that observed for low temperatures (<22ºC) (1.2% [95% CI: 0.51, 1.8]). Unlike Li et al. (2015b), Sun et al. (2015) did not specifically focus on the tails of the temperature distribution, which complicates the interpretation of the results between the two studies, especially considering the low temperature category in Sun et al. (2015) is relatively similar to the high temperature category in Li et al. (2015b). Overall, the evidence across studies is inconclusive as to whether specific temperature ranges modify the association between short-term $PM_{2.5}$ exposure and respiratory mortality.

5.1.10.5 Averaging Time of $PM_{2.5}$ Concentrations

Collectively, the combination of studies evaluated in the 2009 PM ISA and within this section largely support an association between short-term $PM_{2.5}$ exposures and increases in respiratory-related hospital admissions and ED visits, specifically when using a 24-hour average $PM_{2.5}$ concentration averaging time. To date, very few studies have examined associations with subdaily averaging times for $PM_{2.5}$ concentrations (e.g., 1-hour max), with some evidence indicating associations between ED visits and 1-hour max $PM_{2.5}$ concentrations. Previously, in Bronx, NY, RRs for asthma ED visits were similar in magnitude for 24-hour average and 1-hour max $PM_{2.5}$ concentrations (ATSDR, 2006). The two averaging times were found to be highly correlated ($r = 0.78$), but the spatiotemporal variability of 1-hour max concentrations was not reported. Similarly, other studies that examined subdaily averaging times have not provided information on the spatiotemporal variability of other exposure metrics, such as 3-hour average or 6-hour average $PM_{2.5}$ concentrations, which were examined in studies conducted in six Canadian cities (Stieb et al., 2009) and Seoul, South Korea (Kim et al., 2015)]. However, in both studies, the authors reported no evidence of an association between 24-hour average $PM_{2.5}$ concentrations and asthma ED visits, nor was there evidence of an association using the subdaily averaging times.

Darrow et al. (2011) systematically examined a series of averaging times to assess whether the 24-hour exposure metric was appropriate. The authors examined several subdaily averaging times (i.e., 1-hour max, commute time average [7−10 a.m. and 6−9 p.m.], daytime average [8 a.m.−7 p.m.], and nighttime average [12−6 a.m.]) in addition to the traditional 24-hour average when examining the relationship between short-term $PM_{2.5}$ exposure and respiratory-related ED visits. The averaging times were found to be highly correlated with one another with $r = 0.79$−0.94, which is consistent with ATSDR (2006). Across the averaging times examined, the authors reported relatively consistent positive associations of similar magnitude, but confidence intervals were wide (Figure 5-18).



Source: Permission pending, Darrow et al. (2011).

Figure 5-18 Association between short-term $PM_{2.5}$ exposure and respiratory-related emergency department (ED) visits in Atlanta, GA at lag 1 for 24-hour average and subdaily exposure metrics.

While hospital admission and ED visit studies can examine alternative averaging times for the exposure metric if ambient monitoring data is available, panel studies using personal monitors can examine more refined time scales of exposure but are limited to studies of pulmonary inflammation and lung function. A strength of studies of pulmonary inflammation is examination of the hourly lag structure of $PM_{2.5}$ associations. Most (Barraza-Villarreal et al., 2008; Rabinovitch et al., 2006; Mar et al., 2005) but not all (Berhane et al., 2011) results show an increase in inflammation with increases in $PM_{2.5}$ concentration averaged over the preceding 1 to 11 hours. Additional support is provided by associations with mean personal $PM_{1.5}$ exposure in nonhome/school locations (Rabinovitch et al., 2016). Associations also were observed with 1-hour or 8-hour maximum $PM_{2.5}$ that were larger than those for 24-hour average $PM_{2.5}$ (Delfino et al., 2006; Rabinovitch et al., 2006). Maximum concentrations occurred before inflammation was measured. Some results indicate that $PM_{2.5}$ exposure may have a rapid and transient effect on pulmonary inflammation in people with asthma. For Seattle, WA and Riverside and Whittier, CA, distributed lag models show an increase in eNO with the 1-hour average $PM_{2.5}$ concentration up to 5 or 10 hours prior but not with longer lags of 24−48 hours (Delfino et al., 2006; Mar et al., 2005). eNO measured at well-defined intervals after a scripted 2-hour exposure during morning commutes increased

3 hours post-exposure (Mirabelli et al., 2015). Longer lags were not examined, and a similar previous study did not observe any changes up to 22 hours after exposure (McCreanor et al., 2007). It is important to note that most recent studies examined 24-hour or multiday average $PM_{2.5}$, which may explain the inconsistency in associations observed (see section on eNO). However, studies evaluated in the 2009 PM ISA also used 24-hour or multiday average $PM_{2.5}$ concentrations and reported positive associations (Liu et al., 2009; Allen et al., 2008; Delfino et al., 2006).

Additional studies examined subdaily averaging times through 1 to 8-hour scripted outdoor exposures near pollution sources. Epidemiologic studies of scripted outdoor exposures examined $PM_{2.5}$ at high-traffic locations and found inconsistent results with respect to respiratory effects in healthy populations. Among epidemiologic studies of adults commuting by car, bus, or bicycle, working as school crossing guards or traffic police, or spending time in high-traffic areas, $PM_{2.5}$ was associated with increases in pulmonary inflammation (Mirowsky et al., 2015; Zhao et al., 2015; Steenhof et al., 2013) or decreases in lung function (Huang et al., 2016; Shakya et al., 2016; Mirabelli et al., 2015; Weichenthal et al., 2011). Effects were not observed in other studies of pulmonary inflammation (Zuurbier et al., 2011a) or lung function decrements (Matt et al., 2016; Zhao et al., 2015; Zuurbier et al., 2011b; Fan et al., 2008). For $PM_{2.5}$ exposures of 1−8 hours, no distinct pattern of association or effect is observed by exposure duration or concentration. Among epidemiologic studies in the U.S., Canada, and Europe conducted near traffic or a steel plant, 1- to 8-hour average $PM_{2.5}$ concentrations with means 8.1−39 $\mu g/m^3$ were linked to respiratory effects in some studies (Mirabelli et al., 2015; Mirowsky et al., 2015; Dales et al., 2013), but not in others (Strak et al., 2012; Weichenthal et al., 2011). Results are inconsistent at concentrations higher than 39 $\mu g/m^3$ as well, but associations were observed in traffic police, adults exercising outdoors, or adults exposed in a transport hub (Huang et al., 2016; Shakya et al., 2016; Kesavachandran et al., 2015; Zhao et al., 2015) with mean 2- to 8-hour average $PM_{2.5}$ concentrations 53−323 $\mu g/m^3$.

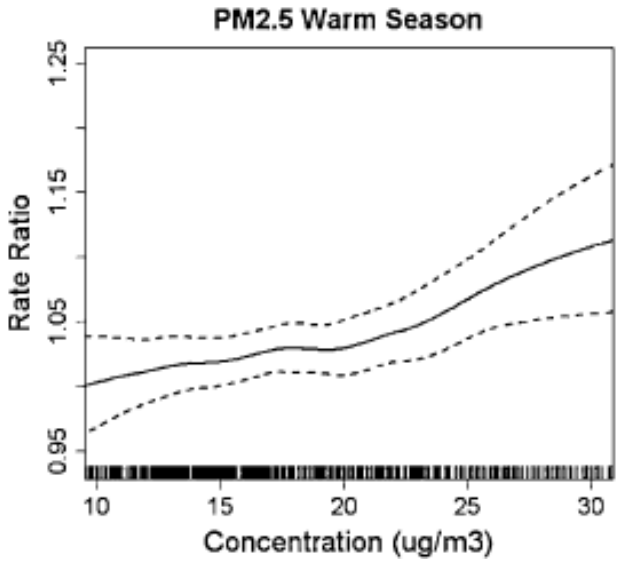
Across the studies evaluated that examined subdaily averaging times and subsequent respiratory effects, the effects tend to be transient. $PM_{2.5}$-associated increases in pulmonary inflammation and oxidative stress (Steenhof et al., 2013; Weichenthal et al., 2011) or decreases in lung function (Mirabelli et al., 2015) often were isolated to immediately or 1 or 2 hours after exposure near traffic, but not 3 to 18 hours after exposure. $PM_{2.5}$ exposure while walking near high-traffic roads and in a forest was associated with eNO 24 hours after exposure (Mirowsky et al., 2015), but lung function decreased only immediately after exposure.

5.1.10.6 Concentration-Response Relationship and Threshold Analyses

At the completion of the 2009 PM ISA, the examination of the PM C-R relationship in epidemiologic studies focused on mortality and cardiovascular outcomes. Recent studies expanded the evaluation of the $PM_{2.5}$ C-R relationship to encompass respiratory-related outcomes, including respiratory-related hospital admissions and ED visits with a focus on examining both the shape of the C-R

curve and whether a threshold exists below which there is no evidence of an effect. Across studies, different analytical methods have been employed to examine the C-R relationship, either explicitly examining the shape of the C-R curve and whether there is evidence of linearity across the full range of $PM_{2.5}$ concentrations, or through cutpoint analyses that examine the risk of a $PM_{2.5}$-related respiratory effect changes within specified ranges of different $PM_{2.5}$ concentrations.

Studies conducted in Atlanta, GA (Strickland et al., 2010), Ontario, Canada (Weichenthal et al., 2016), Dongguan, China (Zhao et al., 2016) and New York, NY (Silverman and Ito, 2010) focused on examining the shape of the $PM_{2.5}$ C-R curve for asthma ED visits or hospital admissions. In Strickland et al. (2010), which focused on pediatric ED visits, a locally weighted scatterplot smoothing (LOESS) C-R analysis provided evidence of a linear C-R relationship for $PM_{2.5}$ in the warm season along the distribution of $PM_{2.5}$ concentrations from the 5th to 95th percentile (Figure 5-19).

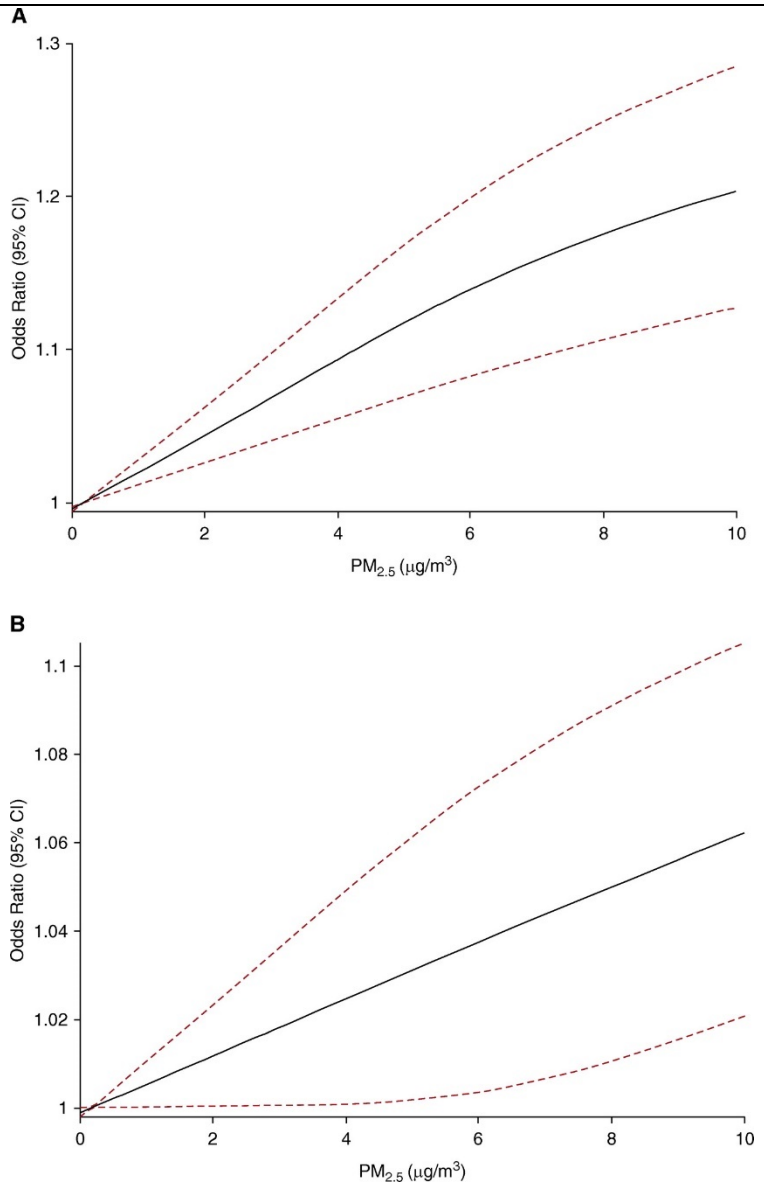


Note: Solid line = smoothed concentration-response estimate. Dashed line = twice-standard error estimates.
Source: Permission pending, Strickland et al. (2010).

Figure 5-19 Concentration-response for associations between 3-day average (lag 0−2) $PM_{2.5}$ concentrations and emergency department (ED) visits for pediatric asthma at the 5th to 95th percentile of $PM_{2.5}$ concentrations in the Atlanta, GA area during the warm season.

Additionally, Weichenthal et al. (2016) examined the C-R relationship for asthma ED visits among children <9 years of age and all ages in 15 Ontario cities in a case-crossover analysis. The authors examined the C-R curve across the range of $PM_{2.5}$ concentrations representing the 95th percentile of the observed difference in lag 0−2 $PM_{2.5}$ concentrations between case and control days, which represented

concentrations ranging from 0−10 μg/m^3, Weichenthal et al. (2016) reported evidence of a linear relationship for both age ranges, but confidence intervals were larger for the all ages analysis (Panel B of Figure 5-20). Evidence of a linear relationship was also observed by Zhao et al. (2016) at $PM_{2.5}$ concentrations much higher than those examined in the U.S. and Canadian studies. Although the results of Strickland et al. (2010), Weichenthal et al. (2016), and Zhao et al. (2016) are informative for assessing the shape of the C-R curve, the authors did not empirically examine alternatives to linearity.

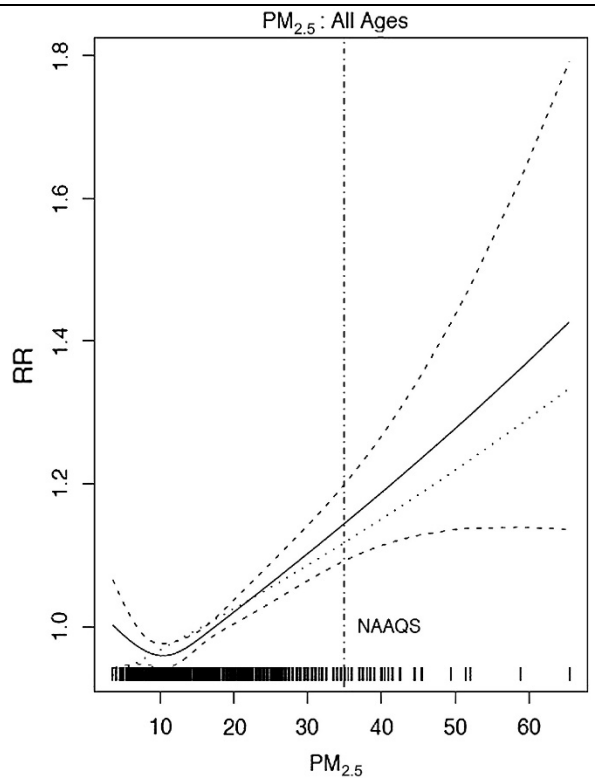


Note: Solid lines represent point estimates, and dashed lines represent 95% confidence intervals.
Source: Permission pending, Weichenthal et al. (2016).

Figure 5-20 Concentration-response curve for lag 0−2-day $PM_{2.5}$ concentrations and asthma emergency department (ED) visits for children (<9 years old) (Panel A) and all ages (Panel B).

Silverman and Ito (2010) assessed whether there was evidence for deviations in linearity for the relationship between short-term $PM_{2.5}$ exposure at lag 0−1 day and asthma hospital admissions by including a smooth function of lag 0−1-day ozone concentrations in the model. When comparing the results from the function including natural splines to account for potential deviations in linearity to a

linear fitted model, the authors observed no evidence that a nonlinear model better represents the C-R relationship (Figure 5-21).



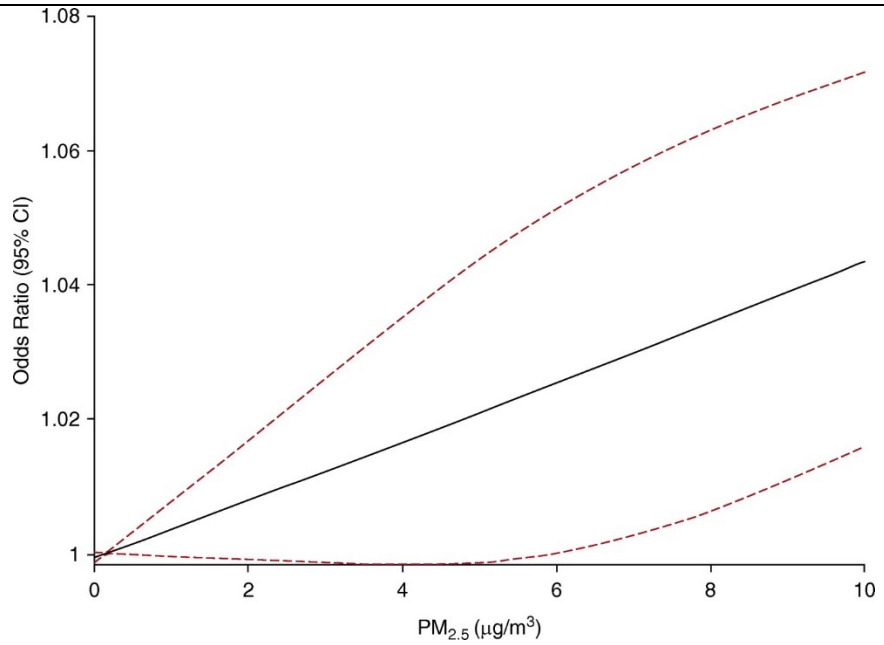
Note: Solid lines = smoothed fitted data, large dashed lines = 95% confidence intervals, short dashed lines = linear fitted data, vertical solid line = current 24-hour average $PM_{2.5}$ NAAQS.

Source: Permission pending, Silverman and Ito (2010).

Figure 5-21 Estimated relative risks (RRs) for short-term $PM_{2.5}$ exposure and asthma hospital admissions at lag 0−1 adjusted for ozone at lag 0−1 allowing for a possible nonlinear relationship in New York, NY.

Additional studies focusing on respiratory-related hospital admissions also examined whether there was evidence of linearity and reported results consistent with the studies focusing on asthma hospital admissions and ED visits.

Weichenthal et al. (2016) also examined the C-R relationship for COPD ED visits in 15 cities in Ontario, Canada. Using the same approach to examine the C-R curve for asthma ED visits, in the COPD analysis the authors reported evidence of a linear relationship (Figure 5-23). The C-R analyses conducted by Weichenthal et al. (2016) and Stafoggia et al. (2013) are also supported by Zhao et al. (2016) in a study conducted in Dongguan, China that demonstrated a linear relationship, albeit at $PM_{2.5}$ concentrations much higher than those examined in the U.S. and Canadian studies.



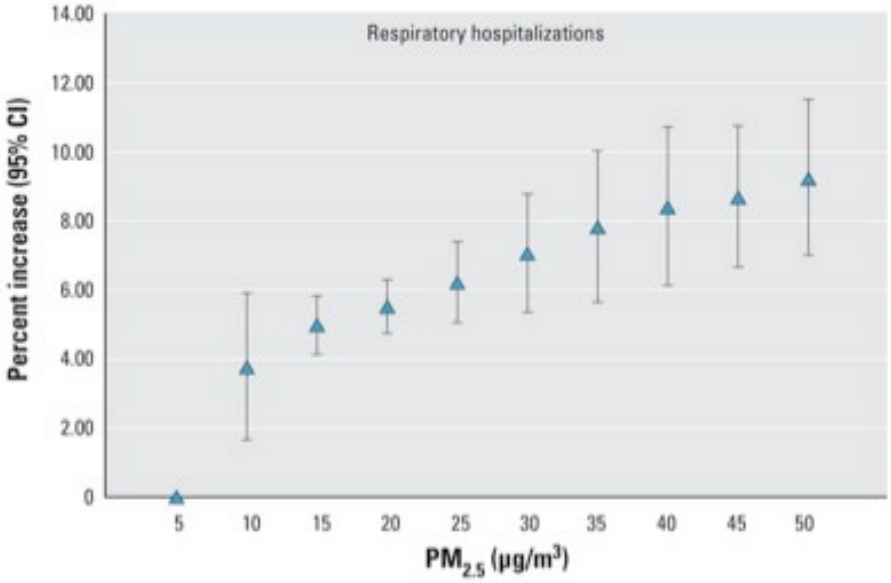
Source: Permission pending, Weichenthal et al. (2016).

Figure 5-22 Concentration-response relationship between 0−2 day mean $PM_{2.5}$ concentrations and chronic obstructive pulmonary disease (COPD) emergency department (ED) visits in Ontario, Canada.

While the studies discussed up to this point have focused specifically on the shape of the C-R curve across the full range of $PM_{2.5}$ concentrations in their respective study locations, other studies focused analyses on specific ranges of $PM_{2.5}$ concentrations to examine whether there is evidence of deviations in linearity. In a study conducted in Detroit, MI, Li et al. (2011) examined whether there is evidence of a nonlinear C-R relationship between air pollutants and pediatric asthma ED visits. Associations with $PM_{2.5}$ were examined in both a time-series and time-stratified, case-crossover study design assuming (1) a linear relationship and (2) a nonlinear relationship starting at 12 $\mu g/m^3$ (i.e., the maximum likelihood estimate within the 10th to 95th percentile concentration where a change in linearity

may occur), which was identified as somewhere in the range of the 35th to 49th percentile of $PM_{2.5}$ concentrations for the time-series and case-crossover analysis, respectively. It is important to note that in the analysis that assumed a nonlinear relationship, the authors did not assume zero risk below the inflection point, which would represent a true threshold. The focus of the analysis by Li et al. (2011) was on identifying whether risk increased above that observed in the linear models at $PM_{2.5}$ concentrations above 12 $\mu g/m^3$. In the analyses assuming linearity, the authors examined single-day lags of 3 and 5 days and multiday lags of 0−2 and 0−4 days. Positive associations were observed for all lags examined and were relatively consistent across models, with the strongest association, in terms of magnitude and precision, for a 0−4-day lag (time series: RR = 1.03 [95% CI: 1.00, 1.07]; case-crossover: OR = 1.04 [95% CI: 1.01, 1.07]). In the models that examined whether there was evidence of nonlinearity, the authors reported larger risk estimates for $PM_{2.5}$ concentrations above 12 $\mu g/m^3$, indicating potential nonlinearity in the $PM_{2.5}$-asthma hospital admissions and ED visit relationship (time series: RR = 1.07 [95% CI: 1.03, 1.11); case-crossover: OR = 1.06 (95% CI: 1.03, 1.09].

Instead of examining the association between short-term $PM_{2.5}$ exposure and asthma hospital admissions and between short-term $PM_{2.5}$ exposure and ED visits at one point along the distribution of $PM_{2.5}$ concentrations as was done by Li et al. (2011), Strickland et al. (2010), in Atlanta, GA, Gleason et al. (2014), in New Jersey, and Stafoggia et al. (2013) in eight European cities examined whether the associations varied across defined cutpoints along the distribution of $PM_{2.5}$ concentrations. Both studies provide some evidence indicating potential nonlinearity in the C-R relationship. In a quintile analysis of lag 0−2-day $PM_{2.5}$ concentrations, Strickland et al. (2010) examined whether risk estimates increased across the quintiles in both the warm and cold season when compared to the 1st quintile (i.e., <10 $\mu g/m^3$). Results were null across all quintiles for the cold season except the highest quintile (i.e., 23.8 ≤ 65.8) (RR = 1.05 [95% CI: 0.99, 1.11]). However, in the warm season, there was evidence of an increase in the magnitude of the association from the 3rd to 5th quintiles, ranging from 1.01−1.05, although confidence intervals were wide. Gleason et al. (2014) which also focused on lag 0−2 $PM_{2.5}$ concentrations, similarly reported a positive association for the highest quintile (i.e., 16.9−47.2 $\mu g/m^3$) (OR = 1.04 [95% CI: 0.98, 1.10]). However, the authors observed no evidence of an association for $PM_{2.5}$ concentrations in the range of the 3rd and 4th quintiles (i.e., 8.5−16.8 $\mu g/m^3$), but reported the association largest in magnitude for the 2nd quintile (i.e., 6.1−8.5 $\mu g/m^3$) (OR = 1.06 [95% CI: 1.01, 1.12]). Instead of focusing on quintiles, Stafoggia et al. (2013) examined associations between short-term $PM_{2.5}$ exposure and respiratory-related hospital admissions across various concentration ranges relative to 5 $\mu g/m^3$. The authors first combined results across each individual city by incorporating a natural spline with two equally spaced knots and then applying a metasmoothing approach to develop a combined result across the cities. As demonstrated in Figure 5-23, Stafoggia et al. (2013) report positive associations across each of the cut-points evaluated indicating no evidence of a threshold.



Source: Permission pending, Stafoggia et al. (2013).

Figure 5-23 Cut-point analysis examining the association between short-term $PM_{2.5}$ exposure and respiratory-related hospital admissions, lag 0−5, relative to 5 µg/m³.

Across the studies that examined the shape of the C-R curve, there is some evidence for a linear relationship for short-term $PM_{2.5}$ exposure and both respiratory disease and asthma hospital admissions and ED visits. However, complicating the interpretation of these results is both the lack of thorough empirical evaluations of alternatives to linearity as well as the results from cutpoint analyses that provide some potential indication for nonlinearity in the relationship between short-term $PM_{2.5}$ exposure and respiratory disease and asthma hospital admission and ED visits.

5.1.11 $PM_{2.5}$ Components and Sources and Respiratory Effects

While many PM components are associated with a range of health effects, the 2009 PM ISA concluded that there was "not yet sufficient evidence to allow differentiation of those [components] or sources that more closely related to specific health outcomes" compared to $PM_{2.5}$ mass (U.S. EPA, 2009). For respiratory effects, studies available at the completion of the 2009 PM ISA that examined PM components were few, and the overall evidence linking increases in respiratory effects with short-term exposure to $PM_{2.5}$ components and sources was less consistent than for other health outcomes (i.e., cardiovascular disease and mortality). However, there was some evidence of positive associations between respiratory ED visits and decrements in lung function with sulfate. In addition, several PM sources (i.e., crustal/soil/road dust and traffic) were associated with increased respiratory symptoms in

children with asthma and decreased PEF in adults with asthma. Generally, studies that evaluated individual PM components with respiratory morbidity and mortality observed inconsistent results, with limited evidence from a few studies that evaluated several metals (i.e., Cu, Pb, Zn) as well as OC were associated with respiratory health effects.

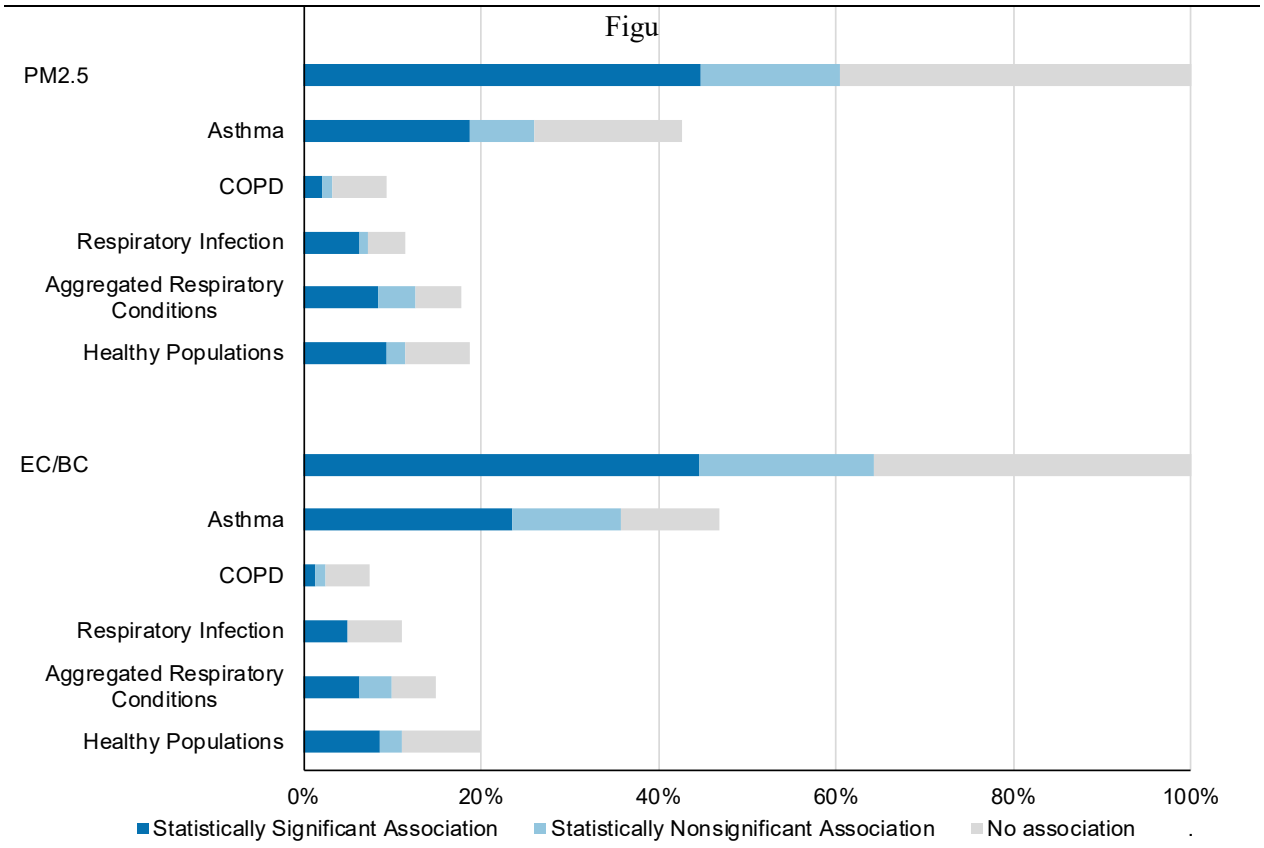
To provide a thorough and consistent evaluation of the evidence with respect to whether a component(s) or source(s) are more strongly related to respiratory effects than $PM_{2.5}$ mass, the evidence is organized by component or source and discussed in the context of associations with $PM_{2.5}$ mass. Additionally, the evidence for components and sources is evaluated in the context of broad health outcome categories, allowing for an integration of evidence related to specific outcomes (e.g., asthma exacerbation). The examination of the relationship between $PM_{2.5}$ components and respiratory effects can generally be divided into two types of analyses: (1) those that examine whether specific components modify the $PM_{2.5}$-respiratory effects association, or (2) those that examine whether an individual component is associated with respiratory effects and potentially a better indicator of PM toxicity compared to PM mass. Although approach 1 is considered one of the techniques used to assess component toxicity as detailed in Mostofsky et al. (2012) these studies are often used to examine heterogeneity in $PM_{2.5}$-respiratory effect risk estimates. As a result, the focus of this section is on population-level epidemiologic studies using those techniques that fall under approach 2, which includes assessing $PM_{2.5}$ component effect by: component concentration; component proportion; component concentration adjusted for $PM_{2.5}$ mass; component residual; or $PM_{2.5}$ residual (Mostofsky et al., 2012).

This section summarizes the evidence evaluating associations between individual components or sources and asthma exacerbation, respiratory infection, or respiratory effects in healthy populations in the context of associations between those respiratory effects and $PM_{2.5}$ mass. EC/BC was the component most often evaluated in studies of respiratory morbidity, and asthma exacerbations were the respiratory effect most commonly examined. Generally, some studies report positive associations between some components and sources and various respiratory health outcomes, though the consistency and coherence of this evidence varies across components and sources. For example, recent studies examined exposure to the EC/BC component of $PM_{2.5}$ and observed consistent associations with indicators of asthma exacerbation in children, though the associations were similar to those observed with $PM_{2.5}$ exposure. Expanded results for NO_3^- and $PM_{2.5}$ from road dust are inconsistent across the array of respiratory outcomes as is new information on PAHs and oxidative potential of $PM_{2.5}$. Overall, associations with respiratory effects are not more clearly linked to a specific PM component or source compared with $PM_{2.5}$ total mass, and within-study comparisons do not show a consistent difference in association between $PM_{2.5}$ and a particular component or source. The evidence for $PM_{2.5}$ components and sources are detailed below.

5.1.11.1 Elemental and Black Carbon

A large body of recent studies consistently links short-term increases in EC/BC concentration with respiratory effects, with the most studies examining asthma-related effects in children. Studies that observed positive associations between exposure to EC/BC and asthma-related effects in children also observed similar associations with $PM_{2.5}$ mass (Figure 5-24). For EC/BC, results are coherent among asthma ED visits, asthma symptoms, and pulmonary inflammation in populations with asthma. However, like trends observed for $PM_{2.5}$ mass, EC/BC associations with lung function are inconsistent. Neither EC/BC nor $PM_{2.5}$ is consistently associated with COPD exacerbation, and the evidence for EC/BC associations with respiratory infection, aggregated respiratory conditions, or respiratory effects in healthy populations is limited and inconsistent. Within most (Sarnat et al., 2015; Winquist et al., 2014b; Kim et al., 2012) but not all (Xiao et al., 2016) U.S. studies, EC was associated with effects related to asthma but not COPD or respiratory infection. Across respiratory effects, there is generally no difference in the pattern or consistency of associations between EC/BC and $PM_{2.5}$ (Figure 5-24).

Most studies associated respiratory effects with both $PM_{2.5}$ and EC/BC, though some showed associations with only one or the other. Many results point to similar magnitude of association for EC/BC and $PM_{2.5}$, often presented per IQR increase in concentration. Some studies estimated larger effects for EC/BC; others estimated larger effects for $PM_{2.5}$. Respiratory effects were associated with EC/BC in cities across regions of the U.S.; no pattern in the presence of an association for EC/BC or the magnitude relative to $PM_{2.5}$ is discerned by geographic location. In the nationwide U.S. Medicare population, EC was not associated with hospital admissions for all respiratory diseases combined (Levy et al., 2012). These results add 2 years to those of Peng et al. (2009a) (2000−2008 vs. 2000−2006), who reported an association with EC. The recent analysis by Levy et al. (2012) indicated the likelihood of greater risk for EC than $PM_{2.5}$ in the East. For locations showing similar magnitude associations for EC/BC and $PM_{2.5}$, correlations ranged 0.23−0.83. Across these studies, no pattern is observed for EC/BC by its correlation with $PM_{2.5}$. Most studies were conducted across seasons, so a pattern of association for EC by season in not discernable. Where stratified by season, EC/BC and $PM_{2.5}$ associations were similar in the same season. Warm season associations with asthma ED visits are indicated in Atlanta, GA and St. Louis, MO (Winquist et al., 2014b; Strickland et al., 2010), and cold season associations with pneumonia hospital admissions are indicated in Boston, MA (Zanobetti and Schwartz, 2006).



BC = black carbon, EC = elemental carbon, $PM_{2.5}$ = particulate matter with nominal mean aerodynamic diameter ≤2.5 µm.

Note: Colored bars indicate the proportion of those studies observing statistically significant positive associations, positive associations, null associations, negative associations, and statistically significant negative associations.

Figure 5-24 Associations for $PM_{2.5}$ total mass and elemental or black carbon with respiratory effects by outcome group.

Potential measurement error is an important consideration in drawing inferences from associations observed with EC/BC and in in comparing the effects relative to $PM_{2.5}$. Consistent with the contribution of local motor vehicle emissions to EC/BC and regional sources to $PM_{2.5}$, some studies indicated greater spatiotemporal variability in concentrations of EC/BC than $PM_{2.5}$. Both BC and $PM_{2.5}$ were highly correlated between two schools in Ciudad Juarez, Mexico (r = 0.85 for BC, r = 0.93 for $PM_{2.5}$) (Sarnat et al., 2012) but not between schools in El Paso, TX, where the correlation was moderate for BC and high for $PM_{2.5}$ ($_r$ = 0.60 for BC, $_r$ = 0.89 for $PM_{2.5}$) (Greenwald et al., 2013; Zora et al., 2013). In New York, NY, correlations between BC and $PM_{2.5}$ were moderate, and varied across schools ($_r$ = 0.47−0.68) (Patel et al., 2010). For these schools that varied in proximity to or intensity of traffic, the school-based EC/BC and $PM_{2.5}$ may have had more comparable exposure error than measurements at

central site monitors. Across studies, concentrations of EC/BC measured at schools were associated with larger increases in symptoms and pulmonary inflammation and larger decreases in lung function among children with asthma (Greenwald et al., 2013; Patel et al., 2013; Zora et al., 2013; Sarnat et al., 2012; Spira-Cohen et al., 2011; Patel et al., 2010).

The associations for respiratory effects and EC or $PM_{2.5}$ measured from personal exposures likely have comparable exposure error. Total personal EC concentrations, but not $PM_{2.5}$ concentrations, were associated with asthma-related effects among children in New York, NY (Spira-Cohen et al., 2011), whereas the opposite was observed for children in Los Angeles, CA (Delfino et al., 2008). One explanation could be variation in sources, for example, indoor exposures. EC and $PM_{2.5}$ were more highly correlated for ambient ($r = 0.51$) than personal measurements ($r = 0.22, 0.43$). Personal EC was weakly correlated with school EC in New York, NY ($r = 0.27$) and uncorrelated with central site EC in Los Angeles, CA ($r = -0.01$). The relative impact of personal ambient $PM_{2.5}$ and EC exposures also varied for adults (mostly healthy populations) exposed for 2−5 hour in high- and low-traffic locations. Some studies estimated larger effects for $PM_{2.5}$, and correlations with EC/BC were low ($r = 0.29, 0.39$) (Kubesch et al., 2015; Mirabelli et al., 2015; Mirowsky et al., 2015). Other studies estimated similar effects for EC/BC and $PM_{2.5}$ (Huang et al., 2016; Steenhof et al., 2013; Strak et al., 2012; Zuurbier et al., 2011b).

Associations with asthma-related hospital admissions and ED visits are generally the same for EC/BC and $PM_{2.5}$ measured at central site monitors. Effect estimates were similar per IQR increases in EC and $PM_{2.5}$ during 1993−2001 (Strickland et al., 2011; Strickland et al., 2010) but stronger for $PM_{2.5}$ in later years (2002−2010) (Strickland et al., 2014). For both EC and $PM_{2.5}$, similar effects were estimated when assigning exposure using concentrations at a monitor in the city center and those averaged across monitors by weighting by population density. The representativeness of EC and $PM_{2.5}$ metrics is supported by high correlations between exposure assessment methods ($r = 0.96$ for $PM_{2.5}$, 0.80 for EC) and the high density of asthma ED visits in the city center. There are greater uncertainties in comparisons in St. Louis, MO showing larger or similar increases in asthma ED visits for $PM_{2.5}$ than EC/BC when a single monitor was used (Sarnat et al., 2015; Winquist et al., 2014b). EC concentrations were spatiotemporally variable relative to $PM_{2.5}$ (median intersite $r = 0.88$ for $PM_{2.5}$ and 0.47 for EC).

Recent statistical analyses support an association for EC/BC independent of $PM_{2.5}$. Robust associations for EC are observed after adjusting for the non-EC portion of $PM_{2.5}$, which made up 96% total mass (Sarnat et al., 2012) or adjusting for the residuals from a model regressing EC with $PM_{2.5}$ (Basagaña et al., 2015). The latter also showed an association for $PM_{2.5}$. In copollutant models, associations for EC/BC persist when adjusted for $PM_{2.5}$, but associations for $PM_{2.5}$ adjusted for EC/BC were attenuated in some cases (Samoli et al., 2016c; Lin et al., 2011). A role for EC in modifying $PM_{2.5}$ effects is unclear based on contrasting results in the Medicare population. The $PM_{2.5}$ association with aggregated respiratory-related hospital admissions or ED visits increased as the EC fraction of long-term average $PM_{2.5}$ increased when assessed in 106 U.S. counties for 2000−2005 (Bell et al., 2009b) but was unaffected when assessed in 26 cities for 2000−2003 (Zanobetti et al., 2009). Across the 26 cities, EC

comprised 2−14% of total $PM_{2.5}$ mass. Other studies showed no consistent difference in association between EC and $PM_{2.5}$ in locations where EC made up 4−8% of $PM_{2.5}$ (Basagaña et al., 2015; Sarnat et al., 2015; Bell et al., 2014; Winquist et al., 2014b; Spira-Cohen et al., 2011; Peng et al., 2009a). Whether EC/BC has an effect independent of traffic-related copollutants is still uncertain. Correlations were high with UFP (r = 0.84−0.86) and wide-ranging with NO_2 or NO_X (r = 0.36−0.76). In copollutant models examined only with NO_2 or NO_X, associations for personal ambient EC were robust in some cases (Strak et al., 2012) but attenuated in others (Steenhof et al., 2013; McCreanor et al., 2007). Among children in New York, NY, associations for total personal EC were robust to adjustment for school NO_2 (Spira-Cohen et al., 2011), but potential differential measurement error limits inferences from the results. A similar uncertainty applies to results for asthma ED visits in Georgia not indicating synergistic interactions for EC with the highly correlated NO_2, CO, and OC (Xiao et al., 2016). The fused-CMAQ model's predictive capacity of EC, CO, and OC concentrations was mediocre (cross-validation R^2 = 0.53−0.54).

Overall, there is generally no difference in the pattern or consistency of associations between EC/BC and $PM_{2.5}$ across respiratory effects. A large body of recent studies that consistently observed positive associations between exposure to EC/BC and respiratory effects also observed similar associations with $PM_{2.5}$ mass. These results continue to support the conclusion in the 2009 PM ISA that there is "not yet sufficient evidence to allow differentiation of those [components] or sources that more closely related to specific health outcomes" compared to $PM_{2.5}$ mass (U.S. EPA, 2009).

5.1.11.2 Organic Carbon

In contrast with studies characterized in the 2009 PM ISA, recent studies consistently report a positive association of OC with asthma-related hospital admissions, ED visits, symptoms, and pulmonary inflammation but not lung function decrements. Recent results from a limited number of studies demonstrate consistent positive associations between OC exposure and aggregated respiratory-related diseases but not COPD exacerbation, respiratory infection, or respiratory effects in healthy population. Across these studies, the consistency and magnitude of respiratory effect associations are generally similar for OC and $PM_{2.5}$, and these studies report moderate to high correlations between OC and $PM_{2.5}$ (r = 0.51−0.87) (Krall et al., 2016; Xiao et al., 2016; Basagaña et al., 2015; Jones et al., 2015; Sarnat et al., 2015; Kim et al., 2012) and a large contribution of OC to total $PM_{2.5}$ mass [Section 2.5.1.1.6 and 11 and 21% in (Jones et al., 2015; Sarnat et al., 2015)]. In exception to most results, a recent analysis of the U.S. Medicare population indicates greater risk of hospital admission for respiratory infection for OC than $PM_{2.5}$ (Levy et al., 2012).

Like $PM_{2.5}$, OC was associated with respiratory effects among people of all ages or children in locations across U.S. regions. During 2000−2008, OC was linked to hospital admissions for respiratory infection in 98 eastern but not 21 western U.S. counties (Levy et al., 2012). Risk estimates for $PM_{2.5}$ with

hospital admissions for COPD plus respiratory infection during 2000−2003 did not vary by the long-term average OC to $PM_{2.5}$ ratio, which ranged 0.10 to 0.99 across 26 cities and four seasons (Zanobetti et al., 2009). Both OC and $PM_{2.5}$ show associations in the cold and warm season, but few seasonal analyses were conducted. Except for pneumonia, associations for OC and $PM_{2.5}$ are larger in the warm season in U.S. locations (Jones et al., 2015; Winquist et al., 2014b; Strickland et al., 2010).

The lack of clear differences in associations between OC and $PM_{2.5}$ is observed across exposure assessment methods, including concentrations at central site monitors in Atlanta, GA where OC and $PM_{2.5}$ similarly showed spatiotemporal homogeneity (r = 0.96 for $PM_{2.5}$, 0.89 for OC between a monitor in the city center and a population-weighted average) (Strickland et al., 2011) and St. Louis, MO where OC was more variable than $PM_{2.5}$ (median intersite r = 0.43 for OC, 0.88 for $PM_{2.5}$) (Sarnat et al., 2015). Results did not consistently differ between OC and $PM_{2.5}$ for weakly correlated (r = 0.26) total personal exposures of children with asthma (Delfino et al., 2008; Delfino et al., 2006) and moderately to highly correlated (r = 0.40−0.79) personal ambient exposures of adults during 2 or 5 hours spent in high- or varying-traffic locations (Mirabelli et al., 2015; Mirowsky et al., 2015; Strak et al., 2012). In addition to the uncertainty of associations of OC that are independent of the effects of $PM_{2.5}$ mass, it is also unclear if the association for OC with respiratory effects is independent of moderately correlated NO_2 or EC/BC (r = 0.44−0.51 with NO_2, 0.53−0.64 with EC) given that no studies examined confounding.

5.1.11.3 Secondary $PM_{2.5}$—Sulfate, Nitrate, Ammonium

Several recent studies add to the limited body of evidence in the 2009 PM ISA for associations of SO_4^{2-} and asthma exacerbation, and several recent studies contribute evidence to characterize the associations between NO_3^-, and ammonium (NH_4^+) and respiratory effects (Figure 5-25). Evidence for effects on asthma exacerbation are generally more consistent than associations for other respiratory outcomes. In most locations, results are similar between $PM_{2.5}$ and SO_4^{2-} or NH_4^+ in direction and magnitude of association. In the U.S., Europe, and Asia, there was consistent evidence of positive associations for SO_4^{2-}, NH_4^+, and NO_3^- (Wang and Lin, 2016; Jones et al., 2015; Steenhof et al., 2013; Kim et al., 2012; Atkinson et al., 2010). However, in some instances, associations were observed with NO_3^- but not SO_4^{2-} (Ostro et al., 2016; Mann et al., 2010), or associations were observed with SO_4^{2-} but not NO_3^- (Sarnat et al., 2015; Darrow et al., 2014; Strickland et al., 2014). Analyses of the U.S. Medicare population did not report consistently positive associations for SO_4^{2-} or NO_3^- across respiratory effects. For 2000−2008, hospital admissions for respiratory infection were not associated with SO_4^{2-} or NO_3^- in the east or west (Levy et al., 2012). For 2000−2006, hospital admissions for respiratory infection and COPD combined were associated with SO_4^{2-} not NO_3^- (Peng et al., 2009a).

For U.S. locations, associations for SO_4^{2-}, NO_3^-, and NH_4^+ tends to follow their relation to total $PM_{2.5}$ mass. Where associations were observed for SO_4^{2-} but not NO_3^-, $PM_{2.5}$ was highly correlated with SO_4^{2-} (r = 0.74−0.81) not NO_3^- (r = 0.02−0.45) (Sarnat et al., 2015; Darrow et al., 2014; Strickland et al.,

2014; Peng et al., 2009a). The converse was observed in California (r for $PM_{2.5}$ = 0.9 with NO_3^- and <0.5 with SO_4^{2-}) (Ostro et al., 2009). Where associations were observed with SO_4^{2-} and NO_3^-, both were highly correlated with $PM_{2.5}$ (r = 0.68−0.97 for SO_4^{2-}, 0.51−0.82 for NO_3^-) (Wang and Lin, 2016; Jones et al., 2015; Kim et al., 2012; Atkinson et al., 2010). The few available seasonal analyses show higher concentrations of SO_4^{2-} and NH_4^+ in the warm season and of NO_3^- in the cold season.

Analyses of effect measure modification also do not clearly show that SO_4^{2-}, NO_3^-, or NH_4^+ influences $PM_{2.5}$-associated respiratory effects. Consistent with previous findings (Bell et al., 2009b), recent results in the Medicare population show no clear difference in $PM_{2.5}$-associated respiratory hospital admissions by the ratio of SO_4^{2-}, NO_3^-, or NH_4^+ to $PM_{2.5}$ in New York State (Jones et al., 2015) and low probability that risk for SO_4^{2-} or NO_3^- is greater than that for $PM_{2.5}$ in the U.S. overall (Levy et al., 2012). An independent association for SO_4^{2-} is not clearly indicated with adjustment for the non-SO_4^{2-} portion of $PM_{2.5}$ in St. Louis, MO (Sarnat et al., 2015) or residuals from a model regressing $PM_{2.5}$ on SO_4^{2-} concentrations in Europe (Basagaña et al., 2015). In California, the association for NO_3^- was robust to adjustment for a factor of traffic-related $PM_{2.5}$ components (Ostro et al., 2016).

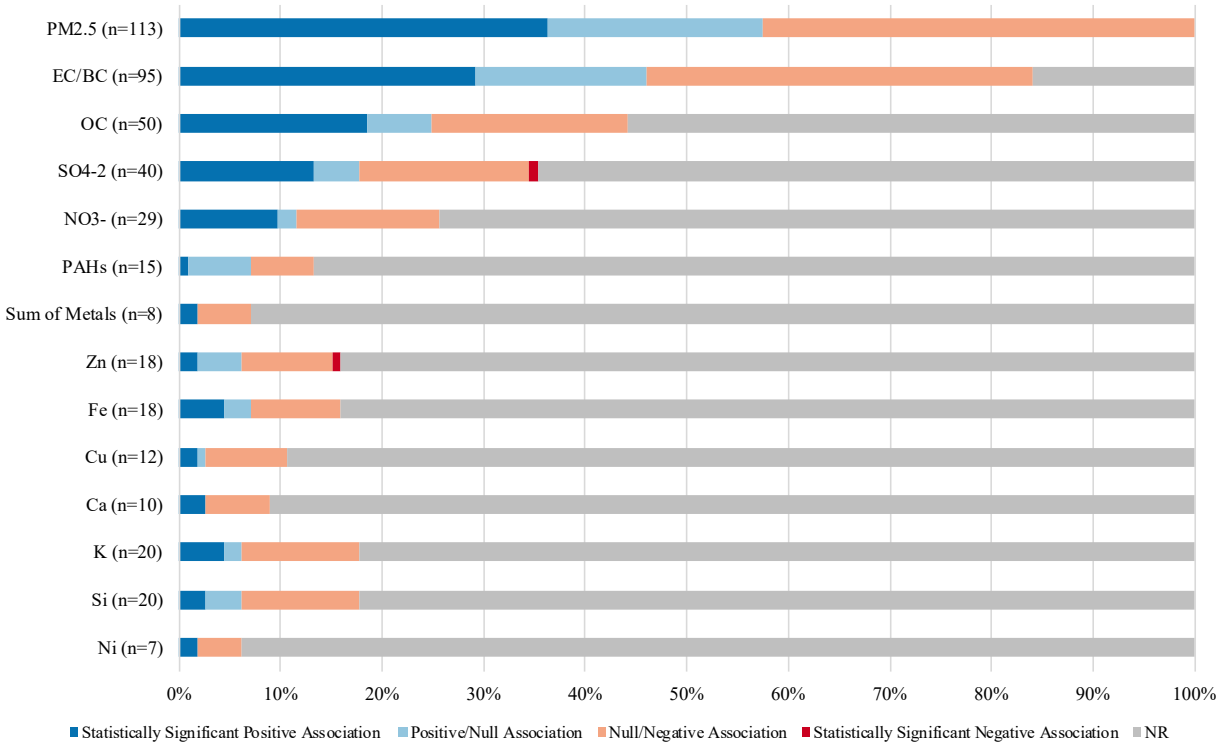
5.1.11.4 Metals

Compared with $PM_{2.5}$ mass, short-term exposures to metal components of $PM_{2.5}$ are inconsistently associated with respiratory effects (Figure 5-25). In the expanded body of recent studies, relatively few observed associations with a metal that differed substantially from the association with $PM_{2.5}$ mass (Ferreira et al., 2016; Bell et al., 2014; Strak et al., 2012; Hong et al., 2010). Most studies that included a metal component of $PM_{2.5}$ observed an association with some metal, and studies that examined numerous metals observed an association with multiple metals. However, findings are inconsistent for any individual metal or the sum of metals. Fe, Zn, Cu, Ca, K, and Si are most studied, and many associations are positive for Fe or Zn with indicators of asthma exacerbation (Prieto-Parra et al., 2017; Mirabelli et al., 2015; Hong et al., 2010; Sinclair et al., 2010; Gent et al., 2009; Ostro et al., 2009). Results are mostly null for Al, Mn, Pb, As, Se, Br, Ti, and V, but associations for V tend to be similar to those for Ni (Basagaña et al., 2015; Bell et al., 2014).

Neither the percentage contribution metals make to $PM_{2.5}$ mass nor the correlation between metal and $PM_{2.5}$ mass concentrations affected the pattern of associations between metal components and respiratory effects. Where metals comprised less than 1% of $PM_{2.5}$, associations with respiratory effects were observed in Bell et al. (2014), but not Sarnat et al. (2015). The range of correlations between metals and $PM_{2.5}$ (r = 0.25−0.63) did not clearly differ between studies that observed (Krall et al., 2016; Basagaña et al., 2015; Ostro et al., 2009) and did not observe (Basagaña et al., 2015; Sarnat et al., 2015) positive associations with metals. Few seasonal analyses were conducted to assess a pattern of association. Previous U.S.-wide analyses indicate that the $PM_{2.5}$ association with respiratory hospital admissions varies across cities depending on the percentage of Na, Ca, Ni or V (Bell et al., 2009b;

Zanobetti et al., 2009), with (Bell et al., 2009b) indicating effect modification by Ni or V only when New York, NY counties were included. Recent studies confirm a positive association with Ni and V in the Northeast (i.e., Connecticut and Massachusetts) (Bell et al., 2014; Gent et al., 2009).

Ambient concentrations of metals can be spatiotemporally more heterogeneous than $PM_{2.5}$ total mass. In St. Louis, MO, $PM_{2.5}$ but not metals were associated with asthma ED visits, and Fe, Cu, and Zn were variable across monitors (median $r = 0.54$ for Fe, 0.03 for Cu and Zn) (Sarnat et al., 2015). Exposure measurement error could contribute to inconsistent findings for metals. However, personal Fe exposures while driving in a car or in locations with varying traffic levels were inconsistently associated with lung function decrements or increases in pulmonary inflammation (Mirabelli et al., 2015; Strak et al., 2012).



BC = black carbon, Ca = calcium, Cu = copper, EC = elemental carbon, Fe = iron, K = potassium, N = the number of studies evaluating $PM_{2.5}$ mass or components, Ni = nickel, NO_3^- = nitrate, OC = organic carbon, PAH = polycyclic aromatic hydrocarbon, $PM_{2.5}$ = particulate matter with nominal mean aerodynamic diameter ≤2.5 µm, Si = silicon, SO_4^{2-} = sulfate, Zn = zinc.

Note: Colored bars indicate the proportion of those studies observing statistically significant positive associations, positive associations, null associations, negative associations, and statistically significant negative associations.

Figure 5-25 Distribution of associations for all respiratory effects and short-term $PM_{2.5}$ mass and $PM_{2.5}$ components exposure.

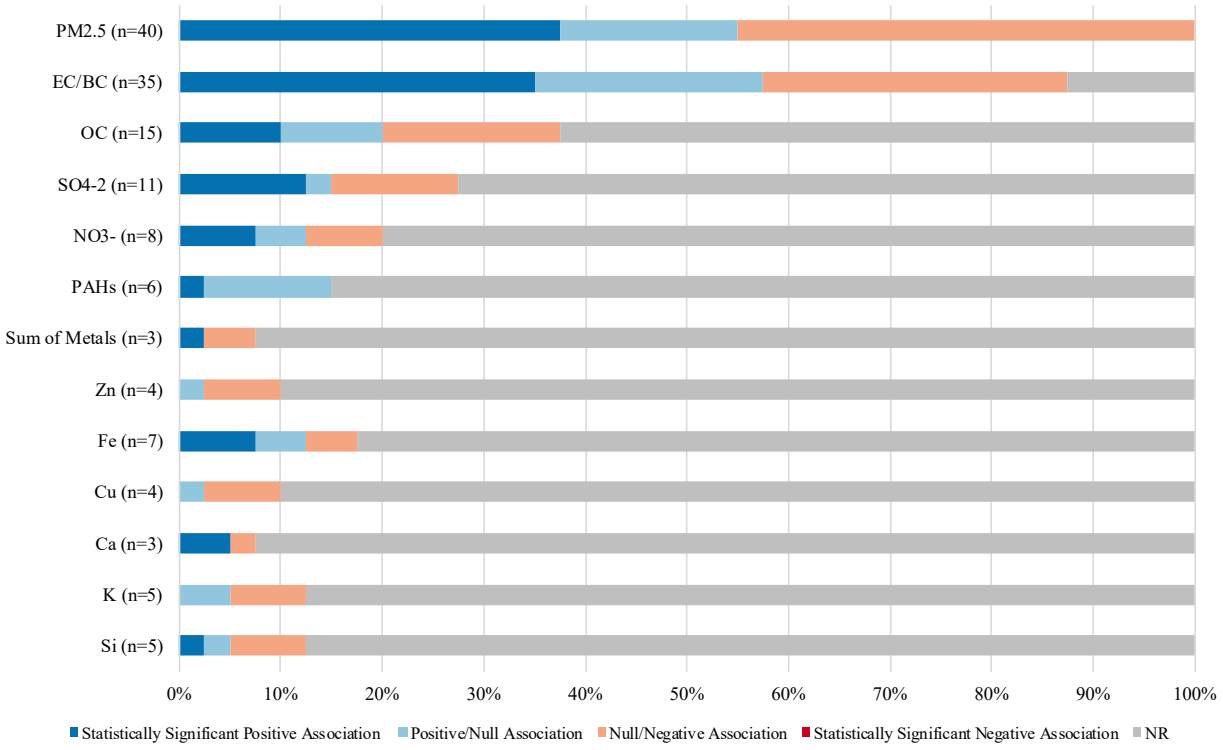
5.1.11.5 Other $PM_{2.5}$ components

Information from a limited number of recent studies links respiratory effects with oxidative potential of $PM_{2.5}$ and chlorine but is inconsistent for polycyclic aromatic hydrocarbons, alkanes, hopanes, and endotoxin. Information is available from a few studies and locations for each of these $PM_{2.5}$ components and for a variety of respiratory effects, with few studies evaluating the same combination of $PM_{2.5}$ component and respiratory effect [e.g., Maikawa et al. (2016); Mirabelli et al. (2015); Sarnat et al. (2015); (Delfino et al., 2013)]. Notably, for the studies examining oxidative potential of $PM_{2.5}$, associations were not observed with total $PM_{2.5}$ mass. Associations for polycyclic aromatic hydrocarbons and alkanes were linked to sources such as traffic or petroleum industries, and associations for endotoxin were linked to farm exposures.

5.1.11.6 Sources of $PM_{2.5}$

A limited number of studies included in the 2009 PM ISA examined associations between respiratory effects and sources of $PM_{2.5}$ (e.g., crustal, soil, road dust, traffic). Several recent studies apportioned $PM_{2.5}$ components into source factors and provide some evidence linking $PM_{2.5}$ from traffic to asthma exacerbation and $PM_{2.5}$ from biomass burning to asthma exacerbation and respiratory infection (Figure 5-25 and Figure 5-26). These respiratory effects also are consistently associated with short-term $PM_{2.5}$ exposures during wildfires. Evidence is inconsistent for $PM_{2.5}$ from dust or soil, and as examined in few studies, oil, salt, long-range transport, and local industry. Results do not appear to depend on the contribution or correlation of a source to $PM_{2.5}$ mass. For example, associations were observed with biomass-related $PM_{2.5}$ comprising 2.8 to 15.8% of mass and showing correlations with $PM_{2.5}$ mass from 0.24 to 0.84. In contrast, long-range transport contributed 30−57% to $PM_{2.5}$ mass. Further, studies that examined numerous sources tended to observe associations with $PM_{2.5}$ with combustion-related activities, specifically traffic and biomass. Some U.S., Canadian, and European studies observed respiratory effects in association with source-specific $PM_{2.5}$ but not with $PM_{2.5}$ mass (Brand et al., 2016; Bell et al., 2014; Alessandrini et al., 2013; Gent et al., 2009), but findings overall are more consistent for $PM_{2.5}$ mass. No clear difference in associations between total $PM_{2.5}$ mass or source-specific $PM_{2.5}$ and respiratory effects is indicated across studies during wildfire and nonwildfire study periods (Kollanus et al., 2016; Salimi et al., 2016; Delfino et al., 2009).

Respiratory effects were associated with $PM_{2.5}$ from motor vehicles or biomass in various U.S. regions, including a study of Atlanta, GA; Birmingham, AL; Dallas, TX; and St. Louis, MO, where $PM_{2.5}$ components were apportioned into similar factors (Krall et al., 2016). Examination of wildfire-related $PM_{2.5}$ mostly focused on the western U.S., including an analysis of 561 counties (Liu et al., 2017), but also included a study focusing on a peat fire in North Carolina (Rappold et al., 2012). No distinct seasonal pattern is discerned for associations with source-specific $PM_{2.5}$, but many wildfires occur during the warm season.



BC = Black carbon, Ca = calcium, Cu = copper, EC = elemental carbon, Fe = iron, K = potassium, N = the number of studies evaluating $PM_{2.5}$ mass or components, NO_3^- = nitrate, OC = organic carbon, PAH = polycyclic aromatic hydrocarbon, $PM_{2.5}$ = particulate matter with nominal mean aerodynamic diameter ≤2.5 µm, Si = silicon, SO_4^{2-} = sulfate, Zn = zinc.

Note: Colored bars indicate the proportion of those studies observing statistically significant positive associations, positive associations, null associations, and negative associations.

Figure 5-26 Associations for asthma exacerbations with $PM_{2.5}$ mass and components.

The results for source-specific $PM_{2.5}$ do not always agree with those for the components that make up the source factors. Respiratory effects are inconsistently associated with dust- or soil-related $PM_{2.5}$, Si, Ca, and Al as well as with salt-related $PM_{2.5}$, Na, and Cl (Section 5.1.11.4). In northeastern U.S. locations, associations were observed with Ni or V but not oil-related $PM_{2.5}$ (Bell et al., 2014; Gent et al., 2009). Similarly, associations are observed with SO_4^{2-} or NO_3^- but inconsistently for factors representing long-range transported $PM_{2.5}$. In New Mexico, no association was observed for $PM_{2.5}$ or for air masses identified as originating from regions in the western U.S. (Rodopoulou et al., 2014). Results agree better for motor vehicle-related $PM_{2.5}$, as evidence also links asthma-related effects to EC (Section 5.1.11.1), OC (Section 5.1.11.2), Zn, and Fe (Section 5.1.11.4), which comprised most motor vehicle source factors. A few studies observed associations with EC/BC or OC but not motor vehicle-related $PM_{2.5}$ (Krall et al., 2016; Bell et al., 2014). The influence of total $PM_{2.5}$ mass or EC/BC does not clearly depend on proximity to traffic. With scripted exposures near roadways, $PM_{2.5}$ and EC/BC are inconsistently associated with

respiratory effects in healthy populations (Section 5.1.7). However, similar inconsistency is observed for children with asthma attending school near major roads (Greenwald et al., 2013; Sarnat et al., 2012). For biomass-related $PM_{2.5}$, results for asthma-related effects tend to correspond with K or OC within studies, but across studies, consistency is observed for OC (Section 5.1.11.2) not K (Section 5.1.11.4).

5.1.11.7 Summary

Generally, some studies report positive associations between some components and sources and various respiratory health outcomes, though the consistency and coherence of this evidence varies across components and sources. Overall, associations with respiratory effects are not more clearly linked to a particular PM component or source compared with $PM_{2.5}$ total mass, and within-study comparisons do not show a consistent difference in association between $PM_{2.5}$ and a specific component or source (Figure 5-25). The majority of studies evaluating $PM_{2.5}$ components examined associations with asthma exacerbation, and these results are presented in Figure 5-26. Some recent studies did not observe increased respiratory effects with $PM_{2.5}$ mass, but did with PM components and sources, typically EC/BC (Section 5.1.11.1) and metals (Section 5.1.11.4). However, in most cases, associations were observed with $PM_{2.5}$ as well as components or sources.

5.1.12 Summary and Causality Determination

The 2009 PM ISA (U.S. EPA, 2009) concluded that a "causal relationship is likely to exist" between short-term $PM_{2.5}$ exposure and respiratory effects (U.S. EPA, 2009).[56] This conclusion was based mainly on epidemiologic evidence demonstrating associations between short-term $PM_{2.5}$ exposure and various respiratory effects. There was more limited evidence from controlled human exposure and animal toxicological studies, which provided coherence and biological plausibility for a subset of epidemiologic findings. Epidemiologic evidence was consistent for COPD exacerbation, respiratory infection, and respiratory mortality and inconsistent for asthma-related hospital admissions and ED visits. However, associations between short-term $PM_{2.5}$ exposure and increased respiratory symptoms and decreases in lung function were observed in children with asthma. Evidence supporting an independent effect of $PM_{2.5}$ on the respiratory system was provided by animal toxicological studies of $PM_{2.5}$ CAPs, which demonstrated changes in some pulmonary function parameters, as well as inflammation, oxidative stress, injury, enhanced allergic responses, and reduced host defenses. Many of these effects have been implicated in the pathophysiology for asthma exacerbation, COPD exacerbation, or respiratory infection. In the few controlled human exposure studies conducted in individuals with asthma or COPD, $PM_{2.5}$ exposure mostly had no effect on respiratory symptoms, lung function, or pulmonary inflammation.

[56] As detailed in the Preface, risk estimates are for a 10 $\mu g/m^3$ increase in 24-hour average $PM_{2.5}$ concentrations unless otherwise noted.

Short-term $PM_{2.5}$ exposure was not clearly related to respiratory effects in healthy people. For many endpoints the recent epidemiologic evidence is expanded compared with evidence available in the 2009 PM ISA. However, recent controlled human exposure and animal toxicological studies are limited in number. While there are more analyses of potential copollutant confounding indicating that associations are robust to the inclusion of gaseous pollutants, uncertainties remain due to the limited experimental evidence supporting an independent $PM_{2.5}$ effect from controlled human exposure and toxicological studies. The evidence for the relationship between short-term exposure to $PM_{2.5}$ and respiratory effects is summarized in Table 5-18, using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015).

For asthma exacerbation, the key epidemiologic evidence consists of hospital admissions and ED visits. Recent studies strengthen the relationship between asthma exacerbation in children and short-term $PM_{2.5}$ exposure, while, in adults, the relationship continues to be inconsistent. Exposure measurement error related to uncharacterized spatial variability tends to be lower in $PM_{2.5}$ mass concentration compared with other size fractions and species (Section 3.4.2.2). Copollutant models are examined in recent studies of children and people of all ages and add evidence of robust $PM_{2.5}$ associations after adjustment for gaseous copollutants or pollen. Recent studies continue to indicate $PM_{2.5}$-related increases in asthma symptoms and medication use in children, with less consistent evidence for lung function decrements and pulmonary inflammation. In adults, asthma studies with personal 2-hour ambient $PM_{2.5}$ exposures on or near a high-traffic road were associated with lung function decrements. While controlled human exposure studies find little evidence for altered lung function and pulmonary inflammation, animal toxicological studies show enhancement of allergic inflammation, other allergic responses, and airway remodeling in animal models of allergic airway disease. These results provide coherence with and biological plausibility for epidemiologic findings of allergic asthma, the most common phenotype in children. Overall, several well-conducted epidemiologic studies with total personal, residential outdoor, and school outdoor $PM_{2.5}$ measurements show associations with asthma-related effects.

Table 5-18 Summary of evidence for a likely to be causal relationship between short-term $PM_{2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Asthma exacerbation			
Consistent epidemiologic evidence from multiple, high-quality studies at relevant $PM_{2.5}$ concentrations	Increases in asthma-related hospital admissions and ED visits in children, and all ages combined in studies conducted in the U.S. and Canada.	Section 5.1.2.1.1 Section 5.1.2.1.2	7.9−12.9 μg/m^3 7.1−19.2 μg/m^3
Epidemiologic evidence from copollutant models provides some support for an independent $PM_{2.5}$ association	Expanded examination of potential copollutant confounding for asthma-related hospital admissions and ED visits in recent studies, with evidence that associations remain robust in models with gaseous pollutants. No studies provide copollutant model results with $PM_{10-2.5}$. When reported, correlations with gaseous copollutants were primarily in the low to moderate range ($r < 0.7$).	Section 5.1.10.1	
Coherence in epidemiologic studies across the continuum of effects	Panel studies in children with asthma provide support for asthma exacerbation in children with consistent associations for respiratory symptoms and medication use, and lung function decrements. Less consistent evidence for pulmonary inflammation.	Section 5.1.2.2 Section 0 Section 5.1.2.4	
Lack of evidence from controlled human exposure studies	In adults with asthma, most measures of lung function are unaffected. There is a lack of evidence for pulmonary inflammation.	Section 0 Section 0 Urch et al. (2010)	64 μg/m^3
Some evidence from toxicological studies at relevant concentrations	Most studies show enhancement of allergic inflammation, other allergic responses, or airway remodeling in animal model of allergic airway disease.	Section 5.1.2.4.2 Harkema et al. (2009) Wagner et al. (2012)	356−596 μg/m^3
Biological plausibility	Evidence from animal toxicological studies provides biological plausibility for epidemiologic findings for exacerbation of allergic asthma, the most common asthma phenotype in children.		

Table 5-18 (Continued): Summary of evidence for a likely to be causal relationship between short term $PM_{2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Exacerbation of COPD			
Consistent epidemiologic evidence from multiple, high-quality studies at relevant $PM_{2.5}$ concentrations	Increases in COPD-related hospital admissions and ED visits in studies conducted in the U.S. and Canada.	Section 5.1.4.1.1 Section 5.1.4.1.2	7.7−18.0 µg/m^3 7.1−19.2 µg/m^3
Epidemiologic evidence from a limited number of copollutant models provide some support for an independent $PM_{2.5}$ association	Limited examination of potential copollutant confounding for COPD-related hospital admissions and ED visits, with evidence that associations remain robust in models with gaseous pollutants. Limited information is available regarding models with $PM_{10-2.5}$. When reported, correlations with gaseous copollutants were primarily in the low to moderate range ($r < 0.7$).	Section 5.1.10.1	
Some coherence in epidemiologic studies across the continuum of effects	Panel studies in adults with COPD provide support for COPD exacerbation with consistent evidence of increased eNO in response to short-term $PM_{2.5}$ exposure. Less consistent evidence for respiratory symptoms and lung function.	Section 5.1.4.2 Section 5.1.4.3 Section 5.1.4.4	
Limited evidence from a controlled human exposure study and animal toxicological studies at relevant concentrations	Lung injury, inflammation and decrements in lung function are observed.	Section 5.1.4.3 Section 5.1.4.4	171−1,200 µg/m^3
Biological plausibility	Evidence from animal toxicological studies provides biological plausibility for epidemiologic findings for COPD.		
Respiratory mortality			
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{2.5}$ concentrations	Consistent evidence of increases in mortality in response to short-term $PM_{2.5}$ exposure in multicity studies in the U.S. and Canada. Evidence of immediate effects (lag 0 to 1 days), and some recent evidence of prolonged effects (lags >2 days).	Section 5.1.9	7.9−19.9 µg/m³
Epidemiologic evidence from a limited number of copollutant models provide some support for an independent $PM_{2.5}$ association	Potential copollutant confounding is examined in a limited number of studies with some evidence that associations remain robust in models with gaseous pollutants and $PM_{10-2.5}$.	Section 5.1.10.1	

Table 5-18 (Continued): Summary of evidence for a likely to be causal relationship between short term $PM_{2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Some coherence with underlying causes of mortality	COPD and respiratory infection evidence provide coherence.		
Other respiratory endpoints			
Epidemiologic studies provide some evidence of an association with respiratory infection and with consistent positive associations when examining combined respiratory-related diseases	Generally positive associations in hospital admissions and ED visits for combinations of respiratory infections; with more limited and inconsistent evidence for specific respiratory infections, such as pneumonia.	Section 5.1.5.1 Section 5.1.5.2	9.8−19.2 μg/m^3 12.9−14.1 μg/m^3
	Increases in hospital admissions and ED visits for combined respiratory-related diseases in multicity studies, with expanded evidence for effects in older adults. Supporting evidence from other multicity studies as well as single city studies in children, adults, older adults, and people of all ages.	Section 5.1.6.1 Section 5.1.6.2	9.6−19.4 μg/m^3 7.1−19.2 μg/m^3
Limited evaluation of confounding by copollutants	Potential copollutant confounding remains unexamined in studies of respiratory infection	Section 5.1.10.1	
	Potential copollutant confounding is examined in a limited number studies, with evidence that associations generally remain robust in models with gaseous pollutants and $PM_{10-2.5}$.	Section 5.1.10.1	
Limited evidence from toxicological studies at relevant concentrations	Results show altered host defense and greater susceptibility to bacterial infection.	Zelikoff et al. (2003)	100−250 μg/m^3
Inconsistent epidemiologic evidence from studies of respiratory effects in healthy populations and allergy exacerbation	Short-term $PM_{2.5}$ exposures are inconsistently related to respiratory effects in panel studies of healthy adults. A limited number of panel studies in healthy children provide some evidence of an association with respiratory effects.	Section 5.1.7.1	
	Inconsistent increases in physician visits for allergic diseases and self-reported allergies across a limited number of studies.	Section 5.1.3	
Inconsistent evidence from controlled human exposure studies	Evidence is inconsistent for decrements in lung function and pulmonary inflammation.	Section 5.1.7.2	90−234 μg/m^3

Table 5-18 (Continued): Summary of evidence for a likely to be causal relationship between short term $PM_{2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Some evidence from toxicological studies at relevant concentrations	Results show pulmonary injury, oxidative stress, inflammation, morphologic changes, and allergic sensitization, but not in every study. Responses tend to be more robust following multiday exposures. Evidence for irritant responses (changes in respiratory rate and lung volumes) is more consistent.	Section 5.1.7.3	48−343 μg/m^3

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

Epidemiologic evidence is also expanded for COPD-related hospital admissions and ED visits. The 2009 PM ISA described consistent associations in most of those studies conducted in the U.S. or Canada. Additional U.S. analyses of the Medicare population provide supporting evidence, as do many multicity U.S. and Canadian studies. However, many studies of single cities do not indicate associations. Although recent studies add inconsistent findings, the overall evidence links recent COPD hospital admission and ED visits to short-term $PM_{2.5}$ exposures. A common uncertainty across the studies is the lack of examination of copollutants to assess the potential for confounding and compare to previous findings showing attenuation of the $PM_{2.5}$ associations with adjustment for NO_2. However, recent observations of $PM_{2.5}$-related increases in COPD symptoms, medication use, pulmonary inflammation, and decreases in lung function in epidemiologic studies support and add coherence for the hospital admission and ED visits studies. Results of controlled human exposure and animal toxicological studies show decrements in lung function, pulmonary inflammation, and lung injury, providing coherence with and biological plausibility for epidemiologic findings.

Studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) consistently observed associations between $PM_{2.5}$ concentrations and hospital admissions or ED visits for respiratory infections, which often encompassed multiple individual respiratory infections, but not for pneumonia alone. Recent studies expand findings but are not consistent with the results of older studies since the respiratory infection-related outcomes examined were heterogeneous. Many studies of respiratory infection did not examine any copollutants, making it unclear whether $PM_{2.5}$ associations are independent of copollutants. Results from an animal toxicological study demonstrate biological plausibility by showing altered host defense and greater susceptibility to bacterial infection as a result of short-term $PM_{2.5}$ exposure.

Studies of combined respiratory-related hospital admissions and ED visits examine groups of specific diseases or examine all respiratory-related diseases. Associations are seen in children, people of all ages, and older adults from single-city studies and in people of all ages in multicity studies. Studies of respiratory mortality also report associations in single and multicity studies, although confidence intervals are sometimes wide, as reflected by the small percentage of deaths that are due to respiratory mortality (~9%) (NHLBI, 2017). Potential copollutant confounding is examined in a few studies of aggregated respiratory condition and respiratory mortality and while there is some evidence indicating that associations remain robust in models with gaseous pollutants or $PM_{10-2.5}$, uncertainty remains.

In epidemiologic studies in healthy populations, changes in lung function and pulmonary inflammation are observed, but changes tend to be transient and copollutant confounding is inadequately examined. Controlled human exposure and animal toxicological studies provide evidence for lung function decrements and pulmonary inflammation, as well as for pulmonary injury, oxidative stress, morphologic changes, and allergic sensitization. However, effects were not observed in every study.

The strongest evidence of an effect of short-term $PM_{2.5}$ exposure on respiratory effects is provided by epidemiologic studies of asthma and COPD exacerbation. While animal toxicological studies provide biological plausibility for these findings, some uncertainty remains with respect to the independence of $PM_{2.5}$ effects. **Overall, the collective evidence is sufficient to conclude that a causal relationship is likely to exist between short-term $PM_{2.5}$ exposure and respiratory effects.**

5.2 Long-Term Exposure $PM_{2.5}$ Exposure and Respiratory Effects

The 2009 PM ISA concluded that a causal relationship is likely to exist between long-term $PM_{2.5}$ exposure and respiratory effects (U.S. EPA, 2009).[57] This conclusion was based mainly on epidemiologic evidence demonstrating associations between long-term $PM_{2.5}$ exposure and changes in lung function or lung function growth rate in children. Biological plausibility was provided by a single animal toxicological study involving pre- and post-natal exposure to $PM_{2.5}$ CAPs which found impaired lung development. Epidemiologic evidence for associations between long-term $PM_{2.5}$ exposure and other respiratory outcomes such as the development of asthma, the development of allergic disease, the development of COPD, respiratory infection, and the severity of disease was limited, both in the number of studies available and the consistency of the results. In an animal toxicological study, long-term exposure to $PM_{2.5}$ CAPs also led to morphological changes in nasal airways of healthy animals. Additional animal toxicological studies involved exposure to mixtures, such as motor vehicle exhaust and woodsmoke, and effects were not attributed to the particulate or gaseous components of the mixture.

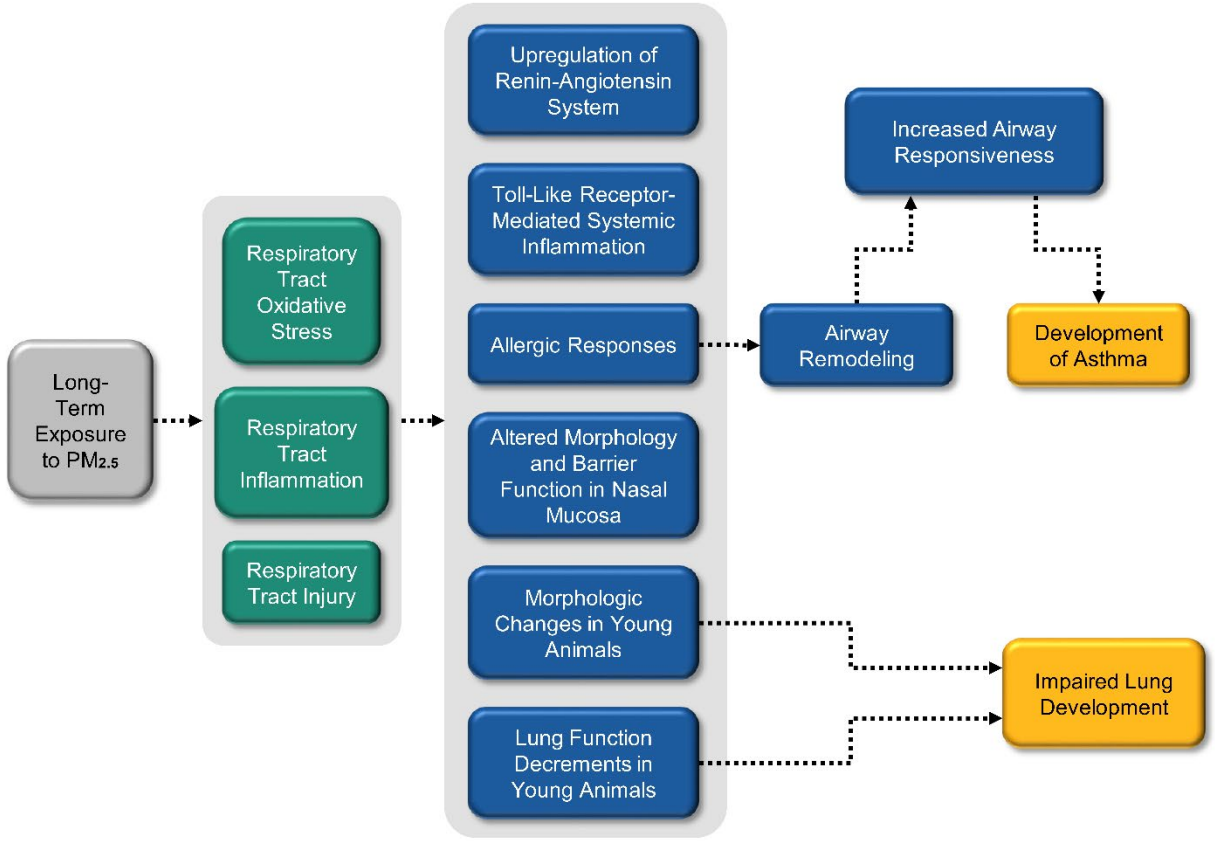
[57] As detailed in the Preface, risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations unless otherwise noted.

Recent evidence continues to link long-term exposure to $PM_{2.5}$ and reduced lung development in children and supports $PM_{2.5}$-related acceleration of lung function decline in adults (Section 5.2.2). The recent body of literature enhances the limited evidence base, providing further evidence that long-term exposure to $PM_{2.5}$ is associated with asthma development in children (Section 5.2.3) and COPD development in adults (Section 5.2.5). Epidemiologic evidence for the development of allergic disease (Section 5.2.4), respiratory infection (Section 5.2.6), and severity of disease (Section 5.2.7) is inconsistent. Recent animal toxicological studies provide evidence for respiratory effects in healthy populations (Section 5.2.8) and animal models of cardiovascular disease (Section 5.2.9), including pulmonary oxidative stress and inflammation. Studies focusing on the nasal airways find inflammation and morphologic changes (Section 5.2.8). The epidemiologic literature provides evidence for respiratory mortality in relationship to long-term $PM_{2.5}$ exposure (Section 5.2.10) and examines the relationship between the decline in $PM_{2.5}$ levels and metrics of respiratory health (Section 5.2.11). Findings that improved respiratory health in children are linked to decreased $PM_{2.5}$ concentrations add to the evidence base linking long-term $PM_{2.5}$ exposure and respiratory effects. However, uncertainty with respect to copollutant confounding remains.

5.2.1 Biological Plausibility

This section describes biological pathways that potentially underlie respiratory health effects resulting from long-term exposure to $PM_{2.5}$. Figure 5-27 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that lead to downstream events observed in epidemiologic studies. This discussion of "how" long-term exposure to $PM_{2.5}$ may lead to respiratory health effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 0.

Once $PM_{2.5}$ deposits in the respiratory tract, it may be retained, cleared, or solubilized (see CHAPTER 4). Insoluble and soluble components of $PM_{2.5}$ may interact with respiratory tract cells, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate reactive oxygen species (ROS) and this capacity is termed "oxidative potential." Furthermore, respiratory tract cells may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, insoluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see CHAPTER 4). Immune system responses due to the presence of particles in the interstitial space may contribute to respiratory health effects.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, whereas the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 5-27 Potential biological pathways for respiratory effects following long-term $PM_{2.5}$ exposure.

Evidence that long-term exposure to $PM_{2.5}$ may affect the respiratory tract generally informs one proposed pathway (Figure 5-27). It begins with injury, oxidative stress, and inflammation in the respiratory tract, as demonstrated by animal toxicological studies. These responses, which are difficult to disentangle, were also observed in some studies of short-term exposure to $PM_{2.5}$ (Figure 5-1). Persistent or intermittent exposure to $PM_{2.5}$ over months to years may lead to cumulative or chronic effects, including the development of asthma or impaired lung development, as measured by decrements in lung function growth.

Inhalation of CAPs resulted in the upregulation of the renin-angiotensin system (RAS), as indicated by an increase in mRNA and protein levels of angiotensin receptor Type 1, in rodent lung tissue

(Aztatzi-Aguilar et al., 2015). Angiotensin receptor Type 1 mediates the effects of angiotensin II, which is a potent vasoconstrictor and mediator in the vasculature. This response was accompanied by upregulation of heme oxygenase-1, an antioxidant enzyme induced in response to oxidative stress. Whether upregulation of the RAS was mediated by inflammation or oxidative stress is not clear. The SNS and the RAS are known to interact in a positive feedback fashion (Section 8.1.2) with important ramifications in the cardiovascular system. But, there is no evidence that long-term exposure to $PM_{2.5}$ leads to activation of sensory nerves or to modulation of ANS responses, as was observed in the case of short-term exposure to $PM_{2.5}$ (Figure 5-1). Thus, there is no evidence to support a relationship between activation of sensory nerves and changes in the RAS following long-term exposure to $PM_{2.5}$.

Some animal toxicological studies shed light on specific types of inflammation such as Th1 and Th2 innate immunity. Long-term inhalation of CAPs increased levels of oxidized phospholipids in the BALF (Deiuliis et al., 2012; Kampfrath et al., 2011). Specific macrophage and T-cell subtypes were also increased in lung tissue. These results are consistent with the known role of oxidized phospholipids in activating the Toll-like Receptor (TLR4) system. The TLR4 system stimulates macrophages to release cytokines that recruit and activate T cells. This response is a proinflammatory Th1 innate immune response capable of transmitting cell signals to the systemic circulation, leading to systemic inflammation (see Section 6.2.1). Th2 innate immune responses were also demonstrated following inhalation of $PM_{2.5}$. Long-term exposure to diesel exhaust particles (DEPs) resulted in increased levels of Th2 cytokines in BALF (Kim et al., 2016a). This response was accompanied by methacholine-induced changes in enhanced pause (Penh), which may indicate an increase in airway responsiveness. These changes are consistent with the development of an allergic asthmatic phenotype and possibly underlie epidemiologic findings linking exposure to $PM_{2.5}$ and the development of asthma (Section 5.2.3).

Other animal toxicological studies focused on respiratory responses in a specific region (e.g., the nose) or in the context of a specific disease state (e.g., cardiovascular disease) or lifestage (e.g., young animals). Oxidative stress, injury, inflammation, and morphologic changes were demonstrated in nasal mucosa following long-term exposure to $PM_{2.5}$ (Guo et al., 2017);(Guo et al., 2017; Ramanathan et al., 2017). Findings of increased malondialdehyde, cytokines, numbers of eosinophils and neutrophils, markers of eosinophil and neutrophil activation, as well as nasal epithelial necrosis, increased septal thickness, and sinonasal epithelial cell barrier dysfunction were reported. Inflammatory responses, such as upregulation of cytokine mRNA and monocytic infiltration in the lung, were found in two animal models of cardiovascular disease following CAPs exposure (Ying et al., 2015; Xu et al., 2012). Experimental studies in young animals exposed to $PM_{2.5}$ also demonstrated oxidative stress-related changes in lungs following pre- and post-natal exposures (Song et al., 2017) and secretory changes in nasal mucosa following neonatal exposure (Pires-Neto et al., 2006). Further, inhalation of CAPs in the pre- and post-natal period resulted in decreased lung function (i.e., decreased inspiratory and expiratory volumes) and altered lung morphology (i.e., decreased alveolar surface to volume ratio) (Mauad et al., 2008). These changes reflect impaired lung development likely due to incomplete alveolarization and the enlargement

of air spaces as a result of exposure to $PM_{2.5}$. They provide plausibility for decrements in lung function growth seen in epidemiologic studies (Section 5.2.2).

As described here, there is one main pathway, with many branches, by which long-term exposure to $PM_{2.5}$ could lead to respiratory health effects. It involves respiratory tract injury, inflammation, and oxidative stress as initial events. There is evidence of Th1 and Th2 innate immune system activation. The latter response, indicating the development of an allergic phenotype, may lead to increases in airway responsiveness, which are linked to the development of asthma. Inflammatory changes in the upper respiratory tract (i.e., the nose) of adult animals likely triggered the observed morphologic changes and barrier dysfunction. Respiratory tract inflammation may also lead to morphologic changes and lung function decrements in young animals, which are linked to impaired lung development. The multibranched pathway described here provides biological plausibility for epidemiologic evidence of respiratory health effects and will be used to inform a causality determination, which is discussed later in the chapter (Section 5.2.13).

In addition, evidence for Type 1 innate immune system activation in the respiratory tract provides a link to systemic inflammation resulting from long-term exposure to $PM_{2.5}$ (Section 6.2.1). This pathway may contribute to extrapulmonary effects following inhalation of $PM_{2.5}$.

5.2.2 Lung Function and Development

In the 2009 PM ISA (U.S. EPA, 2009), the strongest evidence for a relationship between long-term $PM_{2.5}$ exposure and respiratory effects was provided by epidemiologic studies examining lung function or lung function growth rate in children. Changes in lung function over time in children are indicative of lung development. In adults, lung function measurements may provide an indicator of declining lung function over time. Epidemiologic evidence supported an association between long-term $PM_{2.5}$ exposure and reduced lung development in children in different cohorts and locations. An animal toxicological study provided support for the epidemiologic evidence since pre- and post-natal exposure to ambient levels of urban particles was found to impair mouse lung development. Recent studies provide further support demonstrating a relationship between long-term exposure to $PM_{2.5}$ and reduced lung development in children as well as the possible acceleration of lung function decline in adults.

5.2.2.1 Lung Development

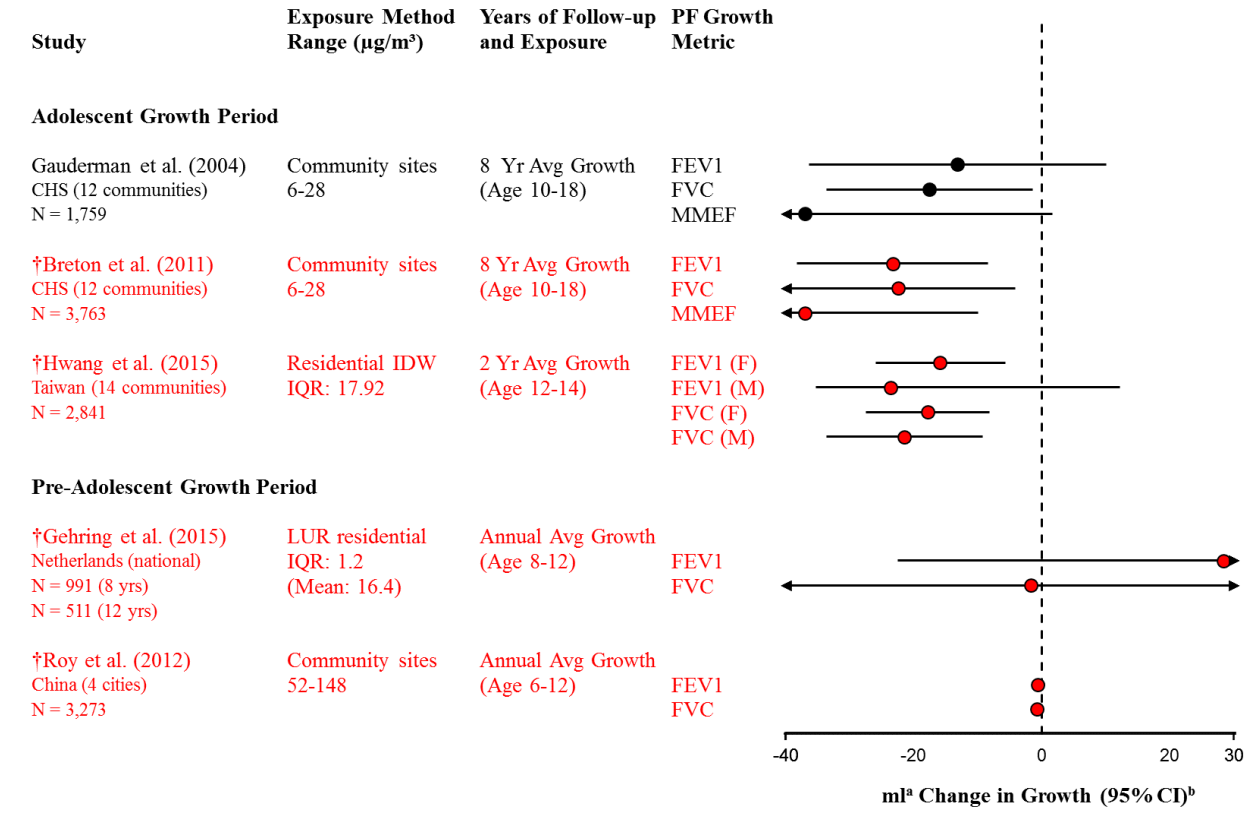
Lung development occurs from the fetal period through early adulthood, comprising a long window of potential vulnerability to environmental stressors, such as PM (Stanojevic et al., 2008; Zeman and Bennett, 2006; Thurlbeck, 1982). Lung function measures capture the cumulative effects of pulmonary growth, damage, and repair (Wang et al., 1993). As such, measures of lung function are

effective indicators of pulmonary health, and changes in lung function over time are indicative of lung development.

5.2.2.1.1 Epidemiologic Studies

Epidemiologic studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) indicated that long-term exposure to $PM_{2.5}$ is associated with decrements in lung development in schoolchildren. Key evidence informing the relationship came from analyses of the Children's Health Study (CHS), a prospective cohort study of children in 12 southern California communities. Two studies of this cohort that were reviewed in the 2004 PM AQCD (U.S. EPA, 2009) observed decrements in annual pulmonary growth rates for all of the examined lung function measures (FVC, FEV_1, MMEF, and FEF_{75}) in relation to long-term in $PM_{2.5}$ exposure (Gauderman et al., 2002; Gauderman et al., 2000). Gauderman et al. (2000) examined lung function growth over a 4-year period for three age cohorts within CHS, including 4th graders, 7th graders, and 10th graders. The authors consistently reported the strongest associations, in magnitude and precision, in 4th graders and the weakest associations in 10th graders for all lung development metrics. A study reviewed in the 2009 PM ISA expanded on the previous CHS analyses, following children for 8 years (Gauderman et al., 2004). Gauderman et al. (2004) reported that PM-related deficits in average lung development between ages 10 and 18 years resulted in clinically important deficits in attained lung function at age 18 (Gauderman et al., 2004).

Recent data from studies based in the U.S. and Asia continue to provide evidence for $PM_{2.5}$-related decrements in lung development in children (Figure 5-28). The focus of this section is on longitudinal epidemiologic studies conducted in cohorts in diverse locations with a wide range of ambient $PM_{2.5}$ concentrations. Study-specific details, air quality characteristics, and select results from these studies are highlighted in Table 5-19. The CHS is further evaluated in recent studies that provide supporting evidence in multiple cohorts recruited in 1993 and 1996 and followed through 2007 (Gauderman et al., 2015; Breton et al., 2011). Recent results from the CHS not only corroborate previous results, but they also indicate improvements in lung development in association with declining $PM_{2.5}$ concentrations (Gauderman et al., 2015) (Section 5.2.11). Results from the CHS indicate that long-term $PM_{2.5}$ exposure may impact lung development during adolescence (age 10−18 years), a period of rapid, nonlinear growth (Wang et al., 1993). Associations during adolescence also are supported in a multicity cohort in Taiwan (Hwang et al., 2015). However, mean $PM_{2.5}$ concentrations in this study were notably higher than those in the CHS studies. As examined in a limited number of recent studies, evidence is less clear for effects during the linear growth period of preadolescence. $PM_{2.5}$ was associated with reduced lung development in a cohort in China that included children ages 6−12 years at baseline (Roy et al., 2012). However, no association was observed between $PM_{2.5}$ and lung development in the PIAMA cohort between ages 8 and 12 years (Gehring et al., 2015a). Information on critical periods of exposure is limited, as most studies examined concurrent exposure. In the PIAMA cohort, lung development was not associated with $PM_{2.5}$ exposure estimated for the concurrent period or birth year (Gehring et al., 2015a).



CHS = Children's Health Study, CI = confidence interval, F = female, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, IDW = inverse distance weighting, IQR = interquartile range, LUR = land use regression, M = male, MMEF = maximum midexpiratory flow.

[a]FEV_1 and FVC are measured in ml, MMEF is measured in ml/s.

[b]Effect estimates are standardized to a 5 µg/m^3 increase in $PM_{2.5}$.

Note: †Studies published since the 2009 PM ISA. Black text/circles = studies evaluated in the 2009 PM ISA. Red text/circles = studies published since the completion of the 2009 PM ISA. Corresponding quantitative results and study details are reported in Table 5-19.

Figure 5-28 Longitudinal repeated measure studies of $PM_{2.5}$ and lung development.

Table 5-19 Associations of $PM_{2.5}$ with lung development in children from longitudinal studies with repeated measures.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI[a]	Copollutant Examination
Gauderman et al. (2004) 12 southern California communities 1993−2000	CHS 1993 cohort n = 1,759 Followed ages 10−18 yr 10% loss to follow up per yr	One monitor in each of 12 communities Children's homes and schools in same neighborhoods as monitoring sites (Navidi et al., 1999; Navidi et al., 1994). Annual avg, concurrent exposure Range of means across communities: 6−28 μg/m^3	Change in 8-yr average growth: FVC (ml): −13.2 (−36.4, 10.1) FEV_1 (ml): −17.5 (−33.6, −1.4) MMEF (ml/s): −37.0 (-75.8, 1.7)	Correlation (*r*): 0.33 O_3, 0.79 NO_2, 0.87 Acid Vapor Copollutant models with: NA
†Breton et al. (2011) 12 southern California communities 1993 or 1996−2000	CHS 1993 and 1996 cohorts N = 2,106 Followed ages 10−18 yr 10% loss to follow up per yr (No evidence of relation between participation and baseline lung function or air pollution exposure)	One monitor in each of 12 communities Children's homes and schools in same neighborhoods as monitoring sites (Navidi et al., 1999; Navidi et al., 1994). Annual avg, concurrent exposure Range of means across communities: 6−28 μg/m^3	Change in 8-yr average growth: FVC (ml): −23.3 (−38.3, −8.4) FEV_1 (ml): −22.5 (−40.7, −4.2) MMEF (ml/s): −37.0 (−64.1, −10.0)	Correlation (*r*): 0.79 NO_2 Copollutant models with: NA

Table 5-19 (Continued): Associations of $PM_{2.5}$ with lung development in children from longitudinal studies with repeated measures.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI[a]	Copollutant Examination
†Gauderman et al. (2015) Five southern California communities 1994−2011	CHS 1994−1998, 1997−2001, and 2007−2011 cohorts N = 2,120 Followed ages 11−15 yr 25% loss to follow up. (No evidence of relation between participation and baseline lung function or air pollution exposure)	One monitor in each of five communities. 4-yr avg Range of means across communities: 21.3−31.5 μg/m^3 in 1994−1997 and 11.9−17.8 μg/m^3 in 2007−2010	Change in 4-yr average growth per decrease in $PM_{2.5}$[b]: FEV_1 (ml): 26.0 (6.8, 45.2) FVC (ml): 50.4 (26.1, 74.6)	Correlation (*r*): 0.82 NO_2, 0.39 O_3 Copollutant models with: NA
†Gehring et al. (2015a) The Netherlands 1996−2010	PIAMA N = 3,702 Followed age 8−12 yr 15% original cohort had data at age 8 and 12 yr	Annual avg estimated at birth residence (birth year) and current address (at time of questionnaire) using LUR. LOOCV R^2 = 0.61. Mean: 16.4 μg/m^3 75th: 25.3 μg/m^3 95th: 26.4 μg/m^3	Change in annual average growth: FVC (ml): −1.7 (−41.3, 37.9) FEV_1 (ml): 28.3 (−22.5, 79.2)	Correlation (*r*): 0.73 NO_2 (at birth address) Copollutant models with: NA
†Hwang et al. (2015) 14 Taiwan communities	TCHS N = 2,941 Followed age 12−14 yr 8.6% loss to follow up	14 monitors combined by IDW to obtain ambient $PM_{2.5}$ concentration estimates outside each home. Annual avg, concurrent exposure Mean: 34.5 μg/m^3 75th: 43.8 μg/m^3	Change in 2-yr average growth: Boys FEV_1 (ml): −23.7 (−35.3, 12.2) FVC (ml): −21.5 (−33.7, −9.2) Girls FEV_1 (ml): −15.9 (−26.0, −5.7) FVC (ml): −17.8 (−27.5, −8.2)	Correlation (*r*): NO_2: 0.25 NO_2, 0.0$_3$ CO, 0.69 SO_2 Copollutant models with: NO_2 and CO

Table 5-19 (Continued): Associations of $PM_{2.5}$ with lung development in children from longitudinal studies with repeated measures.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI[a]	Copollutant Examination
†Roy et al. (2012) Four China cities	N = 3,273 Followed 3 yr from age 6−12 yr 24% with ≥3 measures. Sensitivity analyses show results not biased due to loss to follow-up	School outdoor monitors 3-yr avg and 3-mo avg concurrent exposure Mean: 148 μg/m^3 urban Guangzhou 52 μg/m^3 suburban Wuhan	Change in annual average growth: FEV_1 (ml): −0.7 (−0.9, −0.5) FVC (ml): −0.7 (−1.0, −0.5)	Correlation (*r*): NA Copollutant models with: NA

CHS = Children's Health Study, CI = confidence interval, CO = carbon monoxide, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, IDW = inverse distance weighting, IQR = interquartile range, LOOCV = leave one out cross-validation, LUR = land use regression, M = male, MMEF = maximum midexpiratory flow, NO_2 = nitrogen dioxide, NR = not reported, PIAMA = Prevention and Incidence of Asthma and Mite Allergy, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 μm, *r* = correlation coefficient, SD = standard deviation, SO_2 = sulfur dioxide, TCHS = Taiwan Children's Health Study.

[a]Effect estimates are standardized to a 5 μg/m^3 increase in $PM_{2.5}$.

[b]Effect estimates are standardized to a 5 μg/m^3 decrease in $PM_{2.5}$.

†Studies published since the 2009 PM ISA.

1

Copollutant Confounding and Other Sources of Uncertainty

Due to a limited number of studies that examined potential copollutant confounding, uncertainty remains in distinguishing an independent effect of long-term $PM_{2.5}$ exposure on lung development. In the only study to report results from copollutant models, Hwang et al. (2015) observed that $PM_{2.5}$-associated decrements in lung development persisted in copollutant models that included NO_2 or CO. NO_2 and CO were weakly correlated with $PM_{2.5}$ (r = 0.25 and 0.03, respectively). Other studies that reported copollutant correlations observed moderate to high correlations for most pollutants (NO_2: r = 0.73−0.87, SO_2: r = 0.69, O_3: r = 0.33−0.39; Table 5-19).

Because results for lung development are based on changes in lung function measured over time, loss to follow up and the method of lung function assessment could be additional sources of error or bias. However, neither is indicated to have systematically influenced the evidence for $PM_{2.5}$ associations. As detailed in Table 5-19, attrition of 10% or less was reported in some studies (Hwang et al., 2015; Breton et al., 2011). Others reported higher loss to follow-up (Gauderman et al., 2015; Gehring et al., 2015a; Roy et al., 2012), but reported similar characteristics between participants and nonparticipants, or no relation between participation and either baseline lung function or exposure to air pollution. Additionally, in a study that had changes in the device used to measure lung function, $PM_{2.5}$ associations were robust to adjustment for a factor representing the difference between devices (Gauderman et al., 2015).

Finally, the CHS studies in this section rely on exposure estimates from single fixed-site monitors within each community, which may result in misclassification of exposure. However, analyses of some individual CHS communities show low-to-moderate spatial heterogeneity of ambient $PM_{2.5}$ concentrations. In Long Beach, CA, $PM_{2.5}$ concentrations were moderately to highly correlated (r = 0.67−0.91) across four sites within 6.4 km of each other, including two schools attended by CHS cohort subjects (Krudysz et al., 2008). In Riverside, CA, $PM_{2.5}$ concentrations at a fixed-site monitor explained 96% of the variance in concentrations outside the homes of children with asthma (Ducret-Stich et al., 2012). Further, an analysis of multiple CHS communities described monitoring sites in some but not all communities as well representing the range of residential and school outdoor $PM_{2.5}$ concentrations of subjects. Thus, long-term concentrations measured at fixed-site monitors are unlikely to introduce major exposure measurement error.

5.2.2.1.2 Animal Toxicological Studies

The 2009 PM ISA evaluated studies that examined lung development. These studies involved early life exposure to ambient levels of urban particles in Sao Paulo, Brazil (Mauad et al., 2008; Pires-Neto et al., 2006). Urban air PM mainly consisted of $PM_{2.5}$, but it also contained some PM_{10}; other ambient pollutants were also present. Control mice were exposed to filtered urban air, which contained greatly reduced concentrations of PM. Mauad et al. (2008) found decreased inspiratory and expiratory

volumes in mice exposed both pre- and postnatally compared to control animals. Alveolar surface to volume ratio was also decreased in animals exposed during both the pre- and post-natal periods. No changes in lung function or morphology were observed in animals exposed only prenatally or only postnatally. These results reflect altered lung development resulting from $PM_{2.5}$ exposure. Pires-Neto et al. (2006) found secretory changes in the nasal cavity of neonatal mice exposed for 5 months to urban PM from Sao Paulo Brazil. Specifically, production of acidic mucosubstances was increased, potentially representing impaired respiratory defense mechanisms. Interpretation of effects due to long-term urban air exposure is complicated by the presence of $PM_{10-2.5}$. Recently, Song et al. (2017) demonstrated changes in lung molecular clock gene expression resulting from pre- and post-natal exposure of rats to ambient levels of urban particles in Beijing, China. Control rats were exposed to filtered urban air, which contained greatly reduced concentrations of PM. In addition, altered lung morphology and oxidative stress were observed in rat pups and in pregnant rats. These findings are discussed in Section 9.3.3.

5.2.2.2 Lung Function

The relationship between long-term $PM_{2.5}$ exposure and lung function in children and in adults was examined in numerous epidemiologic studies.

5.2.2.2.1 Children

In addition to lung development, a number of studies examine the effects of long-term $PM_{2.5}$ exposure in relation to attained pulmonary function at a given point in time. Epidemiologic studies reviewed in the 2009 PM ISA (U.S. EPA, 2009) indicated that long-term exposure to $PM_{2.5}$ is associated with decrements in attained lung function in children. Notably, in the CHS analysis described in Section 5.2.2.1.1, Gauderman et al. (2004) observed that 18-year-olds had increased risk of clinically low FEV_1 measurements at age 18 in communities with higher $PM_{2.5}$ concentrations. However, unlike the results reported for lung development, the attained lung function estimates did not include adjustment for potential confounders, introducing uncertainty into the interpretation of the results. European birth cohort studies also generally reported evidence of an effect on lung function metrics when examining long-term $PM_{2.5}$ exposure (Oftedal et al., 2008; Schikowski et al., 2005; Ackermann-Liebrich et al., 1997), but results were not entirely consistent (Gotschi et al., 2008). None of the lung function studies reviewed in the 2009 PM ISA examined copollutant models. Recent studies available for review add to the existing evidence supporting an association between long-term exposure to $PM_{2.5}$ and decreased lung function in children. These studies examine a variety of exposure periods, exposure methods, cohorts, locations, and exposure levels. Additionally, a limited number of copollutant models indicate that the observed $PM_{2.5}$ effect may be independent of NO_2, CO, and O_3 exposures. Study-specific details, air quality characteristics, and select results from these studies are presented in Table 5-20.

Table 5-20 Associations of $PM_{2.5}$ with lung function in children and adults.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI[a]	Copollutant Examination
Children				
†Gehring et al. (2013) Germany, Sweden, the U.K., and the Netherlands	ESCAPE Project: BAMSE, GINIplus, LISAplus, MAAS, and PIAMA n = 5,357 Followed to ages 6−8	Annual avg $PM_{2.5}$ concentrations estimated at birth residence (birth year) and current address (at time of lung function measurement) using LUR. LOOCV R^2 = 0.21−0.78 RMSE: 0.8−1.2 Mean: 7.8−17.4 µg/m^3	Current address exposure FEV_1 (percent diff.): −2.5 (−4.6, −0.4) FVC (percent diff.): −8.8 (−20.5, 4.5) PEF (percent diff.): −2.1 (−4.1, −0.1) FEV_1 <85% predicted (OR): 1.41 (0.74, 2.71)	Correlation (*r*): 0.75 NO_2, 0.57 NO_X, 0.50 PM_{10}, 0.58 $PM_{10-2.5}$ Copollutant models with: NO_2
†Wang et al. (2015b) The Netherlands 1996−2005	PIAMA n = 1,058 Followed to age 8 68% participation rate	Annual avg $PM_{2.5}$ concentrations estimated at current address (at time of lung function measurement) using LUR. LOOCV R^2 = 0.61 RMSE: 1.21 Median: 16.5 µg/m^3 IQR: 15.6−16.7 µg/m^3 Alternatively, dispersion models predicted $PM_{2.5}$ concentration at a 1-km × 1-km grid level. Median: 16.8 µg/m^3 IQR: 13.6−17.3 µg/m^3	Results presented graphically. LUR and dispersion model $PM_{2.5}$ estimates were associated with decreased FEV_1 and FVC, but not PEF. Associations were stronger but less precise using LUR $PM_{2.5}$ estimates.	Correlation (*r*): 0.75 NO_2 (LUR), 0.92 NO_2 (Dis.) Copollutant models with: NO_2

Table 5-20 (Continued): Associations of $PM_{2.5}$ with lung function in children and adults.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI[a]	Copollutant Examination
†Rice et al. (2015b) Massachusetts 1999–2010	Project Viva—pre-birth cohort n = 614 Followed to a mean age of 7.7 yr	Annual avg $PM_{2.5}$ concentrations for first year of life, previous year, and lifetime exposure were estimated at 10 × 10 km grid level using AOD observation data from satellite imagery. Resolved to 50 × 50 m using land use terms and assigned to participants' home addresses. 10-fold cross-validated LOOCV R^2: 0.83 First year mean: 12.1 µg/m^3 Lifetime mean: 10.7 µg/m^3 Last year mean: 9.4 µg/m^3	Last year exposure FEV_1 (ml): −60.3 (−112, −8.5) FVC (ml): −54.5 (−110, 0.5) FEV_1 <80% predicted (OR): 2.4 (1.1, 5.2) FVC <80% predicted (OR): 1.7 (0.4, 6.7)	Correlation (*r*): NA Copollutant models with: NA
†Urman et al. (2014) Southern California 2002–2008	CHS n = 1,811 Followed to ages 5–7 82% participation	One monitor in each of 12 communities Children's homes and schools in same neighborhoods as monitoring sites (Navidi et al., 1999; Navidi et al., 1994). 6-yr avg, (lifetime) exposure Range of means across communities: 6–28 µg/m^3	FEV_1 (percent diff.): −1.1 (−1.7, −0.5) FVC (percent diff.): −0.8 (−1.5, −0.2)	Correlation (*r*): 0.8 PM_{10}, 0.6 NO_2 Copollutant models with: NA
†Eenhuizen et al. (2013) The Netherlands 1996–2001	PIAMA n = 880 Followed to age 4 49% of participants had valid Rint data	Annual avg $PM_{2.5}$ concentrations estimated at current address (at time of lung function measurement) using LUR. LUR model explained 73% of $PM_{2.5}$ spatial variability. Median: 16.9 µg/m^3 IQR: 14.9–18.2 µg/m^3	Change in Rint (kPA•S•L^{-1}) 0.06 (0.02, 0.11)	Correlation (*r*): 0.93 NO_2 Copollutant models with: NA
†Gehring et al. (2015a) The Netherlands 1996–2010	PIAMA n = 3,702 Followed age 8–12 yr 15% original cohort had data at age 8 and 12 yr	Annual avg $PM_{2.5}$ concentrations estimated at current address (at time of lung function measurement) using LUR. LOOCV R^2 = 0.61. Mean: 16.4 µg/m^3 75th: 25.3 µg/m^3 95th: 26.4 µg/m^3	Current address exposure FEV_1 (percent diff.): −4.2 (−9.2, 0.8) FVC (percent diff.): −2.9 (−7.5, 1.7) FEF_{25-75} (percent diff.): −10.0 (−25.4, 6.3)	Correlation (*r*):0.73 NO_2 (at birth address) Copollutant models with: NA

Table 5-20 (Continued): Associations of $PM_{2.5}$ with lung function in children and adults.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI[a]	Copollutant Examination
Adults				
Rice et al. (2015a) Northeastern U.S. 1995−2011	Framingham Heart Study n = 4,872 Participants had at least two spirometry measurements between 1995 and 2011. Mean age was 50.4 yr (SD: 12.4)	Annual average $PM_{2.5}$ concentrations were estimated in the index year (2001) using satellite imagery to create a 10 × 10 km spatial grid across the Northeast. Estimates were resolved to residences within a 50 × 50 m grid using land use terms. 10-fold CV R^2 = 0.85 Mean: 10.8 µg/m^3 Max: 21.7 µg/m^3	Difference in annual rate of change: FEV_1 (ml/yr): −5.25 (−10.25, −0.5) FVC (ml/yr): −5.0 (−10.25, 0.25) FEV_1/FVC (percent/yr): −0.03 (−0.10, 0.05) Difference in mean lung function: FEV_1 (ml): −33.8 (−66.5, −0.8) FVC (ml): −46.8 (−84.0, −9.5) FEV_1/FVC (%): 0.0 (−0.5, 0.5)	Correlation (*r*): NA Copollutant models with: NA
Adam et al. (2015) Cohorts across Europe 1985−2009	ESCAPE project study of five European Cohorts: ECRHS, EGEA, NSHD, SALIA, and SAPALDIA. n = 7,613 Participants had two spirometry measurements. The baseline measurement was between 1985 and 1995, depending on the cohort. The follow-up measurement was between 2001 and 2010. Mean age ranged from 43.0 to 73.3 yr across cohorts.	Annual average $PM_{2.5}$ concentrations estimated using land-use regression to spatially refine estimates from city-level monitors between 2008 and 2011. Mean: 9.5−17.8 across cohorts. IQR: 1.1−7.0 across cohorts.	Difference in annual rate of change: FEV_1 (ml/yr): −0.14 (−2.26, 1.98) FVC (ml/yr): −1.37 (−4.04, 1.29) Difference in mean lung function: FEV_1 (ml): −21.14 (−56.37, 14.08) FVC (ml): −36.39 (−83.29, 10.50)	Correlation (*r*): NA Copollutant models with: NA

Table 5-20 (Continued): Associations of $PM_{2.5}$ with lung function in children and adults.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI[a]	Copollutant Examination
Adar et al. (2015) Six U.S. states 2004−2007	MESA n = 3,791 Randomly selected MESA participants completed spirometry measurements. 45−84 yr old	Time varying annual avg ambient $PM_{2.5}$ concentration based on residential history (spatio-temporal model). 1-yr avg the year prior to baseline exam. 20-yr avg for models derived from AQS estimates of PM_{10} and $PM_{2.5}/PM_{10}$ ratio. Model fit R^2 = 0.90−0.97; CV R^2 = 0.72 1-year mean: 14.2 µg/m^3 20-year mean: 22.2 µg/m^3	Difference in mean lung function: 1-yr avg FEV_1 (ml): −20 (−80, 41) FVC (ml): −59 (−132, 13) FEV_1/FVC (%): 0.2 (−0.9, 1.3) 20-yr avg FEV_1 (ml): −13 (−37, 11) FVC (ml): −6 (−35, 22) FEV_1/FVC (%): −0.3 (−0.7, 0.2)	Correlation (*r*): 0.5−0.6 NO_X, 0.7−0.9 PM_{10} Copollutant models with: NA
Boogaard et al. (2013) The Netherlands (multicity) 2008−2010	12 locations in the Netherlands N = 640 Participants had two respiratory function exams 2 yr apart (pre- and post-traffic policy-related air pollution reduction). 83% ≥30 yr old 89% ≥18 yr old	Average $PM_{2.5}$ concentrations were estimated from monitors at 12 locations that took six 1-week samples over a 6 mo period. Mean: 16.0 µg/m^3 Max: 19.4 µg/m^3	Percent change in FVC per decrease in $PM_{2.5}$[b]: 1.67 (−0.40, 3.75)	Correlation (*r*): NA Copollutant models with: NA

CHS = Children's Health Study, CI = confidence interval, CO = carbon monoxide, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, IDW = inverse distance weighting, IQR = interquartile range, LOOCV = leave one out cross-validation, LUR = land use regression, M = male, MESA = Multi-Ethnic Study of Atherosclerosis, MMEF = maximum midexpiratory flow, NO_2 = nitrogen dioxide, NR = not reported, PIAMA = Prevention and Incidence of Asthma and Mite Allergy, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, *r* = correlation coefficient, Rint = interrupter resistance, SD = standard deviation, SO_2 = sulfur dioxide, TCHS = Taiwan Children's Health Study.

[a]Effect estimates are standardized to a 5 µg/m^3 increase in $PM_{2.5}$.

[b]Effect estimates are standardized to a 5 µg/m^3 decrease in $PM_{2.5}$.

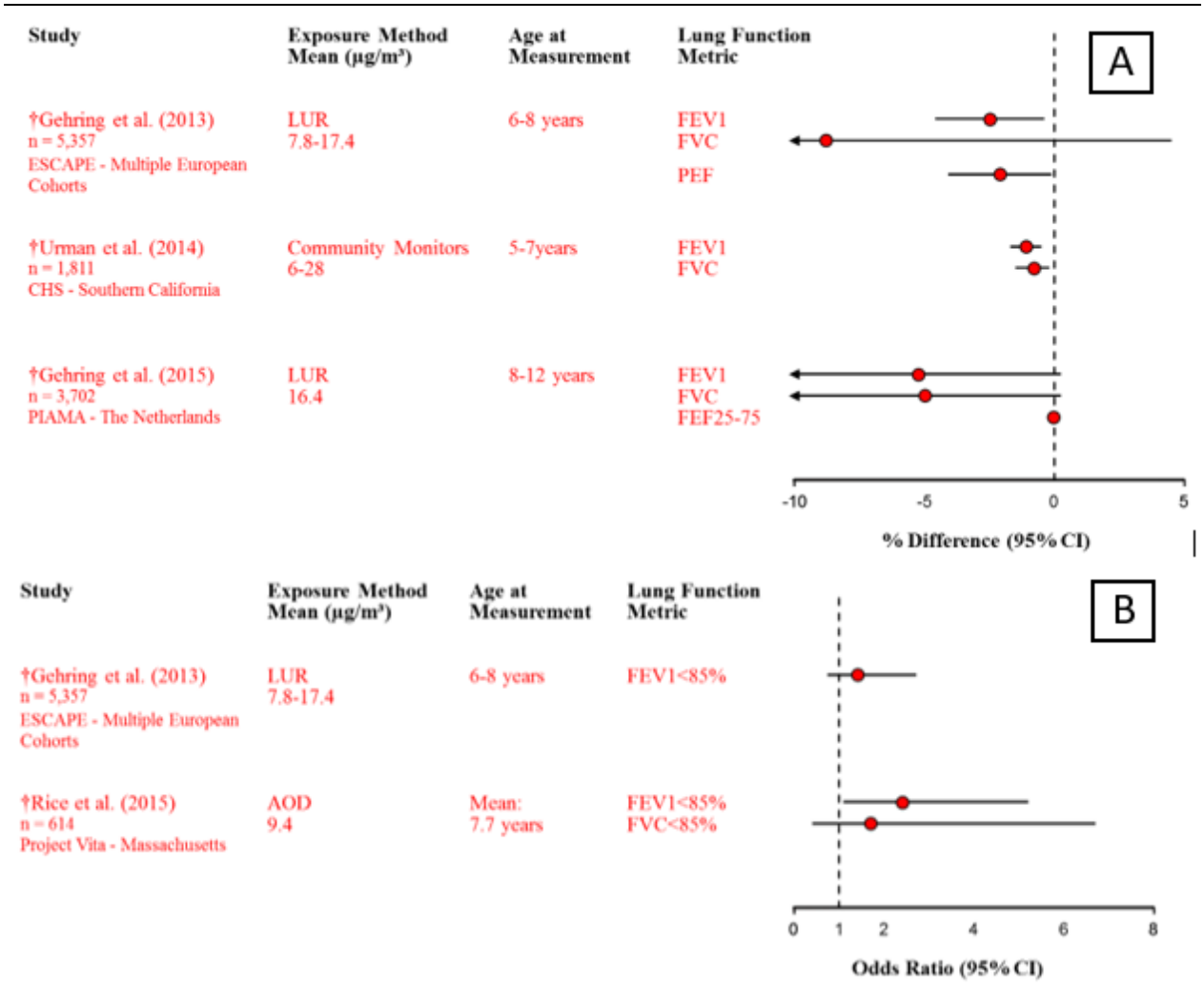
†Studies published since the 2009 PM ISA.

Recently reviewed studies provide consistent evidence that long-term exposure to $PM_{2.5}$ is associated with decreased lung function in children (Figure 5-29 and Table 5-20). Like the results from Gauderman et al. (2004), a small prebirth cohort study in Massachusetts (Rice et al., 2015b) and an ESCAPE analysis of multiple European cohorts Gehring et al. (2013) observed increased odds of clinically low FEV_1 and FVC measurements in relation to long-term $PM_{2.5}$ exposure. Associations between $PM_{2.5}$ and lung function were also observed as a measure of percent difference or absolute change in spirometry measures in the aforementioned studies (Rice et al., 2015b; Gehring et al., 2013), the CHS cohort (Urman et al., 2014), and the PIAMA cohort (Gehring et al., 2015a; Wang et al., 2015b).

The reviewed studies used an array of exposure assessment methods to produce long-term $PM_{2.5}$ estimates, including LUR models, dispersion models, hybrid models incorporating AOD observation data with land use variables, and fixed-site monitors. Associations were evident across the various exposure assignment techniques. Wang et al. (2015b) directly compared results from dispersion- and land-use regression (LUR)-modeled $PM_{2.5}$ estimates in relation to lung function metrics. The authors observed $PM_{2.5}$-related decreases in FEV_1 and FVC for both exposure assessment techniques, but noted larger but less precise (i.e., wider 95% CIs) decreases for LUR-modeled increases in $PM_{2.5}$ (quantitative results not provided; results presented graphically). These results suggest robust evidence of an association despite differences in exposure measurement error across exposure assessment methods.

Most of the reviewed studies focused on lung function in 6 to 8-year-old children. Obtaining valid spirometric lung function data is sometimes not possible in younger children. Alternatively, interrupter resistance (Rint) is a reliable technique to assess airway resistance in preschool aged children. In the PIAMA cohort, Eenhuizen et al. (2013) reported increases in Rint consistent with long-term $PM_{2.5}$ exposure estimated outside participants' birth addresses. Higher Rint was associated with lower FEV_1 levels at age 8, suggesting that Rint may be a predictor of later lung function.

A few studies examined varying windows of exposure to assess periods of potential sensitivity to PM exposure. Rice et al. (2015b) incorporated satellite-derived aerosol optical depth (AOD) observations into a land use regression model to estimate participants' exposure to ambient $PM_{2.5}$ in the first year of life, in the year prior to lung function testing, and averaged over their lifetime. The observed associations across lung function metrics were consistently stronger in magnitude, but not always precision, for $PM_{2.5}$ concentrations estimated in the year prior to examination. A similar finding was reported in the European study of cohorts for air pollution effects (ESCAPE) project analysis. Gehring et al. (2013) noted higher effect estimates for FEV_1 in relation to a 5 $\mu g/m^3$ increase in outdoor $PM_{2.5}$ concentrations estimated at current residence at the time of lung function measurement (−2.49% difference [95% CI: −4.57, −0.36]) compared to exposure assigned at the participants' birth address (−1.22% [95% CI: −3.30, 0.80]). Notably, the ESCAPE project and the prevention and incidence of asthma and mite allergy (PIAMA) cohort, discussed with regards to exposure windows in Section 5.2.3.1, use LUR models to estimate exposure after follow-up. The LUR was constructed for the cohort's current age and adjusted based on the year of lung function testing. The ratio of $PM_{2.5}$ concentration at a fixed-site monitor in the year of birth and during the year of lung function testing was used to extrapolate concentrations back to birth year at the birth residential location for each participant. Hence, changes in spatial variability between birth and the year of lung function testing were not captured. Despite the resulting uncertainty, the potentially enhanced lung-function sensitivity to $PM_{2.5}$ exposures closer to lung function examination may explain why the CHS analysis by Urman et al. (2014), which implemented a surrogate for lifetime-exposure, observed a smaller effect estimate than studies that used current address or previous year $PM_{2.5}$ estimates (Table 5-20).



AOD = aerosol optical depth, CHS = Children's Health Study, CI = confidence interval, FEF_{25-75} = forced expiratory flow at 25−75% of the pulmonary volume, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, LUR = land use regression.

Note: †Studies published since the 2009 PM ISA. Panel A depicts percent difference in lung function metrics. Panel B depicts odds of lung function metrics below normal levels (85% predicted). Red text/circles = studies published since the completion of the 2009 PM ISA. Effect estimates are standardized to a 5 µg/m^3 increase in $PM_{2.5}$. Corresponding quantitative results and study details are reported in Table 5-20.

Figure 5-29 Long-term exposure to $PM_{2.5}$ and lung function in children.

Copollutant Confounding

Several studies of pulmonary function in children provide information on potential copollutant confounding through the evaluation of two-pollutant models. These studies add to the strength of the evidence by establishing a $PM_{2.5}$ relationship with observed lung function decrements that is generally unchanged in models with other pollutants [quantitative results presented in Supplemental Material (U.S. EPA, 2018)]. $PM_{2.5}$ correlations with NO_2 ranged from 0.25 to 0.75, across studies. In studies that reported higher correlations (r = 0.75), associations between $PM_{2.5}$ and lung decrements were attenuated

but still negative in copollutant models adjusting for NO_2 (Wang et al., 2015b; Gehring et al., 2013). Meanwhile, in studies with low $PM_{2.5}$-NO_2 correlations (r = 0.25−0.33), associations were relatively unchanged in copollutant models (Chen et al., 2015a; Hwang et al., 2015). Hwang et al. (2015) and Chen et al. (2015a) also reported declines in lung function that persisted in copollutant models adjusting for CO, O_3, and SO_2. However, these studies of school-children in Taiwan lack generalizability given $PM_{2.5}$ concentrations that are much higher than studies in North America and Europe.

5.2.2.2.2 Adults

Lung function generally peaks in adults around the age of 25, and then slowly declines throughout adulthood (Götschi et al., 2008). In addition to studies of lung function in children, some studies have investigated whether long-term $PM_{2.5}$ exposure accelerates the rate of decline in lung function as adults age. A limited number of studies reviewed in the 2009 PM ISA (U.S. EPA, 2009) observed contrasting evidence of an association between long-term exposure to $PM_{2.5}$ and lung function in adults. A longitudinal study of adults from 10 European countries found that annual $PM_{2.5}$ concentrations were not associated with lung function decrements measured from two spirometry tests taken approximately 10 years apart (Götschi et al., 2008). However, $PM_{2.5}$ exposures were estimated at the end of the study period, which may have introduced bias if the pattern of spatial variability of $PM_{2.5}$ concentrations did not remain constant across cities over the 10-year study period. In contrast, cross-sectional studies reported associations between annual average $PM_{2.5}$ and mean lung function (Schikowski et al., 2005; Ackermann-Liebrich et al., 1997). A limited number of recent longitudinal and cross-sectional studies in the U.S. and Europe have reported more consistent evidence that $PM_{2.5}$ is associated with decreased lung function parameters in adults. As with past studies, lung function in these cohorts was assessed either as a measure of lung function decline over time or cross-sectionally as a single measure in time. These cross-sectional measurements are generally less informative than longitudinal studies because they do not establish a temporal relationship between the exposure and outcome of interest. Study-specific details, air quality characteristics, and select results from these studies are presented in Table 5-20.

The Framingham Heart Study examined the association between long-term exposure to $PM_{2.5}$ and longitudinal decline in lung function over a 15-year period (Rice et al., 2015a). Rice et al. (2015a) reported a 5.25 ml/year (95% CI: 0.5, 10.5) faster rate of decline in FEV_1 and a 5 ml/year (95% CI: −0.25, 10.25) faster decline in FVC per 5 μg/m^3 increase in annual average $PM_{2.5}$ concentrations in the index year. The authors also observed $PM_{2.5}$ associations with cross-sectional FEV_1 and FVC measures but did not observe evidence of associations with FEV_1/FVC in longitudinal or cross-sectional analyses. In an ESCAPE project analysis of five European cohorts, Adam et al. (2015) also reported evidence of an association between long-term exposure to $PM_{2.5}$ and lung function in adults. Lung function measurements taken approximately 10 years apart indicated that long-term $PM_{2.5}$ exposure was associated with an accelerated decrease in FVC (−1.37 ml/year [95% CI: −4.04, 1.29]), but not FEV_1 (−0.14 ml,

95% CI [−2.26, 1.98]). However, similar to Götschi et al. (2008), discussed above, $PM_{2.5}$ was estimated (2008−2011) after the two spirometry tests were conducted (1985−2010). $PM_{2.5}$ was also negatively associated with cross-sectional FEV_1 and FVC levels measured during the second exam (Adam et al., 2015). Supporting evidence of a longitudinal association between $PM_{2.5}$ concentrations and lung function in adults, Boogaard et al. (2013) examined traffic policy-related reductions in air pollution and found improvements in lung function associated with declining $PM_{2.5}$ concentrations (Section 5.2.11).

In the Multi-Ethnic Study of Atherosclerosis (MESA), the association between long-term exposure to $PM_{2.5}$ and lung function was examined cross-sectionally (Adar et al., 2015). $PM_{2.5}$ was estimated using area-specific prediction models based on pollution measurements at the community or residential level in a subset of participants (MESA Air), which were incorporated with local geographic, meteorological, and emission data into a hierarchical spatiotemporal model to predict long-term exposure outside of participants' homes. $PM_{2.5}$ levels 1 year prior to baseline exam and 20-year average exposures were estimated and both were negatively associated with FEV_1 and FVC and with higher odds of airflow limitation. Similar to the Framingham Heart Study (Rice et al., 2015a), the authors found null associations between long-term exposure to $PM_{2.5}$ and FEV_1/FVC (Adar et al., 2015).

5.2.2.3 Summary of Lung Function and Development

In summary, recent epidemiologic studies enhance the evidence that was available in the 2009 PM ISA (U.S. EPA, 2009) suggesting that long-term exposure to $PM_{2.5}$ is associated with impaired lung function and lung function growth in children. Notably, extended CHS analyses continue to report $PM_{2.5}$-related decrements in lung development during the adolescent growth period. These updated analyses comprise additional cohorts with differing demographics and indicate that declining $PM_{2.5}$ concentrations are associated with improvements in lung development. Studies of attained lung function in children provide consistent evidence supporting the association observed with lung development. The strength of the epidemiology evidence was in the variety of exposure methods, study locations, and exposure levels for which associations were present. Additionally, a limited number of copollutant models indicate that the observed $PM_{2.5}$ effect may be independent of NO_2, CO, and O_3. The available evidence also indicates that $PM_{2.5}$ concentrations estimated proximate to lung function examination are most strongly associated with measures of attained lung function. These findings are supported by an animal toxicological study that demonstrated impaired lung development, as measured by decrements in lung function and changes in alveolar structure, as a result of pre- and post-natal exposure to $PM_{2.5}$. In a limited number of studies, altered nasal morphology and evidence of respiratory tract inflammation and oxidative stress were found in animals exposed to $PM_{2.5}$ during early lifestages.

While the 2009 PM ISA (U.S. EPA, 2009) noted inconsistent evidence of an association between long-term exposure to $PM_{2.5}$ and lung function in adults, more recent large prospective cohort studies have consistently observed $PM_{2.5}$-related accelerations of lung function decline in adults. This finding is

corroborated by evidence of lung function improvement in areas with declining $PM_{2.5}$ concentrations. Studies of lung function in adults have not adequately examined potential copollutant confounding.

5.2.3 Development of Asthma

Asthma is described by the National Heart, Lung, and Blood Institute as a chronic inflammatory disease of the airways that develops over time (NHLBI NAEPP, 2007). Pulmonary inflammation can increase airway responsiveness and induce airway remodeling, resulting in bronchoconstriction (bronchial smooth muscle contraction), and in turn, episodes of shortness of breath, coughing, wheezing, and chest tightness. When the pathophysiology of asthma advances in its development to the stage where the symptoms lead people to seek medical treatment, a diagnosis of asthma can result. A potential outcome of asthma development is that the pattern of reduced growth in lung function seen in early childhood persists into adulthood (McGeachie et al., 2016), potentially resulting in alterations to lung structure as adults (Donohue et al., 2013). In this section, asthma in children is discussed first, followed by asthma in adults, and subclinical effects underlying asthma development, such as pulmonary inflammation and increased airway responsiveness. While the evidence-base remains limited for subclinical effects and asthma in adults, recent studies of asthma in children supplement the limited number of studies reviewed in the 2009 PM ISA (U.S. EPA, 2009), and provide evidence of an association between long-term $PM_{2.5}$ exposure and asthma development in children.

5.2.3.1 Asthma in Children

Epidemiologic studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) that examined asthma development in children were limited in number. In a birth cohort study in the Netherlands, early-life $PM_{2.5}$ exposure was associated with doctor-diagnosed asthma at age 4 years (Brauer et al., 2007). In the southern California Children's Health Study (CHS), $PM_{2.5}$ was examined in relation to the association between lung function and asthma incidence. The protective association between lung function and new onset asthma observed in the overall population was not present in high $PM_{2.5}$ communities (Islam et al., 2007).

The recent body of literature enhances the limited evidence base, providing further evidence that long-term exposure to $PM_{2.5}$ is associated with asthma development in children. The strongest evidence supporting the relationship between long-term exposure to $PM_{2.5}$ and childhood asthma comes from a number of recent prospective and retrospective cohort studies conducted in North America and Europe. Longitudinal epidemiologic studies, which follow subjects over time, can better characterize the temporal sequence between $PM_{2.5}$ exposures and the incidence of asthma by ascertaining the first record of a physician diagnosis. In this regard, longitudinal studies distinguish between asthma onset and asthma exacerbation. Study-specific details, air quality characteristics, and select results from these studies,

discussed throughout this section, are highlighted in Table 5-21. In the majority of studies, asthma incidence was ascertained through validated questionnaires that asked parents about the child ever having a physician diagnosis of asthma at baseline, and, at each follow-up, questions about a diagnosis of asthma in the intervening period. In other studies, asthma was assessed by pediatric allergist evaluation (Carlsten et al., 2011) and primary care physician diagnosis or hospitalization due to asthma (Tétreault et al., 2016a; Clark et al., 2010).

Most recent asthma incidence studies focus on birth year as the period of potentially heightened sensitivity to $PM_{2.5}$ exposure and examine asthma incidence across varying follow-up times. The association between birth-year $PM_{2.5}$ exposure and diagnosis of asthma at age 7 was examined in a birth cohort of children at high-risk for asthma (n = 186) in Vancouver, Canada (Carlsten et al., 2011). The smaller sample size compared to other recent studies is balanced by using a high-risk cohort, which results in a higher proportion of cases compared to general population studies. Despite low mean outdoor $PM_{2.5}$ concentrations at birth residences (5.6 $\mu g/m^3$), Carlsten et al. (2011) observed that $PM_{2.5}$ was associated with increased odds of asthma diagnosis (OR: 4.0 [95% CI: 1.4, 11.5). In a larger study with relatively low mean $PM_{2.5}$ concentrations (9.9 $\mu g/m^3$; max: 14.9), Tétreault et al. (2016a) reported a positive and precise association between $PM_{2.5}$ and onset of asthma in an administrative cohort study of over 1 million children (HR: 1.23 [95% CI: 1.21 to 1.24]). The observed HR was robust to sensitivity analyses examining the impact of time-varying $PM_{2.5}$ concentrations and more rigorous case definitions for children under 5. Other studies conducted at higher $PM_{2.5}$ concentrations also reported generally positive associations between $PM_{2.5}$ and asthma incidence (Figure 5-30). A pooled retrospective case-control analysis of minority children provided an exception to the generally consistent evidence of an association (Nishimura et al., 2013). However, the study had low statistical power due to missing $PM_{2.5}$ concentration measurements for some regions.

Table 5-21 Longitudinal studies of long-term $PM_{2.5}$ exposure and asthma incidence in children.

Study	Study Population	Exposure Assessment	Effect estimates 95% CI[a]	Copollutant Examination
Brauer et al. (2007) The Netherlands 1997−2001 Prospective cohort	PIAMA n = 3,934 Follow-up: At 4 yr old 85.3% follow-up participation at 4 yr	GIS model Long-term avg $PM_{2.5}$ concentration for the first 4 yr of life Mean: 16.9 µg/m^3 Max: 25.2 µg/m^3	OR: 1.6 (1.1, 2.2)	Correlation (*r*): 0.96 NO_2 Copollutant models with: NA
†Carlsten et al. (2011) Vancouver, Canada 1995−2002 Prospective cohort	CAPPS: A high-risk asthma birth cohort n = 184 Follow-up: At 7 yr old 63% follow-up participation at 7 yr	Annual avg $PM_{2.5}$ concentration estimated at birth residence (birth year) using LUR. Mean: 5.6 µg/m^3	OR: 4.0 (1.4, 11.5)	Correlation (*r*): 0.7 NO_2 Copollutant models with: NA
†Gehring et al. (2010) The Netherlands 1996−2004 Prospective cohort	PIAMA n = 3,863 Follow-up: Annually from birth to 8 yr 94.4% participation at Yr 1, 82% at Yr 8	Annual avg $PM_{2.5}$ concentration estimated at birth residence (birth year) using LUR. Cross-validation RMSE for validation 1.59 µg/m^3; Model R^2 = 0.78 Mean: 17.5 µg/m^3 Max: 25.7 µg/m^3	Without adjustment for study region OR: 1.5 (1.2, 1.9) With adjustment for study region OR: 1.4 (0.95, 2.1)	Correlation (*r*): 0.93 NO_2 Copollutant models with: NA
†Gehring et al. (2015a) The Netherlands 1996−2008 Prospective cohort	PIAMA n = 3,702 children Follow-up: Annually from birth to 8 yr and again at age 11−12 yr	Annual avg $PM_{2.5}$ concentration estimated at birth residence (birth year) and current address (at time of questionnaire) using LUR. LOOCV R^2 = 0.61 Median: 16.5 µg/m^3 75th: 25.3 µg/m^3 95th: 26.4 µg/m^3	Birth address OR: 1.6 (0.9, 2.9) Current address OR: 1.2 (0.6, 2.4) (Birth address $PM_{2.5}$ vs current address $PM_{2.5}$ correlation (*r*): 0.74)	Correlation (*r*): 0.73 NO_2 (at birth address) Copollutant models with: NA
†Yang et al. (2016) The Netherlands 1996−2011 Prospective cohort	PIAMA n = 3,701 children Follow-up: Annually from birth to 8 yr and again at age 11−12 yr and 14 yr	Annual avg $PM_{2.5}$ concentration estimated at birth residence (birth year) and current address (at time of questionnaire) using LUR. LOOCV R^2 = 0.61; Model R^2 = 0.67	Birth address OR: 1.4 (0.8, 2.5) Current address OR: 1.1 (0.6, 2.0)	Correlation (*r*): NA Copollutant models with: NA

Table 5-21 (Continued): Longitudinal studies of long term $PM_{2.5}$ exposure and asthma incidence in children.

Study	Study Population	Exposure Assessment	Effect estimates 95% CI[a]	Copollutant Examination
†MacIntyre et al. (2014a) Vancouver, Canada; Munich and Wesel, Germany; the Netherlands; and East and West Germany. Pooled analysis of prospective cohorts.	TAG: A pooled analysis of CAPPS Vancouver, PIAMA, LISA, and GINI birth cohorts N = 2,743	Annual avg $PM_{2.5}$ concentration estimated at birth residence (birth year) using LUR. For LISA/GINI R^2 = 0.56; RMSE for model validation: 1.35 µg/m^3 Model validation for CAPPS and PIAMA as noted above Mean: 15.2 µg/m^3 Max: 25.1 µg/m^3	Current asthma OR: 2.5 (1.5, 4.3) Ever asthma OR: 1.2 (0.8, 1.8)	Correlation (*r*): 0.23 NO_2 Copollutant models with: NO_2
†Gehring et al. (2015b) Sweden, Germany, and the Netherlands. Pooled and meta-analyses of prospective cohorts	BAMSE, PIAMA, LISA, and GINI n = 14,126 Followed to 14 −16 yr of age	LUR was used to estimate annual avg $PM_{2.5}$ concentrations at the participant's birth and current home addresses. Model R^2 BAMSE: 87%; GINI/LISA North: 83%; GINI/LISA South: 69%; and PIAMA: 67%. $PM_{2.5}$ concentrations at birth address Mean across cohorts: 7.8 to 17.4 µg/m^3	Random-effects meta-analysis Birth year OR: 1.3 (0.9,1.7) Current address OR: 1.1 (0.9, 1.5)	Correlation with NO_2 "high". Quantitative results not reported. Copollutant models with: NA
†Mcconnell et al. (2010) Southern California 2002−2006 Prospective cohort	CHS n = 2,497 children; ages 4.8−9.0 yr at enrollment Follow-up: 3 yr 74% follow-up participation	Annual avg $PM_{2.5}$ concentration from one fixed-site monitor per community. Concurrent exposure.	HR: 1.2 (0.97, 1.4)	Correlation (*r*): NA Copollutant models with: NA
†Clark et al. (2010) Southwest British Columbia, Canada 1999−2004 Prospective case control	British Columbia population-based birth cohort n = 20,130 Follow-up: 3−4 yr to diagnosis by age 4 yr	LUR model used to estimate annual avg $PM_{2.5}$ concentration at birth residence for 1st-year and in utero exposure. Also assessed exposure concentration estimated by $PM_{2.5}$ concentrations at industrial point sources using an IDW However, there was no association for prenatal exposure estimated by an IDW summation of emissions from point sources. Mean: LUR 4.5 µg/m^3 IDW 5.62 µg/m^3	Prenatal IDW: 0.8 (0.6, 1.0) LUR: 1.1 (1.0, 1.2) First year IDW: 1.3 (0.9, 1.9) LUR: 1.1 (0.95, 1.2)	Correlations among pollutants were stated to be generally high. Quantitative results not reported. Copollutant models with: NA

Table 5-21 (Continued): Longitudinal studies of long term $PM_{2.5}$ exposure and asthma incidence in children.

Study	Study Population	Exposure Assessment	Effect estimates 95% CI[a]	Copollutant Examination
†Nishimura et al. (2013) Chicago, IL; Bronx, NY; Houston, TX; San Francisco Bay Area, CA; Puerto Rico. Retrospective case-control	GALA II and SAGE II n = 948 Ages 8−21 yr	Average $PM_{2.5}$ concentration for 1st yr and first 3 yr of life estimated using IDW of four closest monitors within 50 km of birth residence. Mean across cities: 8.1 to 17.0 μg/m^3	First year of life exposure All cities combined: 1.2 (0.6, 2.3) [Houston: 1.2 (0.6, 15.5); Puerto Rico: 1.6 (0.8, 3.3); Chicago: 0.5 (0.1, 1.6); New York: 3.7(1.0, 13.7) San Francisco (GALA): 0.4(0.1 to 1.8); San Francisco (SAGE): 0.7 (0.2, 2.4)]	Correlation (*r*): NA Copollutant models with: NA
†Tétreault et al. (2016a) Quebec, Canada 1996−2011	The Quebec Integrated Chronic Disease Surveillance System was used to create an open birth cohort n = 1,183,865	Mean $PM_{2.5}$ concentrations at birth address estimated at the postal code scale during 2001−2006 derived using satellite imagery and a CTM, Concentrations were assumed to be constant throughout the study period. Mean: 9.86 μg/m^3 Max: 14.85 μg/m^3	Birth address HR: 1.23 (1.21 to 1.24)	Correlation (*r*): NA Copollutant models with: NA

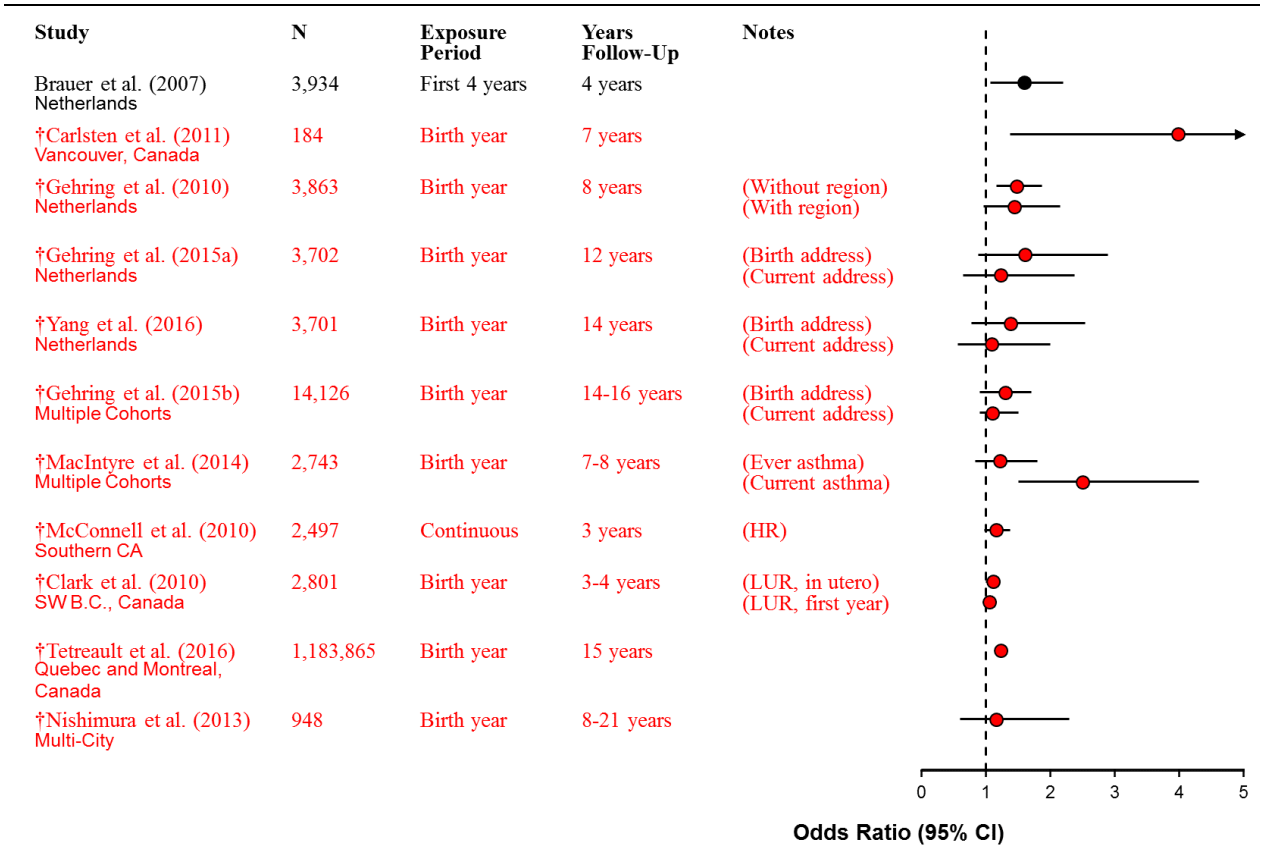
BAMSE = The Children, Allergy, Milieu, Stockholm, Epidemiological Survey, CAPPS = Canadian Asthma Primary Preventions Study, CHS = Children's Health Study, GALA II = Genes environments and Admixture in Latino Americans, GINI = German Infant Nutrition Intervention Study, GIS = geographic information system, HR = hazard ratio, IDW = inverse distance weighting, IQR = interquartile range, LISA = Lifestyle Factors on the Development of the Immune System and Asthma, LOOCV = leave one out cross-validation, NO = nitric oxide, NO_2 = nitrogen dioxide, NR = not reported, OR = odds ratio, PIAMA = Prevention and Incidence of Asthma and Mite Allergy, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 μm, *r* = correlation coefficient, RMSE = root mean square error, SAGE II = Study of African Americans, Asthma, Genes, and Environments, SD = standard deviation, TAG = The Traffic, Asthma and Genetics study, CTM = chemical transport model.

[a]Effect estimates are standardized to a 5 μg/m^3 increase in $PM_{2.5}$.

†Studies published since the 2009 PM ISA.

A number of studies examined alternate exposure windows to assess other periods of potential sensitivity to PM exposure in the development of asthma. Two studies of the PIAMA cohort in the Netherlands (Yang et al., 2016; Gehring et al., 2015a), and one pooled analysis of four European birth cohorts (Gehring et al., 2015b), observed that asthma incidence was associated with $PM_{2.5}$ concentrations outside birth residences, and reported attenuated but still positive associations with $PM_{2.5}$ concentrations at the address of the participant at the time of follow-up (quantitative results presented in Table 5-21). As

discussed in Section 5.2.2.2.1, exposure was modeled after follow-up for all of these cohorts, such that exposure estimates are representative of spatially relative concentrations. An earlier PIAMA study stratified by participants who had and had not moved from their birth address (movers vs. nonmovers) and observed associations between $PM_{2.5}$ and incident asthma that were slightly stronger in magnitude in nonmovers (OR: 1.6 [95% CI: 1.1, 2.3]) than movers (OR: 1.3 [95% CI: 0.97, 1.8]) (Gehring et al., 2010). While the difference in ORs is not large, the stratified results may suggest continued sensitivity to $PM_{2.5}$ exposure later in life. In a nested case-control study in British Columbia, Clark et al. (2010) examined asthma incidence at ages 3−4 years in association with $PM_{2.5}$ concentrations in both the prenatal period and first year of life. The authors reported similar asthma-$PM_{2.5}$ associations for prenatal and first year of life exposures estimated by LUR (OR [95% CI]: 1.1 [1.0, 1.2] and 1.1 [0.95, 1.2] for prenatal and first year $PM_{2.5}$ averages, respectively).



CI = confidence interval, HR = hazard ratio, LUR = land use regression.

Note: †Studies published since the 2009 PM ISA. Black text/circles = studies evaluated in the 2009 PM ISA. Red text/circles = studies published since the completion of the 2009 PM ISA. Odds ratios are standardized to an increment of 5 $\mu g/m^3$. Corresponding quantitative results and study details are reported in Table 5-21.

Figure 5-30 Long-term exposure to $PM_{2.5}$ and asthma incidence in children.

Recent studies of asthma prevalence generally provide supporting evidence for an association with $PM_{2.5}$ (Hasunuma et al., 2014 Macintyre, 2014, 2230511, Gehring, 2015, 3070314; Mölter et al., 2014), though some did not (Fuertes et al., 2013b; Akinbami et al., 2010). Supporting evidence was also reported in studies examining $PM_{2.5}$ and wheeze, a common symptom of asthma. Repeated wheeze in 2-year-olds was prospectively studied in a pregnancy cohort of women (n = 708) receiving care at Brigham & Women's Hospital in Boston (Chiu et al., 2014). Prenatal $PM_{2.5}$ exposure, estimated using a hybrid model incorporating AOD observations with land use predictors to yield residence-specific ambient $PM_{2.5}$ concentration estimates, was associated with increased odds of repeated wheeze at age 2 (OR: 2.0 [95% CI: 1.2, 3.4] for above median vs. below median $PM_{2.5}$ concentrations). In the larger PIAMA cohort study detailed in Table 5-21, Gehring et al. (2010) observed increased odds of parental-reported prevalent wheeze during the first 8 years of life associated with long-term $PM_{2.5}$ concentration (OR: 1.3 [95% CI: 1.1, 1.6]).

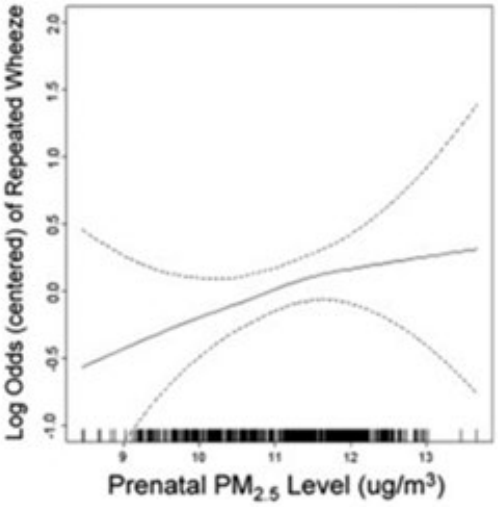
5.2.3.1.1 Copollutant Confounding

Most of the reviewed studies of asthma incidence in children did not present results from copollutant models. This may be the result of consistently high correlations reported between $PM_{2.5}$ and other pollutants across studies (Table 5-21), which reduces the reliability of copollutant models. MacIntyre et al. (2014a) observed a weak correlation between $PM_{2.5}$ and NO_2 ($r = 0.23$) in a pooled analysis of four birth cohorts. The association observed between birth-year $PM_{2.5}$ exposure and having a current asthma diagnosis (OR [95% CI]: 2.5 [1.5, 4.3]) remained after adjustment for NO_2 in a copollutant model (4.5 [1.4, 14.2]). However, given the lack of additional studies, uncertainties remain regarding whether the association between $PM_{2.5}$ and asthma incidence in children is independent of coexposure to other pollutants.

5.2.3.1.2 Concentration-Response Relationship

The shape of the C-R relationship between asthma incidence in children and long-term exposure to $PM_{2.5}$ was examined in (Tétreault et al., 2016a). To examine whether there is evidence of linearity in the relationship restricted cubic splines with three knots were included in the model. For $PM_{2.5}$, as well as O_3 and NO_2, nonlinear models did not result in better fits than the linear models for both exposures outside the home address at birth and for time-varying exposures during the follow-up period. Carlsten et al. (2011) examined the $PM_{2.5}$-asthma incidence association across exposure quartiles and reported monotonically increasing risk. However, this analysis stratified an already small sample size, resulting in wide CIs for each quartile estimate of risk. A C-R relationship was also evaluated in a study of childhood wheeze. Chiu et al. (2014) used penalized spline models to assess the nature of the relationship between prenatal $PM_{2.5}$ exposure and repeated wheeze. As depicted in Figure 5-31, the C-R relationship was approximately linear with some evidence of a less steep relationship at the higher exposure levels, albeit

with high uncertainty due to limited data at higher exposures. Confidence in the shape of the curve, as indicated by the dotted lines surrounding the spline curve, is highest from about 10 to 12 µg/m^3, where most of the observations occur. None of the evaluated studies provide a thorough empirical evaluation of alternatives to linearity, limiting the conclusions that can be drawn with respect to the shape of the C-R relationship.



Solid lines depict the penalized spline curve, and dotted lines indicate the 95% confidence bounds.
Source: Permission pending, Chiu et al. (2014).

Figure 5-31 Concentration-response relationship of prenatal $PM_{2.5}$ with children's repeated wheeze.

5.2.3.2 Asthma in Adults

No studies of long-term $PM_{2.5}$ exposure and asthma in adults were discussed in the 2009 PM ISA (U.S. EPA, 2009). Since then, a number of recent studies have examined incidence and prevalence of asthma and wheeze in adults in several cohorts. Contrary to the recent evidence supporting the presence of an association in children, the results for adult populations have been largely inconsistent. Study-specific details, including study locations, cohort descriptions, air quality characteristics, and select results from these studies, are highlighted in Table 5-22. A forest plot of the effect estimates, depicting the heterogeneity of results across studies, is presented in Figure 5-32.

Table 5-22 Long-term $PM_{2.5}$ exposure and asthma and wheeze incidence and prevalence in adults.

Study	Study Population	Exposure Assessment	Effect estimates (95% CI) per 5 µg/m^3	Copollutant Examination
Asthma incidence				
†Young et al. (2014) U.S. 2003−2012 Prospective cohort	The Sister Study; cohort of women with at least one sister with a diagnosis of breast cancer. n = 39,350 Enrollment from 2003−2006. Follow-up from 2008−2012 (Participation >99%)	Kriging regression monitor values using geographic variables. Annual avg $PM_{2.5}$ concentration estimated outside home address at enrollment. Cross-validated R^2: 0.88 Mean: 10.8 µg/m^3 Range: 1.9−18.0 µg/m^3	Incident asthma OR: 1.3 (0.99, 1.7) Incident wheeze OR: 1.2 (1.1, 1.4)	Correlation (*r*): NA Copollutant models with: NA
†To et al. (2015) Ontario, Canada 1980−2003 Prospective cohort	The Canadian National Breast Screening Study n = 29,549 women, ages 40−59 at enrollment Enrollment from 1980−1985. Follow-up using administrative databases from 1992−2003	Long-term avg $PM_{2.5}$ concentrations from 1998−2006 estimated at 10 ×10 km grid level using AOD observations from satellite imagery. R^2 with ground monitors: 0.77 Mean (SD): 12.47 (2.40) µg/m^3	RR: 1.0 (0.92, 1.25)	Correlation (*r*): NA Copollutant models with: NA
†Jacquemin et al. (2015) 24 European Cities Combination of six prospective cohorts	The European Study of Cohorts for Air Pollution Effects n = 17,098	LUR models of annual avg $PM_{2.5}$ concentration at participants' address at follow-up. Range of means across cities: 10 to 18 µg/m^3	OR: 1.0 (0.88, 1.2)	Correlation (*r*): (range across cities) 0.60−0.90 NO_2; 0.51−0.94 NO_X; 0.63−0.88 PM_{10}; 0.22−0.67 $PM_{10-2.5}$ Copollutant models with: NA Copollutant models NR

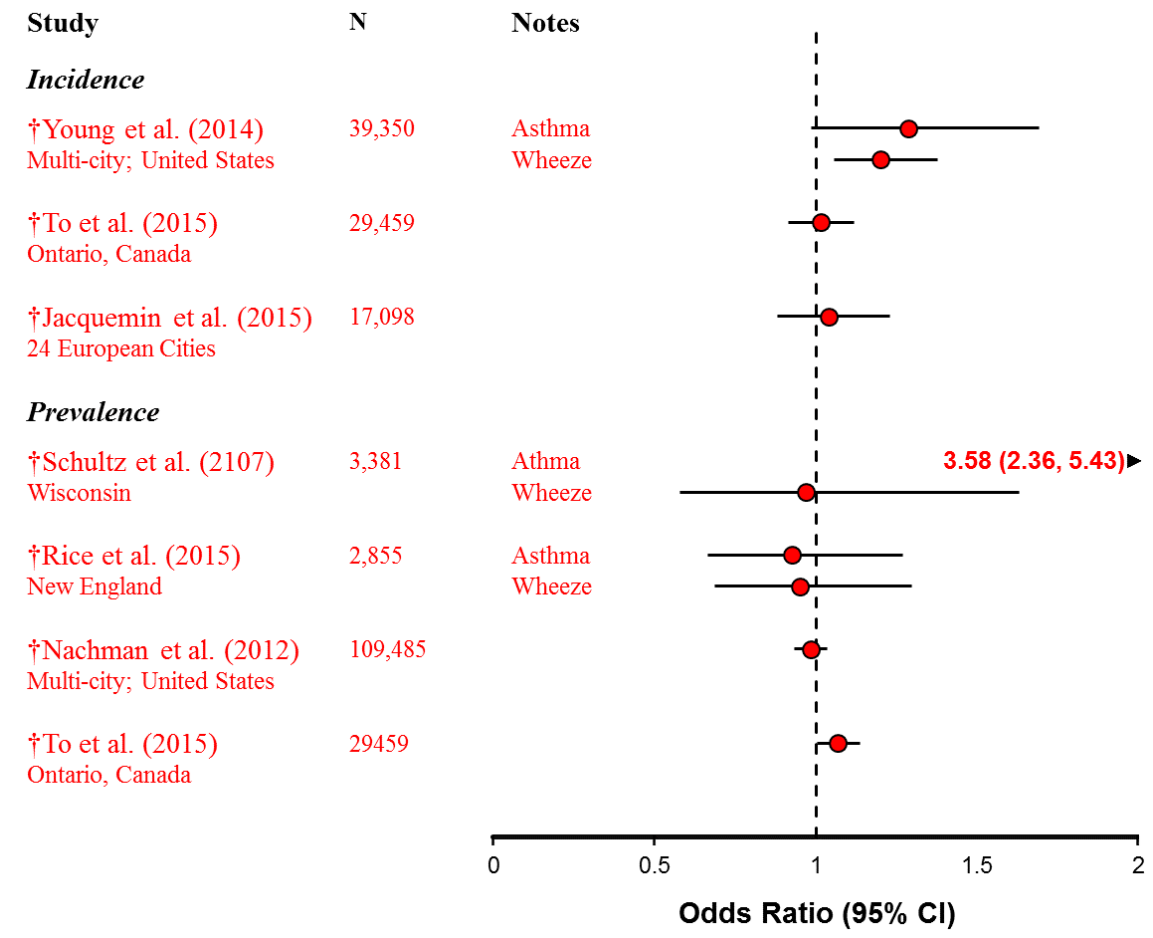
Table 5-22 (Continued): Long term $PM_{2.5}$ exposure and asthma and wheeze incidence and prevalence in adults.

Study	Study Population	Exposure Assessment	Effect estimates (95% CI) per 5 µg/m^3	Copollutant Examination
Asthma prevalence				
†Schultz et al. (2017) Wisconsin 2008–2013 Cross-sectional	Survey of the Health of Wisconsin (SHOW); probabilistic survey design n = 3,381 adults ages 21+	Annual avg $PM_{2.5}$ concentration estimates from U.S. EPA Bayesian space-time downscaler. 12 × 12 km gridded estimates were linked to participants' home addresses. 1-yr lag. 5th: 10.9 µg/m^3 Max: 15.1 µg/m^3	Prevalent asthma OR: 3.6 (2.4, 5.4) Prevalent wheeze OR: 0.97 (0.58, 1.6)	Correlation (*r*): NA Copollutant models with: NA
†Rice et al. (2015a) New England Enrollments Offspring: 1971–1975 Third generation: 2002–2005 Cross-sectional analysis of longitudinal data	Framingham Offspring and Third Generational Cohorts n = 2,855 Biennial follow-up	Annual avg $PM_{2.5}$ concentrations for 2001 were estimated at 10 × 10 km grid level using AOD observations from satellite. Resolved to 50 × 50 m using land use terms and assigned to participants' home addresses. 10-fold cross-validated LOOCV R^2: 0.85 Mean: 10.8 µg/m^3 Max: 21.7 µg/m^3	Prevalent asthma OR: 0.93 (0.67, 1.3) Prevalent wheeze OR: 0.95 (0.68, 1.3)	Correlation (*r*): NA Copollutant models with: NA
†Nachman and Parker (2012) U.S. 2002–2005 Cross-sectional	National Health Interview Survey (NHIS); multistage probability survey n = 109,485 adults ages 18+	Annual avg $PM_{2.5}$ concentrations were estimated from a kriging model used to interpolate monitor concentrations. Median: 12.6 µg/m^3 Max: 24.7 µg/m^3	OR: 0.99 (0.93, 1.03)	Correlation (*r*): NA Copollutant models with: NA
†To et al. (2015) See details above	See details above	See details above	RR: 1.1 (1.0, 1.3)	See details above

LOOCV = leave one out cross-validation, NO = nitric oxide, NO_2 = nitrogen dioxide, NR = not reported, OR = odds ratio; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, *r* = correlation coefficient, RR = relative risk, SD = standard deviation.

[a]Effect estimates are standardized to a 5 µg/m^3 increase in $PM_{2.5}$.

†Studies published since the 2009 PM ISA.



CI = confidence interval.

Note: †Studies published since the 2009 PM ISA. Black text/circles = studies evaluated in the 2009 PM ISA. Red text/circles = studies published since the completion of the 2009 PM ISA. Odds ratios are standardized to an increment of 5 μg/m^3. Corresponding quantitative results and study details are reported in Table 5-22.

Figure 5-32 Asthma and wheeze incidence and prevalence in adults in relation to long-term $PM_{2.5}$ exposure.

A limited number of studies on incident asthma in adults reported inconsistent evidence of an association. In a large prospective cohort study of women across the U.S., asthma incidence was associated 1-year average $PM_{2.5}$ concentrations at the beginning of follow-up (OR: 1.3 [95% CI: 0.99, 1.7]) (Young et al., 2014). Cases were defined by self-reporting of all three of the following conditions: asthma diagnosis by a doctor, use of asthma medication, and presence of asthma symptoms. In support of the association seen with incident asthma, Young et al. (2014) also reported an increase in wheeze incidence associated with long-term exposure to $PM_{2.5}$. In contrast, the ESCAPE study, an analysis of six

European cohorts, did not observe an association between long-term $PM_{2.5}$ concentrations and asthma onset in adults (Jacquemin et al., 2015). The finding was unchanged in a sensitivity analysis aimed at reducing exposure measurement error by restricting the analysis to cities with better LUR model validation. Similarly, in a large cohort study of chronic disease prevalence in women living in Ontario, Canada, To et al. (2015) also reported a null association. However, because $PM_{2.5}$ concentrations were estimated from satellite observations of AOD taken in the middle of the study period, asthma cases were restricted to the years after exposure estimates were available, which reduced the case number and power of the study. Utilizing the entire study population, To et al. (2015) did observe an association between long-term $PM_{2.5}$ exposure and asthma prevalence.

In addition to the To et al. (2015) study, there were a few other studies that examined asthma prevalence in adults. These studies were of cross-sectional design and the results, similar to studies of asthma incidence, were also inconsistent. While a health survey-based study of adults in Wisconsin reported evidence of a large increase in odds of asthma prevalence in association with annual average $PM_{2.5}$ concentration in the previous year (OR [95% CI]: 3.58 [2.36, 5.43]), the authors did not observe an association with prevalent wheeze (Schultz et al., 2017). In contrast, cross-sectional analyses of a longitudinal cohort (Rice et al., 2015a) and a national health survey (Nachman and Parker, 2012) observed null associations between long-term exposure to $PM_{2.5}$ and asthma prevalence in adults.

5.2.3.3 Subclinical Effects Underlying Development of Asthma

Subclinical effects underlying the development of asthma, including airway inflammation and airway hyperresponsiveness, have been examined in both epidemiologic studies and animal toxicological studies. The 2009 PM ISA (U.S. EPA, 2009) reported a cross-sectional analysis of school children in Windsor, Ontario that observed an increase in airway inflammation (eNO) corresponding to an increase in annual $PM_{2.5}$ concentrations (Dales et al., 2008). Also reviewed in the 2009 PM ISA were several studies that reported subclinical effects underlying the development of asthma following long-term exposure to DE or woodsmoke. However, these studies did not distinguish between effects due to gases or particles in the mixture.

5.2.3.3.1 Epidemiologic Studies

Recently, a longitudinal study of the CHS cohort reported that, in models adjusted for short-term $PM_{2.5}$ exposure, annual $PM_{2.5}$ concentrations were associated with a 10.3 ppb (95% CI: 3.0, 17.6) increase in FeNO (Berhane et al., 2014). Results from a prior CHS analysis (Bastain et al., 2011) showed that elevated eNO was associated with increased risk of new onset asthma. However, potential copollutant confounding was not examined in either study. Thus, there are a limited number of epidemiologic studies

providing evidence for subclinical effects underlying the development of asthma in association with long-term exposure to $PM_{2.5}$.

5.2.3.3.2 Animal Toxicological Study

Recently, a study evaluating the effects of $PM_{2.5}$ on the development of asthma has become available. Kim et al. (2016a) exposed BALB/c mice to nebulized DEPs for 4, 8, and 12 weeks and found increased BALF levels of the Th2 cytokines IL-5 (8 and 12 weeks) and IL-13 (4 and 12 weeks) ($p < 0.05$). Since these mice were naïve and not sensitized or challenged with allergens, this result provides evidence that $PM_{2.5}$ can induce an immune phenotype in the absence of an allergen. In addition, airway responsiveness to methacholine was assessed using whole-body plethysmography to measure Penh. Methacholine is a muscarinic receptor agonist that elicits bronchoconstriction and is used to evaluate airway hyperresponsiveness, a hallmark of asthma. DEP exposure resulted in increased Penh at all three-time points studied ($p < 0.01$). As discussed in Section 5.1.2.3.3, there is uncertainty associated with the use of Penh for the determination of airway responsiveness. Additional study details are found in Table 5-23.

Table 5-23 Study-specific details from an animal toxicological study of long-term $PM_{2.5}$ exposure and subclinical effects underlying development of asthma.

Study/Study Population	Pollutant	Exposure	Endpoints
Kim et al. (2016a) Species: Mouse Strain: BALB/c Sex: Female Age/Weight: 5−6 weeks	DEP nebulized Particle size: Mean diameter 0.4 μm before nebulization and 1−5 μm after nebulization Control: Saline solution	Dose/Concentration: 0.1 and 3 mg/m^3 DEP or saline (Only results from 0.1 mg/m^3 reported here) Duration: 1 h/day, 5 days/week for 4, 8, and 12 weeks Time to analysis: 1 day after last exposure	Penh- methacholine challenge BALF cells BALF cytokines Histochemistry • Masson trichome staining of lung

DEP = diesel exhaust particles; Penh = enhanced pause.

5.2.4 Development of Allergic Disease

The 2009 PM ISA (U.S. EPA, 2009) reviewed a limited number of epidemiologic studies examining a range of allergic indicators that found a mix of positive and null associations with long-term exposure to $PM_{2.5}$. While a number of studies reported $PM_{2.5}$ associations with hay fever/allergic rhinitis, indoor and outdoor allergic sensitization, and/or eczema, there was comparable evidence of null

associations across the same endpoints within the reviewed studies. Most studies examining allergic endpoints assessed prevalence outcomes cross-sectionally. In addition to a lack of prospective studies on allergic disease incidence, none of the studies reviewed in the 2009 PM ISA used copollutant models to evaluate the independent effect of $PM_{2.5}$. Studies published since the completion of the 2009 PM ISA encompass two main indicators of allergic disease: hay fever/allergic rhinitis diagnosis and allergic sensitization. In addition, a single recent animal toxicological study provided evidence that long-term $PM_{2.5}$ exposure can promote the development of a Th2 phenotype (see Section 5.2.3.3.2).

Allergic sensitization, measured by detectable allergen-specific IgE levels, was examined in the recent evidence base. A pooled analysis of five European birth cohorts reported that annual average $PM_{2.5}$ concentrations outside participants' birth addresses were associated with higher odds of sensitization to any common allergen at ages 4 and 8 (Gruzieva et al., 2014). However, the association was driven by results from the PIAMA cohort in the Netherlands (Gehring et al., 2010), whereas analyses of other cohorts included in the pooled analysis, such as the LISA and GINI cohorts (Fuertes et al., 2013b), did not observe associations. The PIAMA cohort study observed associations with $PM_{2.5}$ concentrations outside birth addresses that were larger in magnitude compared to current addresses, but also reported associations that were larger in magnitude among nonmovers compared to movers (Gehring et al., 2010). As discussed in Section 5.2.3 on asthma development, early life exposure may be important to allergic sensitization, but the critical exposure window may continue into later childhood. In a 2005−2006 NHANES study comprising a nationally representative sample of the U.S. population, Weir et al. (2013) found that annual average $PM_{2.5}$ concentration was associated with increased odds of sensitization to indoor allergens for exposure assigned from monitors within 20 miles of the participants' home address (OR: 1.27 [95% CI: 1.12, 1.45]) and using geocoded CMAQ $PM_{2.5}$ concentration estimates (OR: 1.26 [95% CI: 1.16, 1.38]). Associations with sensitization to food allergens were positive but imprecise, while sensitization to outdoor allergens were not related to annual average $PM_{2.5}$ concentrations. Although copollutant models were not examined, $PM_{2.5}$ was weakly correlated with NO_2 and O_3.

Other recent studies examined parental and self-reported hay fever/allergic rhinitis and rhino conjunctivitis in children and adults. A few studies of the PIAMA cohort reported that $PM_{2.5}$ assigned at birth address was not associated with increased odds of hay fever (Gehring et al., 2010) or rhino conjunctivitis incidence (Gehring et al., 2015b) in children. However, an association of $PM_{2.5}$ with hay fever was present in children who did not move during follow-up (OR [95% CI]: 1.43 [1.01, 2.04]). The lack of an association in the overall population may have been due to exposure measurement error for children who moved, as evident in the association amongst nonmovers. In contrast to Gehring et al. (2010), a pooled analysis of six Canadian and European cohorts (CAPPS, SAGE, PIAMA, BAMSE, and GINI/LISA), reported that birth-year $PM_{2.5}$ was associated with a 37% increase in odds of allergic rhinitis at age 7−8 (95% CI: 1, 86%) (Fuertes et al., 2013a). Wang et al. (2015a) also observed a positive association between parental-reported allergic rhinitis and cumulative long-term $PM_{2.5}$ exposure in a cohort of kindergarteners living within 10 km of an air quality monitoring station. In a cross-sectional study of adults in Wisconsin, Schultz et al. (2017) observed no evidence of a linear association between

annual $PM_{2.5}$ concentrations and subjects who self-reported a physician diagnosis of allergies or hay fever (OR: 1.06 [95% CI: 0.74, 1.53]). However, the authors reported increased odds of allergies or hay fever for participants in the second (9.32−10.20 µg/m^3; OR: 1.38 [95% CI: 1.03, 1.76]) and third (10.21−10.85 µg/m^3; OR: 1.33 [95% CI: 1.00, 1.76]) quartiles of PM exposure compared to those in the first (6.59−9.31 µg/m^3), suggesting a potential nonlinear association.

In summary, recent studies evaluated associations between long-term exposure to $PM_{2.5}$ and various allergic outcomes in a mix of large representative cohort and cross-sectional survey studies. While recent evidence includes more longitudinal study designs, there are no studies that evaluate copollutant models. Despite this limitation, there is generally consistent evidence of an association between long-term $PM_{2.5}$ exposure and allergic sensitization in single pollutant models. However, as seen in Weir et al. (2013) and studies reviewed in the 2009 PM ISA (U.S. EPA, 2009), consistent associations with specific allergens have not emerged. The findings for allergic rhinitis were inconsistent, although a limited number of studies that aimed to reduce exposure measurement error, either by restricting distance between study participants and monitors or by excluding participants who moved, did observe associations. Overall, evidence indicates an association between long-term exposure to $PM_{2.5}$ and at least some manifestations of allergic disease. Limited evidence from a single animal toxicological study showing that long-term exposure to DEP promotes the development of an allergic phenotype supports for epidemiologic findings of allergic responses.

5.2.5 Development of Chronic Obstructive Pulmonary Disease (COPD)

There were no epidemiologic studies examining the association between long-term exposure to $PM_{2.5}$ and COPD available for inclusion in the 2009 PM ISA (U.S. EPA, 2009). An animal toxicological study provided evidence for the development of emphysema, a form of COPD, following long-term exposure to woodsmoke, but did not distinguish between effects due to gases or particles in the mixture. Several recent epidemiologic studies examined COPD as an outcome using medical records data, lung function measures, and imaging data obtained in cohorts and cross-sectional studies based in North America and Europe. Studies also examined specific forms of COPD, including emphysema, marked by destruction of the alveolar region of the lungs, and chronic bronchitis, or long-term inflammation of the bronchial tubes. These studies are discussed below. There are no recent animal toxicological studies examining long-term exposure to $PM_{2.5}$ and COPD.

Recent large cohort studies examined the association between long-term $PM_{2.5}$ and COPD development. In a study of COPD incidence in the U.K., a dispersion model was used to assign annual-average $PM_{2.5}$ exposure to nearest postcode centroid for each patient (Atkinson et al., 2015). The authors reported that $PM_{2.5}$ was associated with higher odds of first COPD hospitalization (OR [95% CI]: 1.14 [0.96, 1.36]), but not for COPD diagnosis from a general practitioner (0.98 [0.84, 1.16]). Hospital admissions records may represent more severe cases of COPD, which may explain the difference in effect

estimates. The COPD hospitalization results persisted in two-pollutant models with SO_2, NO_2 and O_3 ($r < 0.5$ for all pollutants). Similarly, 5-year average $PM_{2.5}$ was associated with an increase, with wide confidence intervals, in the risk of hospitalization due to COPD (RR [95% CI]: 1.06 [0.93, 1.20]) in a large population-based cohort in metropolitan Vancouver (Gan et al., 2013). The study was limited to participants who had no previous record of COPD diagnosis, but hospitalization records were analyzed only for a few years prior. Thus, the hospitalization could reflect exacerbation of a previously diagnosed disease, rather than COPD onset. In a large cohort study of chronic disease prevalence in women living in Ontario, Canada, To et al. (2015) assigned $PM_{2.5}$ exposure at a postal code level using satellite-based AOD observation data. The authors reported that the incidence and prevalence of COPD were associated with 8-year average $PM_{2.5}$ concentrations. Contrasting evidence was observed in an ESCAPE Project pooled analysis of four European cohorts (Schikowski et al., 2014). COPD was defined using prebronchodilator FEV_1/FVC below the lower limit of normal (LLN) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition (FEV_1/FVC <0.70). Annual $PM_{2.5}$ concentrations, estimated by LUR, were not associated with incidence (OR [95% CI]: 1.06 [0.73, 1.53]) or prevalence (OR [95% CI]: 0.95 [0.47, 1.9]) of COPD defined by LLN. Similar estimates were obtained using the GOLD definition of COPD.

A limited number of studies examined specific forms of COPD, including emphysema and chronic bronchitis. As discussed in the 2009 PM ISA (U.S. EPA, 2009), McConnell et al. (2003) reported associations between annual and 4-year average $PM_{2.5}$ and bronchitic symptoms in a prospective study of children in 12 CHS communities. A recent pooled analysis of five European cohorts also examined chronic bronchitis in relation to $PM_{2.5}$ (Cai et al., 2014). Annual average $PM_{2.5}$ concentrations were not associated with chronic bronchitis in the overall population (OR [95% CI]: 0.90 [0.74, 1.09]), but was associated with chronic bronchitis in a subanalysis of nonsmokers (OR [95% CI]: 1.28 [0.95, 1.72]). A U.S. cross-sectional study using data from the National Health Interview Survey (NHIS) also observed an association between $PM_{2.5}$ concentrations in the past year and the odds of chronic bronchitis (OR [95% CI]: 1.08 [0.94, 1.24]) (Nachman and Parker, 2012). The association between emphysema and exposure to $PM_{2.5}$ was examined cross-sectionally in the MESA study (Adar et al., 2015). PM concentrations 1 year prior to baseline exam and 20-year average exposures were estimated. Percent emphysema, determined from CT scans, was positively associated with both 1-year average and 20-year average $PM_{2.5}$. However, these results were driven by lower mean percent emphysema in one city (St. Paul) with the lowest $PM_{2.5}$ concentrations, and the associations were no longer positive after adjustment for study site, or in analyses excluding St. Paul.

Recent studies provide some evidence that long-term $PM_{2.5}$ exposure may be associated with development of COPD in adults, but uncertainties remain. Notably, studies of COPD hospitalization may reflect exacerbation of previously diagnosed disease rather than disease onset. Additionally, hospitalizations may represent severe cases of COPD and may not account for the potential effect of short-term exposures leading to these acute events. There is also a lack of available studies that examine potential copollutant confounding. However, one study observed that $PM_{2.5}$ was associated with first-time

COPD hospitalization independent of gaseous pollutants (Atkinson et al., 2015). Overall, a limited number of studies also provide evidence of an association between long-term exposure to $PM_{2.5}$ and chronic bronchitis, a specific form of COPD.

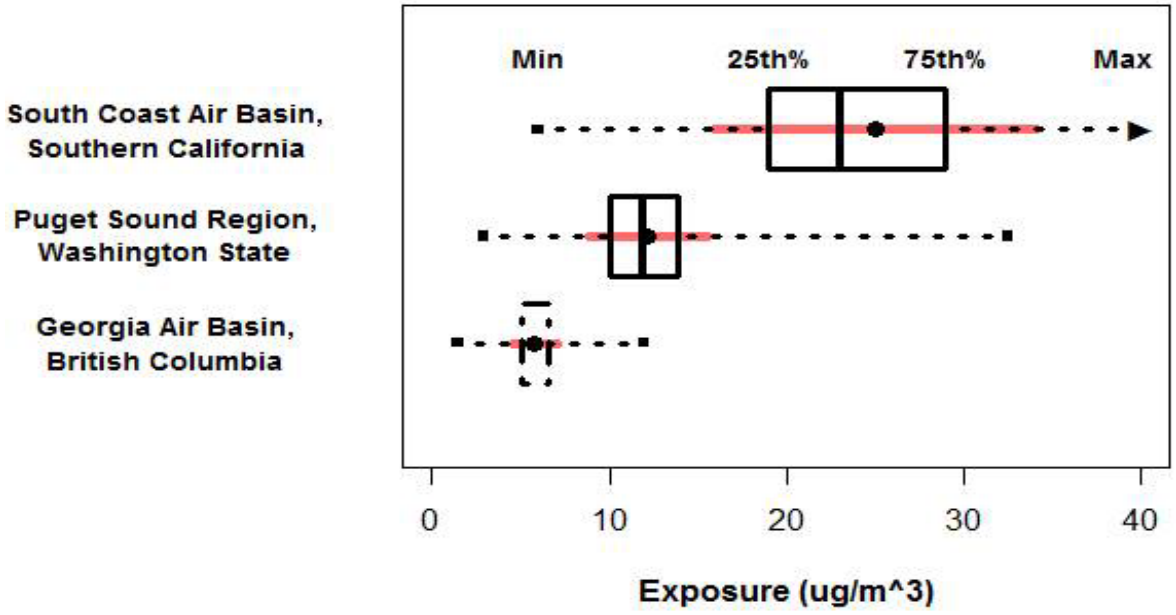
5.2.6 Respiratory Infection

In the 2009 PM ISA (U.S. EPA, 2009), results from epidemiologic studies indicated an association between PM and respiratory infection. However, this association was largely evident in studies of short-term PM exposure, as only one study examined the relationship between long-term exposure to $PM_{2.5}$ and respiratory infection. Several animal toxicological studies examined the effects of long-term exposure to DE on host defense. While evidence for altered host defense was found, these studies did not distinguish between effects due to gases or particles in the DE mixture. Recent epidemiologic studies in North America and Europe have examined the associations between long-term exposure to $PM_{2.5}$ and infant bronchiolitis, pneumonia, croup, and otitis media. There are no recent animal toxicological studies of long-term $PM_{2.5}$ exposure and host defense.

The association between infant bronchiolitis and long-term $PM_{2.5}$ exposure was examined in three large cohorts (Karr et al., 2009b; Karr et al., 2009a; Karr et al., 2007). A prominent respiratory infection in infancy, bronchiolitis is primarily caused by the respiratory syncytial virus (RSV), and results in inflammation of the bronchioles. As discussed in the 2009 PM ISA (U.S. EPA, 2009), Karr et al. (2009b) examined infant bronchiolitis hospitalization in a birth registry cohort in the Puget Sound region of Washington. Two similar studies, which were not reviewed in the 2009 PM ISA, also examined infant bronchiolitis in the Georgia Air Basin of British Columbia (Karr et al., 2009a) and the South Coast Air Basin of California (Karr et al., 2007). Each nested case-control study examined cumulative lifetime exposure to $PM_{2.5}$ in relation to bronchiolitis incidence in the first year of life. The results were inconsistent across studies.

Karr et al. (2009b) assigned lifetime average $PM_{2.5}$ from the closest fixed-site monitor within 20 km of subjects' residential postal code. The authors reported that $PM_{2.5}$ concentrations were associated with RSV bronchiolitis, but not all bronchiolitis, which includes bronchiolitis due to other infectious agents. However, in a model examining effect modification, Karr et al. (2009b) reported an association with all bronchiolitis for infants living within 5 km of a fixed-site monitor. The restricted analysis may have reduced exposure measurement error, as infants spend most of their time in or near their homes (Wiley et al., 1991). Karr et al. (2007) did not exclude maternal-infant pairs based on distance to monitor but reported that 90% of study participants lived within 17.7 km of a monitor. The authors observed a 4% increase in the odds of bronchiolitis hospitalization in the first year of life in relation to cumulative lifetime $PM_{2.5}$ exposure (95% CI: 2, 7%). The association with $PM_{2.5}$ was robust to the inclusion of O_3 in a copollutant model (4% [95% CI: 1.03 to 1.15]; $r = -0.24$). In contrast to evidence observed in Washington (Karr et al., 2009b) and California (Karr et al., 2007), Karr et al. (2009a) reported null

associations between lifetime $PM_{2.5}$ exposure and infant bronchiolitis in British Columbia. The analysis included infants living within 10 km of a monitor and modeled exposure concentrations using an LUR model to produce similar results. A comparison of the $PM_{2.5}$ distributions across the three studies shows that mean concentration and variance are smallest in British Columbia (Figure 5-33). The narrow exposure range, resulting in limited variability in $PM_{2.5}$ concentrations, may have contributed to the lack of an observed association.



Note: Large dots represent means; bold vertical lines represent medians. Red lines represent ± one standard deviation. For British Columbia, 25th and 75th percentiles were not reported, and so the IQR was assumed to center around the mean value. The maximum value for Southern California was 111.0 μg/m^3. The IQR's were 10, 3.8, and 1.5 μg/m^3, respectively.

Figure 5-33 Exposure measurements from South Coast Air Basin (Karr et al., 2007), Puget Sound Region, WA (Karr et al., 2007), and Georgia Air Basin, British Columbia (Karr et al., 2009b).

A limited number of studies evaluated other respiratory infection endpoints in infants or adults. MacIntyre et al. (2014b) examined parental reported pneumonia, otitis media, and croup in an ESCAPE Project pooled analysis of 10 European cohorts. $PM_{2.5}$ estimated outside birth residence was associated with an imprecise increase in odds of pneumonia in the first 36 months of life across all cohorts (OR [95% CI]: 2.58 [0.91, 7.27]). The association with $PM_{2.5}$ was attenuated, but still positive, in a two-pollutant model adjusting for NO_2 (1.91 [0.56, 6.57]; r = 0.42−0.8). A sensitivity analysis looking at alternative outcome windows showed the strongest association between long-term $PM_{2.5}$ and pneumonia diagnosed in the first year of life. Associations were null or negative for croup and otitis media. In a

case-control study in Ontario, Canada, Neupane et al. (2010) assessed the risk of hospitalization for community-acquired pneumonia in adults 65 years of age or older in relation to long-term exposure to $PM_{2.5}$. A notable strength of this study was the use of radiologically confirmed pneumonia to reduce potential outcome misclassification. The authors assigned exposure at the residential level using two deterministic interpolation methods, bicubic splines and inverse distance weighting, to estimate $PM_{2.5}$ concentrations at locations not coinciding with four air-quality monitors. Risk of hospitalization for pneumonia was associated with annual average $PM_{2.5}$ concentration, as estimated by both bicubic splines (OR [95% CI]: 1.6 [0.99, 2.63]) and inverse-distance weighting (3.7 [1.3, 10.1]). However, given the acute nature of the examined outcome, some uncertainty remains regarding potential confounding due to short-term $PM_{2.5}$ exposure.

In summary, recent epidemiologic studies do not indicate a clear relationship between long-term $PM_{2.5}$ exposures and respiratory infection in infants or adults. While the limited number of studies reviewed generally reported associations between $PM_{2.5}$ and at least some of the examined respiratory infection outcomes, there was limited overlap in endpoints across studies. Where the same endpoint was examined across multiple studies, large birth cohort studies found some evidence of an association between $PM_{2.5}$ and infant bronchiolitis (Karr et al., 2009b; Karr et al., 2007), but the results were not entirely consistent (Karr et al., 2009a).

5.2.7 Severity of Respiratory Disease

The 2009 PM ISA (U.S. EPA, 2009) reported evidence of an association between long-term $PM_{2.5}$ concentrations and increased severity of respiratory disease in two cohort studies. In one of these, an association between long-term $PM_{2.5}$ concentrations and increased disease severity was indicated by higher odds of bronchitic symptoms in children with asthma (McConnell et al., 2003). Stages of asthma can range in severity from mild, moderate, moderate-persistent, to severe (NHLBI NAEPP, 2007). In a second cohort study reported in the 2009 PM ISA (U.S. EPA, 2009), there was evidence for higher odds of exacerbation in persons with cystic fibrosis (CF). Goss et al. (2004) observed that long-term $PM_{2.5}$ exposure was associated with increased odds of two or more CF exacerbations. CF exacerbations were defined as a CF-related pulmonary condition requiring admission to the hospital or use of home intravenous antibiotics. Particle deposition is increased in CF and particle distribution in the lungs is enhanced in poorly ventilated tracheobronchial regions in CF patients (Brown et al., 2001). Such focal deposition may partially explain the reported association of PM and CF exacerbation. No recent studies examined CF exacerbations in relation to long-term $PM_{2.5}$ concentrations. The 2009 PM ISA also evaluated an animal toxicological study that reported exacerbation of an asthma-like phenotype following long-term DE exposure. However, this study did not distinguish between effects due to gases or particles in the mixture. In addition, animal toxicological evidence for COPD exacerbation following long-term exposure to urban air exposure was reported, however there was no measurement of $PM_{2.5}$ concentrations.

A limited number of recent epidemiologic studies show an association between long-term exposure to $PM_{2.5}$ and severity demonstrated by increased risk of asthma hospitalizations and ED visits in children. A recent study also provides evidence of a similar association in adults. However, potential confounding by short-term exposures remains an uncertainty in ascertaining the independent effect of long-term $PM_{2.5}$ exposure. One recent animal toxicological study evaluated the exacerbation of asthma in an animal model of allergic airway disease.

5.2.7.1 Epidemiologic Studies

Exacerbation of asthma symptoms is an indicator of severity, with more severe symptoms potentially resulting in hospitalization. Recent studies have evaluated the relationship between long-term exposure to $PM_{2.5}$ and asthma-related hospitalizations and ED visits in children. In a cross-sectional analysis using data from the California Health Interview Survey (CHIS), Wilhelm et al. (2008) assessed asthma hospitalization and emergency room visits in children 0 to 17 years old. Annual average $PM_{2.5}$ concentrations in Los Angeles and San Diego counties, measured by the nearest monitor within a 5-mile range, were not strongly associated with increased odds of asthma-related hospitalizations or emergency room visits (OR: 1.04 [95% CI: 0.68, 1.58]). However, there was an association in a copollutant model controlling for O_3 (OR: 1.9 [95% CI: 0.99, 3.7]). Meanwhile, a population-based cohort study of children in Quebec, Canada, the design of which is described in more detail in Tétreault et al. (2016a) and Section 5.2.3.1, also examined exacerbation of asthma in children (Tétreault et al., 2016b). The authors reported increases in hospital admissions and ED visits in relation to $PM_{2.5}$ concentrations measured outside birth residence (HR: 1.15 [95% CI: 1.14 to 1.15]) and using a time-varying model (HR: 1.07 [95% CI: 1.05 to 1.09]). $PM_{2.5}$ concentrations were estimated over a 10 × 10 km grid using satellite-based AOD observation data downscaled by the GEOS-Chem CTM. While these studies provide some evidence of an association between long-term exposure to $PM_{2.5}$ and asthma severity, neither study controlled for short-term exposures. Given the acute nature of the health endpoint, the observed effect could be partially or fully attributable to short-term increases in air pollution on the days prior to admission. Increases in asthma symptoms were also associated with long-term $PM_{2.5}$ concentrations in a cross-sectional study of adults (Balmes et al., 2014). Although asthma symptoms were self-reported using a nonvalidated ordinal questionnaire, responses are unlikely to be differentially misclassified according to exposure. Overall, recent studies examine asthma exacerbation in children and adults and provide additional evidence of a $PM_{2.5}$ effect on asthma severity. However, given the acute nature of the examined outcomes, some uncertainty remains regarding potential confounding due to short-term $PM_{2.5}$ exposure.

5.2.7.2 Animal Toxicological Study

Recently, a study evaluating the effects of $PM_{2.5}$ on severity of disease has become available. In Farraj et al. (2010), the effects of long-term DEP exposure were studied in an allergic mouse model.

BALB/c mice, which had been sensitized with OVA, were exposed to DEP for 4 weeks, with OVA challenges occurring at 2 and 4 weeks. DEP exposure had no effect on the many OVA-induced changes in BALF cells, cytokines, and injury markers (LDH, albumin, protein), except for a decrease in IL-4 ($p < 0.05$). This may be due to the analysis occurring 5 days after the last DEP exposure. Typically, acute inflammatory responses are measured at 24−48 hours after exposure to PM. Furthermore, Farraj et al. (2010) found that DEP exposure had no effect on airway responsiveness, as assessed by methacholine-induced changes in lung resistance, in the allergic mice. Additional study details for this study are found in Table 5-24.

Table 5-24 Study-specific details from an animal toxicological study of long-term $PM_{2.5}$ exposure and severity of an asthma-like phenotype.

Study/Study Population	Pollutant	Exposure	Endpoints
Farraj et al. (2010) Species: Mouse Sex: Male Strain: BALB/c Age/Weight: 6 weeks	Diesel exhaust particles (DEP) NIST SRM 29 + 5 Particle size: 1.2 µm MMAD Control: Saline aerosol	Route: Nose only inhalation Dose/Concentration: 2.0 mg/m³ Duration: 1 time per week for 4 weeks Time to analysis: 5 d from last DEP Coexposure: Sham sensitization and saline aerosols. Diesel combustion gases not defined.	Lung injury • BALF LDH, albumin, and protein BALF cytokines Lung function

BALF = bronchoalveolar lavage fluid; LDH = lactate dehydrogenase; MMAD = mass median aerodynamic diameter; NIST SRM = National Institute of Standards and Technology Standard Reference Material.

5.2.8 Subclinical Effects in Healthy Populations

Animal toxicological studies provide evidence for subclinical effects potentially underlying the development of respiratory disease in healthy populations. The 2009 PM ISA (U.S. EPA, 2009) reported several studies that evaluated the effects of long-term exposure to $PM_{2.5}$ on subclinical effects in healthy populations. These studies provided evidence of pulmonary injury, inflammation, oxidative stress, and morphological alterations following long-term exposure to DE, GE, and woodsmoke. While most studies made no effort to distinguish between effects due to gases or particles in the mixture, one study examined the effects of particle filtration. Injury and inflammatory responses to DE were diminished as a result of particle filtration, indicating that PM played a role in the responses. Recent animal toxicological studies examined subclinical effects related to an asthma-like phenotype as discussed above (see

Section 5.2.3.3.2 and Section 5.2.7). Other respiratory-related subclinical effects, including oxidative stress, inflammation, and altered morphology have been investigated in studies of long-term $PM_{2.5}$ exposure. These results are discussed below, with additional study details found in Table 5-25.

Pulmonary Oxidative Stress

The 2009 PM ISA (U.S. EPA, 2009) evaluated several studies that examined pulmonary oxidative stress following long-term exposure to DE. These studies did not distinguish between effects due to gases or particles in the mixture. Recently, Kampfrath et al. (2011) investigated the effects of a 20-week exposure to $PM_{2.5}$ CAPs in Columbus, OH on oxidized phospholipids in the lung. Responses were compared in wild type and Toll-like receptor 4 (TLR4) deficient BALB/c mice. Increased levels of two oxidized forms of 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphocholine (PAPC), the most common phospholipid in BALF, were observed in wild type mice exposed to $PM_{2.5}$ CAPs. Statistical analysis of these results was not presented. In a follow up study, Deiuliis et al. (2012) demonstrated the presence of oxidized PAPC in BALF in C57BL/6 mice exposed for 28 weeks to $PM_{2.5}$ CAPs in Columbus, OH ($p = 0.001$), thus confirming the results of (Kampfrath et al., 2011). Since oxidized lipids play a role in activating T cells, inflammatory T cells were also examined (see below). Aztatzi-Aguilar et al. (2015) found increased lung tissue heme oxygenase-1 activity in Sprague Dawley rats following 8-weeks exposure $PM_{2.5}$ CAPs in Mexico City ($p < 0.05$), while no changes in γ-glutamyl cysteine ligase catalytic subunit, another index of oxidative stress, were observed.

Table 5-25 Study-specific details from animal toxicological studies of long-term $PM_{2.5}$ exposure and subclinical effects.

Study/Study Population	Pollutant	Exposure	Endpoints
Aztatzi-Aguilar et al. (2015) Species: Rat Sex: Male Strain: Sprague Dawley	$PM_{2.5}$ CAPs Mexico City Particle size: $PM_{2.5}$ Control: Filtered air	Route: Inhalation Dose/Concentration: $PM_{2.5}$ 178 µg/m^3 Duration: Acute 5 h/day, 3 days Subchronic 5 h/day, 4 days/week, 8 weeks Time to Analysis: 24 h	Gene and protein expression • IL-6 • Kallikrein-kinin system • RAS • Heme oxygenase-1
Deiuliis et al. (2012) Species: Mouse Sex: Male Strain: C57BL/6 (wild type) • CXCR3 knockout • Foxp3-GFP knockout Age/Weight: 12 weeks	$PM_{2.5}$ CAPs Columbus, OH Particle size: ≤$PM_{2.5}$ Control: HEPA-filtered air	Route: Whole-body inhalation Dose/Concentration: 115.5 µg/m³ Duration: 6 h/day, 5 days/week, 24−28 weeks Time to analysis: 1 h	Histopathology—lung Oxidative stress: • oxidized PAPC in BALF T cell subsets • $CD3^+$ lymphocytes—T regs Gene expression-1L-17α, and CXCR3 gene expression in $CD4^+$ T cells from lung
Guo et al. (2017) Species: Rat Strain: Sprague Dawley Sex: Female Age/Weight: 4−5 weeks	Ambient particles (Shanghai, China), liquid aerosol generator Particle size: $PM_{2.5}$ Control: Saline aerosol	Route: Whole-body inhalation Dose/Concentration: 200, 1,000, and 3,000 µg/m³ Duration: 3 h/day for 30 days	Nasal mucosa- • Malondialdehyde • SOD • ATPases • Mitochondrial mRNA and protein • Histological and ultrastructural analysis • Serum cytokines
Kampfrath et al. (2011) Species: Mouse Sex: Male Strain: BALB/c (wild type) and TLR4 knockout Age/Weight: 6 weeks	$PM_{2.5}$ CAPs Columbus, OH Particle size: ≤$PM_{2.5}$ Control: HEPA-filtered air	Route: Whole-body inhalation Dose/Concentration: 92.4 µg/m³ Duration: 6 h/day, 5 days/week, 20 weeks	Oxidative stress: Oxidized PAPC in BALF

Table 5-25 (Continued): Study specific details from animal toxicological studies of long term $PM_{2.5}$ exposure and subclinical effects.

Study/Study Population	Pollutant	Exposure	Endpoints
Kim et al. (2016a) Species: Mouse Strain: BALB/c Sex: Female Age/Weight: 5−6 weeks	DEP nebulized Particle size: Mean diameter 0.4 μm before nebulization and 1−5 μm after nebulization Control: Saline aerosol	Dose/Concentration: 0.1 and 3 mg/m^3 DEP or saline (only results from 0.1 mg/m^3 reported here) Duration: 1 h/day, 5 days/week for 4, 8, and 12 weeks Time to analysis: 1 day after last exposure	BALF cells BALF cytokines Histochemistry • Masson trichome staining of lung
Ramanathan et al. (2017) Species: Mouse Strain: C57BL/6 Sex: Male Age/Weight: 8 weeks	$PM_{2.5}$ CAPs Baltimore, MD Particle size: $PM_{2.5}$ Control: Filtered air	Dose/concentration: 60.92 ± 21.31 μg/m^3 Controls: 8.09 ± 2.61 μg/m^3 Duration: 6 h/day, 5 days/week, 16 weeks	Nasal histopathology Nasal airway lavage: Inflammatory cells, cytokines, albumin
Tyler et al. (2016) Species: Mouse Strain: C57BL/6 and ApoE knockout Age/Weight: 6−8 weeks	DEP, resuspended Particle size: 1.5−3.0 μm ± 1.3−1.6 μm Control: Filtered air	Route: Whole-body inhalation Dose/Concentration: 315.3 ± 50.7 μg/m^3 Duration: 6 h/days for 30 days	BALF cells and cytokines Particle uptake in bronchial macrophages

ApoE = apolipoprotein E; ATPase = adenosine triphosphatase; BALF = bronchoalveolar lavage fluid; CD = cluster of differentiation; CXCR3 = chemokine receptor CXCR3; DEP = diesel exhaust particle; Foxp3 = forkhead box P3; IL-6 = interleukin-6; IL-17 α = interleukin-17 α; PAPC = 1-palmitoyl-2-arachidonoyl-sn-phosphatidylcholine; RAS = renin-angiotensin system; SOD = superoxide dismutase, T-regs = regulatory T lymphocytes; TLR4 = toll-like receptor 4.

Pulmonary Inflammation

The 2009 PM ISA (U.S. EPA, 2009) reported several studies evaluating pulmonary inflammation following long-term exposure to DE and woodsmoke. These studies did not distinguish between effects due to gases or particles in the mixture. Recently, Deiuliis et al. (2012) exposed wild type C57BL/6 mice and mice deficient in T cell chemokine receptor 3 (CXCR3) for 28 weeks to PM $_{2.5}$ CAPs in Columbus, OH. $PM_{2.5}$ CAPs exposure resulted in increased numbers of CD11c+, but not CD11b+, macrophages ($p < 0.0002$) in the lungs of wild type mice, as assessed by flow cytometry. CXCR3 deficiency decreased basal numbers of these macrophage subtypes and responses to $PM_{2.5}$ CAPs exposure. In wild type mice, $PM_{2.5}$ CAPs exposure resulted in increased numbers of T cell subsets, including $CD3^+$ ($p = 0.005$), $CD4^+$ ($p = 0.007$), and CD8+ lymphocytes ($p = 0.04$), Basal levels of these subsets and responses to $PM_{2.5}$ CAPs exposure were attenuated in CXCR3-deficient mice. A similar pattern of response was observed for activated CD44 + CD62L - CD4 + T cells ($p = 0.01$). However, in the case of central memory CD44 + CD62L - CCR7 + T cells, $PM_{2.5}$ CAPs exposure induced increases in both wild-type ($p = 0.01$) and CXCR4-deficient mice ($p = 0.04$). Expression of CXCR3 on $CD4^+$($p = 0.005$), but not $CD8^+$, T cells was increased by $PM_{2.5}$ CAPs. Gene expression was also evaluated in isolated lung $CD4^+$ T cell.

Long-term $PM_{2.5}$ CAPs exposure increased expression of CXCR3 and, IL-17α, but not CCR3, CCR4, and IL-4. These results show that long-term exposure to $PM_{2.5}$ CAPs induced T cell infiltration and increased activation of effector T cells in the lungs and suggests a Th1 rather than a Th2 response. The role of CXCR3 in mediating the effects of $PM_{2.5}$ CAPs is unclear since its deficiency had effects on both basal and PM-stimulated inflammation. Results of this study indicate that activation of macrophages by oxidized phospholipids (see above) may lead to the release of cytokines which recruit and activate T cells as part of a proinflammatory Th1 response.

Kim et al. (2016a) exposed BALB/c mice to nebulized DEP for 4, 8, and 12 weeks. DEP exposure resulted in increased numbers of BALF lymphocytes at 4 and 12 weeks ($p < 0.05$). Numbers of other inflammatory cells and total cells in BALF were not altered. However, increased levels of cytokines IFN-γ, IL-6, VEGF, and TGF-β were observed in BALF at 12 weeks ($p < 0.05$). In contrast, two other studies found no evidence of inflammation following long-term $PM_{2.5}$ exposure. No increase in BALF inflammatory cells or cytokines or particle uptake into bronchial macrophages was observed in C57BL/7 mice exposed to resuspended DEP for 30 days (Tyler et al., 2016). However, inflammatory effects were observed in the hippocampus (Section 8.1.3). Aztatzi-Aguilar et al. (2015) exposed Sprague Dawley rats for 8 weeks to $PM_{2.5}$ CAPs in Mexico City and found decreased protein expression of IL-6 in lung tissue ($p < 0.05$). However, long-term $PM_{2.5}$ CAPs exposure also had several effects on the RAS in the lung ($p < 0.05$). This included induced lung expression of the angiotensin 1 receptor gene, and increased angiotensin 1 receptor protein levels. Protein levels and mRNA of angiotensin converting enzyme were not impacted. Components of the RAS play an important role in the pulmonary circulation.

Morphological Effects

In a long-term exposure study involving DEP, Kim et al. (2016a) found increased collagen deposition, as assessed by Masson trichrome staining, at 4, 8, and 12 weeks ($p < 0.05$) (see Section 5.2.3.3.2). Increased and disordered collagen deposition underlies lung fibrosis, which is mediated in part by the cytokine TGF-β, whose levels were increased as a result of DEP exposure in this study ($p < 0.05$).

Recent studies also examine effects on nasal mucosa (Guo et al., 2017) (Ramanathan et al., 2017). (Guo et al., 2017) evaluated nasal injury and oxidative stress in Sprague Dawley rats following 30-day inhalation of two concentrations of resuspended $PM_{2.5}$ from Shanghai, China. Long-term Exposure to $PM_{2.5}$ resulted in increased malondialdehyde levels in nasal mucosa ($p < 0.05$). Morphological alterations were observed, including nasal epithelial necrosis, disarray of cilia, vascular congestion, and edema. At the ultrastructural level, mitochondrial alterations were observed, including swelling, cristae disorder, and vacuolization. Activities of several enzymes (superoxide dismutase, sodium potassium ATPase, calcium ATPase) in nasal mucosa were decreased by exposure ($p < 0.01$). Gene expression and protein levels of OPA1 and Mnf1, which are involved in mitochondrial fusion and fission, were increased by long-term exposure to both concentrations of $PM_{2.5}$ ($p < 0.01$). Ramanathan et al. (2017) examined the effects of a

16-week exposure to $PM_{2.5}$ CAPs in Baltimore, MD on the sinonasal barrier of C57BL/6 mice. Numbers of macrophages, neutrophils, and eosinophils were increased in NALF ($p < 0.05$). Levels of proinflammatory cytokines were also increased in NALF, including IL-1β, IL-13, and eotaxin-1. Immunostaining of sinonasal mucosa revealed increased staining for myeloperoxidase and eosinophil major basic protein positive cells ($p < 0.05$). Evidence for sinonasal epithelial cell barrier dysfunction was provided by decreased expression of tight junction and adherens junction proteins claudin-1 and E-cadherin and by increased levels of serum albumin in NALF ($p < 0.05$). Furthermore, morphometric analysis of the septal subepithelial thickness showed an increase as a result of long-term exposure to $PM_{2.5}$ ($p < 0.001$).

Summary of Subclinical Effects in Healthy Populations

Recent studies and one older study provide evidence for several subclinical effects potentially underlying the development of respiratory disease following long-term $PM_{2.5}$ exposure in healthy animal models. These include pulmonary injury, oxidative stress, inflammation and altered morphology. In particular, increases in tissue and BALF expression of antioxidant genes and proteins and increases in BALF levels of oxidized phospholipids were found. Upregulation of cytokines in the lungs and infiltration of inflammatory cells, including lymphocytes, monocytes, and specific T-cells subtypes consistent with a Th1 proinflammatory response, were also observed. In addition, long-term $PM_{2.5}$ exposure resulted in increased collagen deposition, an early step in the development of lung fibrosis, and upregulation of the RAS. While the above-mentioned studies focused on the lower airways, changes to the upper airways were also demonstrated. Two studies found evidence of oxidative stress, injury, inflammation, and morphologic changes in nasal mucosa resulting from long-term exposure to $PM_{2.5}$.

5.2.9 Subclinical Effects in Populations with Cardiovascular Disease

Animal toxicological studies provide evidence for subclinical effects potentially underlying the development of respiratory disease in populations with cardiovascular disease. The 2009 PM ISA (U.S. EPA, 2009) reported several studies that evaluated the effects of long-term exposure to $PM_{2.5}$ in animal models of cardiovascular disease, mainly focusing on pulmonary inflammation. In ApoE and LDL knock-out mice, exposure for 1−5 months to $PM_{2.5}$ CAPs resulted in upregulation of gene expression in lung tissue, although no increases in BALF inflammatory cells were found. Inflammation and altered morphology were observed following long-term exposure to DE in spontaneously hypertensive (SH) rats. However, there was no attempt to distinguish between effects due to gases or particles in the DE mixture.

Recent studies examined pulmonary oxidative stress and inflammation. Evidence for pulmonary inflammation was found in SH rats exposed to $PM_{2.5}$ CAPs in Columbus, OH for 15 weeks (Ying et al., 2015). Expression of TNFα and IL-6 mRNA in lung tissue was increased at 15 weeks ($p < 0.05$) and remained elevated 5 weeks following the end of exposure. Xu et al. (2012) exposed ApoE knockout mice

to $PM_{2.5}$ CAPs in Tuxedo, NY for 3 months. Monocytic infiltration into the lung was observed, as evidenced by increased numbers of $F4/F80^+$ macrophage ($p < 0.001$). Wan et al. (2014) conducted a 2-month long field study of ApoE knockout mice exposed to ambient air in Beijing and fed a Western diet. Urban air PM mainly consisted of $PM_{2.5}$, but it also contained some PM_{10}; other ambient pollutants were also present. Control mice were exposed to filtered ambient air, which contained greatly reduced concentrations of $PM_{2.5}$. Long-term exposure to Beijing urban air increased BALF levels of oxidized LDL and MDA, decreased BALF SOD and GSHPx activity and increased BALF levels of IL-6 and TNF-a protein ($p < 0.05$). In contrast, Tyler et al. (2016) exposed ApoE knockout mice to resuspended DEP for 30 days and found no increase in inflammatory cells or cytokines in the BALF, although particle uptake into bronchial macrophages was increased ($p < 0.001$). Effects were also seen in the hippocampus (Section 8.2.3). Overall, evidence for inflammation was found in lung tissue following long-term exposure to $PM_{2.5}$ CAPs, but not in BALF following long-term exposure to DEP. Interpretation of effects due to long-term urban air exposure is complicated by the presence of $PM_{10–2.5}$. Additional study details are found in Table 5-26.

Table 5-26 Study-specific details from animal toxicological studies of long-term $PM_{2.5}$ exposure and subclinical effects in populations with cardiovascular disease.

Study/Study Population	Pollutant	Exposure	Endpoints
Tyler et al. (2016) Species: Mouse Strain: ApoE knockout Age/Weight: 6−8 weeks	DEP, resuspended Particle size: 1.5−3.0 μm ± 1.3−1.6 μm Control: Filtered air	Route: Whole-body inhalation Dose/Concentration: 315.3 ± 50.7 μg/m^3 Duration: 6 h/day for 30 days	BALF cells and cytokines Particle uptake in bronchial macrophages
Wan et al. (2014) Species: Mouse Strain: Apo E knockout C57BL/6) Sex: Male Age/Weight: 9 weeks	Beijing PM Particle sizes: $PM_{2.5}$ + PM_{10} Control: HEPA-filtered ambient air	Route: Ambient Beijing air Dose/concentration: $PM_{2.5}$ 63.1 μg/m^3 $PM_{10-2.5}$ 37.2 μg/m^3 (estimated as the difference of PM_{10} and $PM_{2.5}$ concentration measurements made with one continuous monitor) Duration of exposure: 24 h/day, 7 days/week for 2 mo Coexposure Western Diet	BALF Cytokines- IL-6 and TNF-α Oxidative stress markers—Ox LDL, malondialdehyde, SOD and GSHPx
Xu et al. (2012) Species: Mouse Strain: Apo E knockout Sex: Male Age/Weight: 8 weeks	$PM_{2.5}$ CAPs Tuxedo NY Particle sizes: $PM_{2.5}$ Control: Filtered air	Route: Whole-body inhalation Dose/concentration: $PM_{2.5}$ CAPs 70 μg/m^3 Duration of exposure: 6 h/day, 5 days/week for 3 mo	Histopathology—lung
Ying et al. (2015) Species: Rat Strain: SHR Sex: Male Age/Weight: 5 weeks	$PM_{2.5}$ CAPs from Columbus, OH Particle sizes: $PM_{2.5}$ Control: Filtered air	Route: Whole-body inhalation Dose/Concentration: 128.3 ± 60.4 μg/m^3 Duration: 6 h/day, 5 days/week for 15 weeks Time to analysis: Immediately or 5 weeks later	Gene expression—inflammatory markers in lung

ApoE = apolipoprotein E; BALF = bronchoalveolar lavage fluid; DEP = diesel exhaust particle; GSHPX = glutathione peroxidase; HEPA = high efficiency particulate absorber; IL-6 = interleukin-6; OxLDL = oxidized low density lipoprotein; SHR = spontaneously hypertensive rat; SOD = superoxide dismutase; TNF α = tumor necrosis factor α.

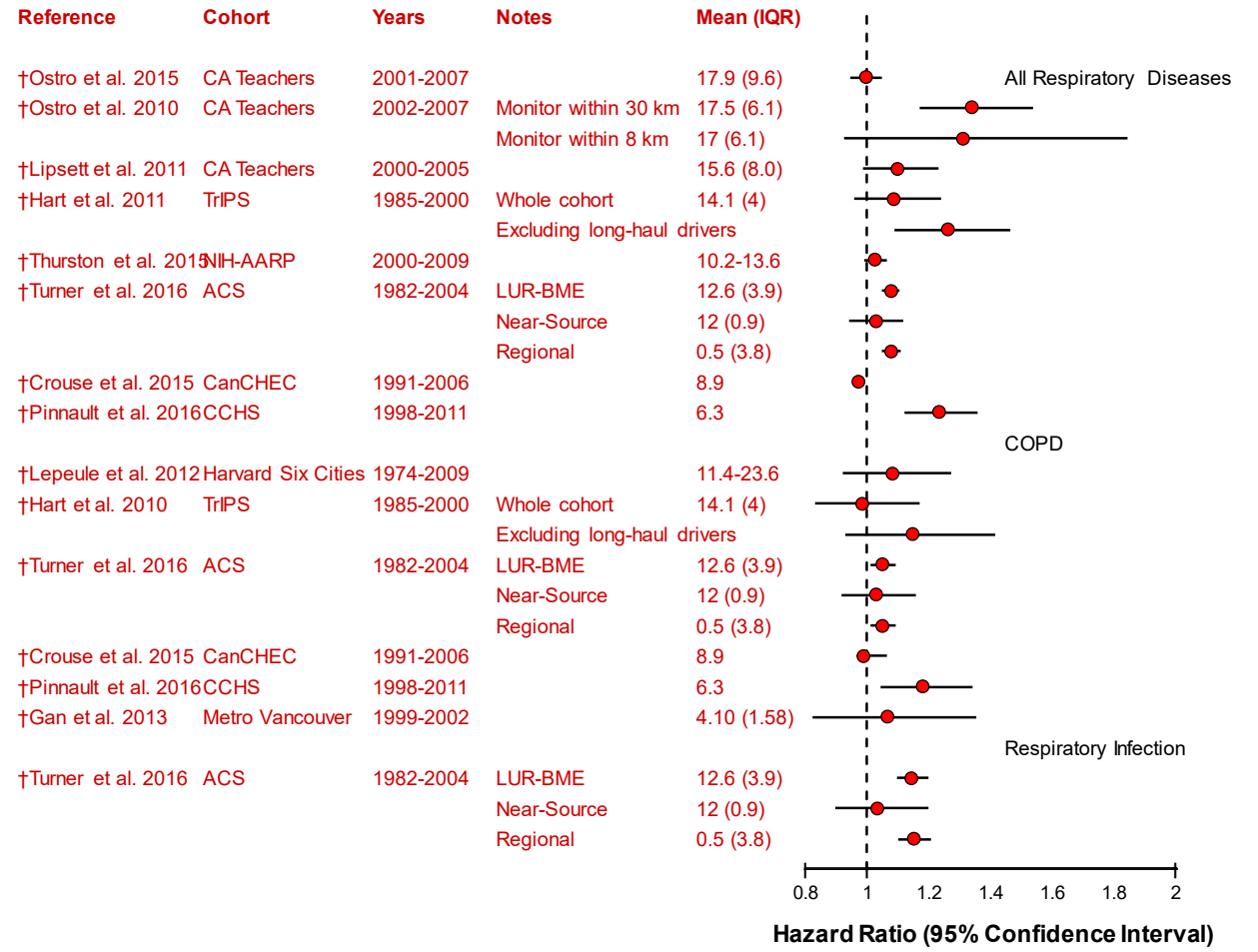
5.2.10 Respiratory Mortality

Studies that examine the association between long-term $PM_{2.5}$ exposure and cause-specific mortality outcomes, such as respiratory mortality, provide additional evidence for $PM_{2.5}$-related respiratory effects, specifically whether there is evidence of an overall continuum of effects. Evidence from studies of long-term $PM_{2.5}$ exposure and mortality are presented in detail in CHAPTER 11.

Evidence from studies investigating respiratory mortality provided limited and inconsistent evidence for a respiratory effect related to long-term $PM_{2.5}$ exposure in the 2009 PM ISA (U.S. EPA, 2009) and are summarized here to inform the effect of long-term $PM_{2.5}$ exposure on the continuum of respiratory health effects. The 2009 PM ISA (U.S. EPA, 2009) included evidence from two large, multicity U.S. studies: the American Cancer Society (ACS) cohort (Pope III et al., 2004) and the Harvard six cities cohort (Laden et al., 2006). Recent updates to these studies, as well as results from recent cohort studies, contribute to the body of evidence for this relationship (Figure 5-34).

Several recent analyses further evaluated the associations of long-term $PM_{2.5}$ exposures with risk of respiratory mortality based on the original ACS study (Pope et al., 1995), adding details about deaths due to respiratory disease (including COPD), and extending the follow-up period for the ACS to 22 years (1982−2004). In particular, Pope et al. (2014) and Turner et al. (2016) used the extended follow-up period of the ACS to examine the associations between long-term $PM_{2.5}$ exposure and respiratory disease and COPD. The results of these extended analyses demonstrated positive associations with respiratory disease and COPD mortality, which had not been previously evaluated among the ACS cohort. Similarly, Lepeule et al. (2012) reported the results of an extended analysis of the Harvard Six Cities cohort, extending the follow-up period to include deaths between 1974 and 2009. This was the first time that COPD mortality was evaluated among the Harvard Six Cities cohort; the relative risk was positive, but imprecise due to the smaller number of COPD deaths compared to deaths from other causes.

Several additional U.S. cohort studies evaluated the association between long-term $PM_{2.5}$ exposure and respiratory mortality. In a nationwide cohort of older Americans, Thurston et al. (2015) used monthly estimates of $PM_{2.5}$ concentration to assign annual mean concentrations to participants in the NIH-AARP cohort study and observed a positive association with respiratory mortality. The California Teachers Study (Lipsett et al., 2011; Ostro et al., 2010) examined the association between $PM_{2.5}$ and mortality among female public-school teachers and observed positive associations between long-term $PM_{2.5}$ exposure and respiratory mortality. In a reanalysis of the cohort with refined exposure assessment, Ostro et al. (2015) used a chemical transport model (CTM) to predict $PM_{2.5}$ concentrations with a 4-km spatial resolution, observing a null association between $PM_{2.5}$ exposure and respiratory mortality. Hart et al. (2011) examined the association between residential exposure to $PM_{2.5}$ estimated from a single year of monitoring data (2000) and mortality among men in the U.S. trucking industry in the Trucking Industry Particle Study (TrIPS). The results for respiratory mortality were similar to those reported by Lipsett et al. (2011) for respiratory mortality. The results for COPD mortality were null for the cohort and positive, though imprecise for a sensitivity analyses excluding long-haul drivers.



CanCHEC = Canadian Census Health and Environment Cohort; IQR = interquartile range; TrIPS = Trucking Industry Particle Study; NIH-AARP = National Institutes of Health American Association of Retired Persons Diet and Health Cohort; ACS = American Cancer Society Cohort; CCHS = Canadian Community Health Survey; LUR-BME = land use regression-Bayesian maximum entropy exposure model.

Note: †Studies published since the 2009 PM ISA. Associations are presented per 5 μg/m^3 increase in pollutant concentration. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Study results from Lepeule et al. (2012) are representative of results from the Harvard Six Cities Cohort; Study results from Turner et al. (2016) are representative of the results from the American Cancer Society Cohort.

Figure 5-34 Associations between long-term exposure to $PM_{2.5}$ and respiratory mortality in recent North American cohorts.

In an extended reanalysis of the Canadian CanCHEC cohort Crouse et al. (2015) observed associations for respiratory and COPD mortality that were just below the null value. The general pattern and magnitude of these associations were generally unchanged in cumulative risk models that include O_3 and/or NO_2. Pinault et al. (2016) linked a subset of participants from the CanCHEC cohort to the Canadian Community Health Survey and observed positive associations with respiratory mortality. Pinault et al. (2016) was able to make use of the individual-level covariate data on age, sex, smoking, alcohol consumption, obesity, and fruit/vegetable consumption that was not available in the larger

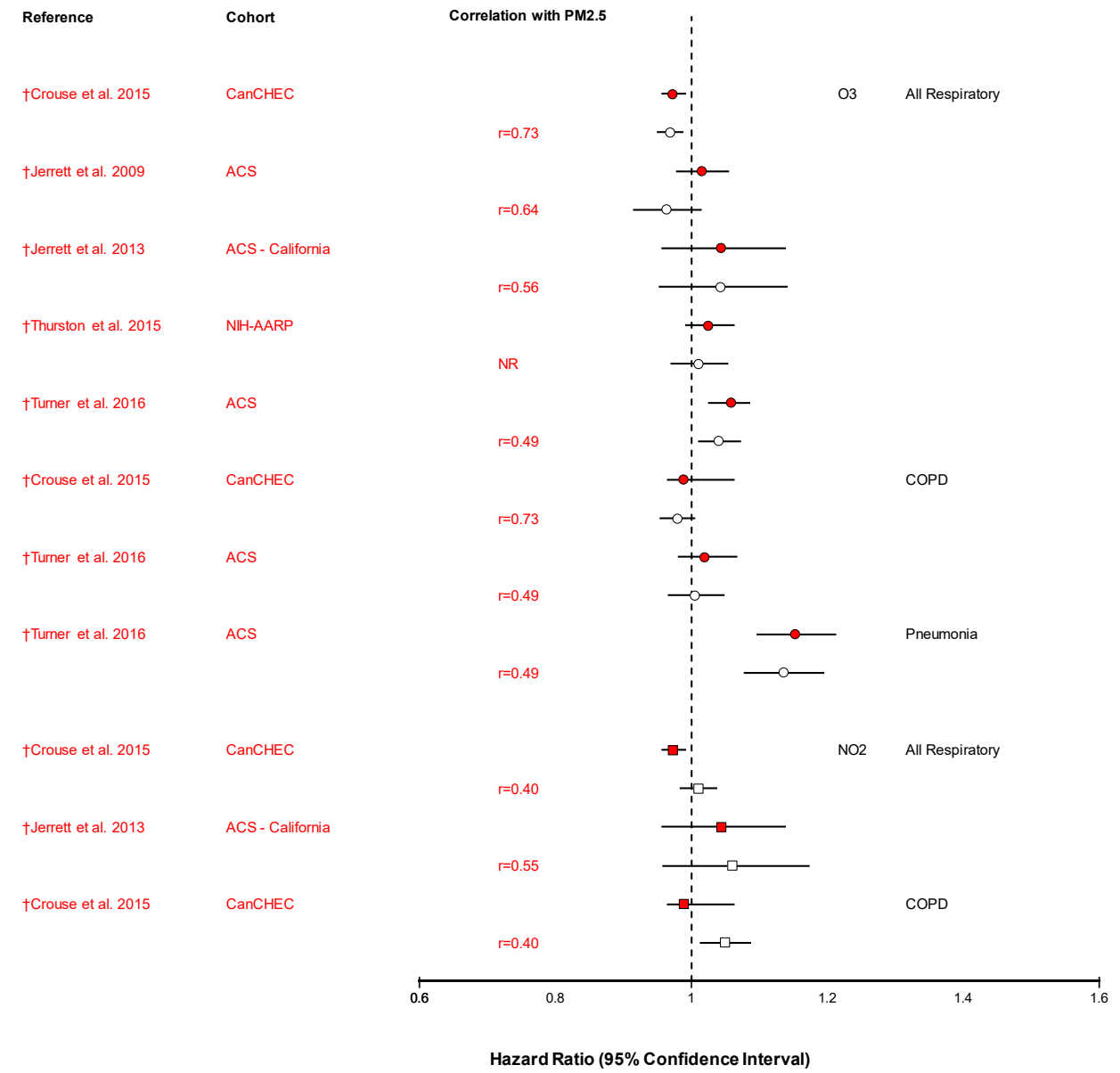
CanCHEC cohort. The inclusion of these individual-level data may help to explain the inconsistent results observed by Crouse et al. (2015) and Pinault et al. (2016).

Overall, the results of these recent U.S. cohort studies demonstrate a generally consistent, positive association between long-term $PM_{2.5}$ exposure and respiratory mortality, though the results from the two Canadian studies are inconsistent. In addition, a study conducted in Europe that pooled data from 22 existing cohort studies and evaluated the association between long-term $PM_{2.5}$ exposure and respiratory mortality observed an association for respiratory mortality near the null value (Dimakopoulou et al., 2014). The associations for respiratory mortality in analysis of pooled data were generally positive, though some inconsistencies among the results from different analyses of the same cohort provide some uncertainty in the stability of these results (Pinault et al., 2016; Crouse et al., 2015; Ostro et al., 2015; Ostro et al., 2010). Recent studies have evaluated the association between long-term $PM_{2.5}$ exposure and COPD mortality, a cause of death for which there has previously been little examination. These studies report modest positive associations with COPD mortality and the hazard ratios are generally less precise than those for respiratory mortality. A single study (Turner et al., 2016) examined deaths due to respiratory infection and long-term $PM_{2.5}$ exposure and observed a positive association.

5.2.10.1 Potential Copollutant Confounding of the $PM_{2.5}$-Mortality Relationship

In the examination of potential confounding effects of copollutants on the relationship between long-term $PM_{2.5}$ exposure and respiratory mortality, it is informative to evaluate whether $PM_{2.5}$ risk estimates are changed in copollutant models. Recent studies have examined the potential for copollutant confounding by evaluating copollutant models that include O_3 and NO_2 (Figure 5-35). These recent studies address a previously identified data gap by informing the extent to which effects associated with exposure to $PM_{2.5}$ are independent of coexposure to correlated copollutants in long-term analyses.

The results for associations between long-term $PM_{2.5}$ exposure and respiratory mortality in single pollutant models and copollutant models adjusted for O_3 and NO_2 are shown in Figure 5-35. The correlations between $PM_{2.5}$ and O_3 exposures in the studies that conducted copollutant analyses were generally positive and moderate to strong, ranging from $r = 0.49$ to 0.73. Generally, the $PM_{2.5}$ effect estimates remained relatively unchanged in copollutant models adjusted for O_3. The associations persisted across different specific causes of respiratory mortality. The correlations between $PM_{2.5}$ and NO_2 exposures in studies that conducted copollutant analyses were positive and moderate ($r = 0.40$; $r = 0.55$). In one study (Jerrett et al., 2013), the $PM_{2.5}$ effect estimates remained relatively unchanged in a copollutant model adjusted for NO_2, while in another (Crouse et al., 2015), the $PM_{2.5}$ estimates increased and changed from negative to positive after adjusting for NO_2 for respiratory and COPD mortality.



ACS: American Cancer Society Cohort; CanCHEC = Canadian Census Health and Environment Cohort; AHSMOG = Adventist Health Air Pollution Study; COPD = chronic obstructive pulmonary disease; NR = not reported.

Note: †Studies published since the 2009 PM ISA. Circles and squares represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Filled symbols represent effect of $PM_{2.5}$ in single pollutant models, open circles represent effect of $PM_{2.5}$ adjusted for O_3; open squares represent effect of $PM_{2.5}$ adjusted for NO_2. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration.

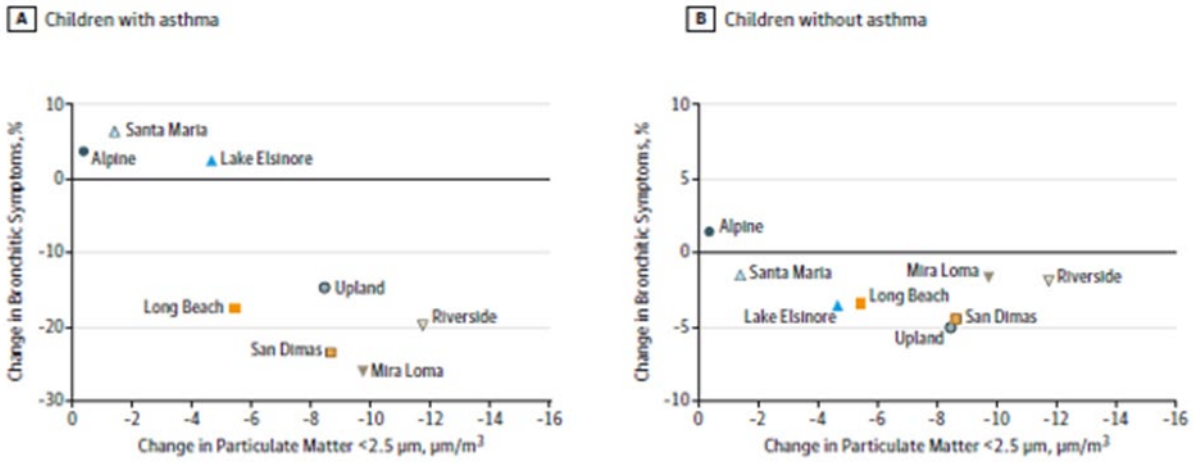
Figure 5-35 Long-term exposure to $PM_{2.5}$ and mortality in single pollutant models and models adjusted for ozone or nitrogen dioxide.

5.2.11 Respiratory Effects and Declining $PM_{2.5}$ Concentrations

In the 2009 PM ISA (U.S. EPA, 2009), none of the reviewed studies related declining concentrations of long-term $PM_{2.5}$ to respiratory health endpoints. A reduction in air pollution can restore "biological normality by removal of an abnormal exposure" (Rose, 1981). In populations, this has been shown to lead to a reduction of risk in a large number of people and result in a decline in cases of respiratory disease or improved lung function and development. Recent studies examine $PM_{2.5}$ decreases and improvements in respiratory health in children and adults. The majority of this recent evidence comes from prospective cohort studies of decreased $PM_{2.5}$ concentrations in CHS communities that observed improved respiratory health in children (Berhane et al., 2016; Gauderman et al., 2015).

5.2.11.1 Bronchitis

Since the beginning of the CHS studies, pollutant levels have been declining in the CHS southern California communities. Recently, Berhane et al. (2016) prospectively examined the relationship between declining pollutant levels and self-reported chronic bronchitis symptoms in three cohorts of children (n = 4,602) in eight communities. From 1992 to 2012, mean $PM_{2.5}$ concentrations declined across all communities from 20.5 to 14.4 $\mu g/m^3$. Due to significant differences in chronic bronchitis prevalence by asthma status, the authors presented separate results for children without asthma and children with asthma. As depicted in Figure 5-36, communities with greater reductions of $PM_{2.5}$ had larger unadjusted reductions of bronchitis symptoms. The relationship was noticeably stronger in children with asthma. In adjusted models, a 5 $\mu g/m^3$ decrease in $PM_{2.5}$ was associated with a 25% (95% CI: 11, 37%) decrease in odds of bronchitic symptoms in 10-year old children with asthma. Berhane et al. (2016) also observed decreases in bronchitic symptoms in 10-year olds without asthma (OR = 0.84 [95% CI: 0.76, 0.93] per 5 $\mu g/m^3$ decrease in $PM_{2.5}$). The observed associations were relatively unchanged in copollutant models controlling for O_3 ($r = 0.54$). Copollutant models with other pollutants were not examined due to high correlations (NO_2: $r = 84$; PM_{10}: $r = 0.88$). Meanwhile, observed decrements in bronchitic symptoms in 15-year olds were similar, but slightly stronger than those seen in 10-year-olds.

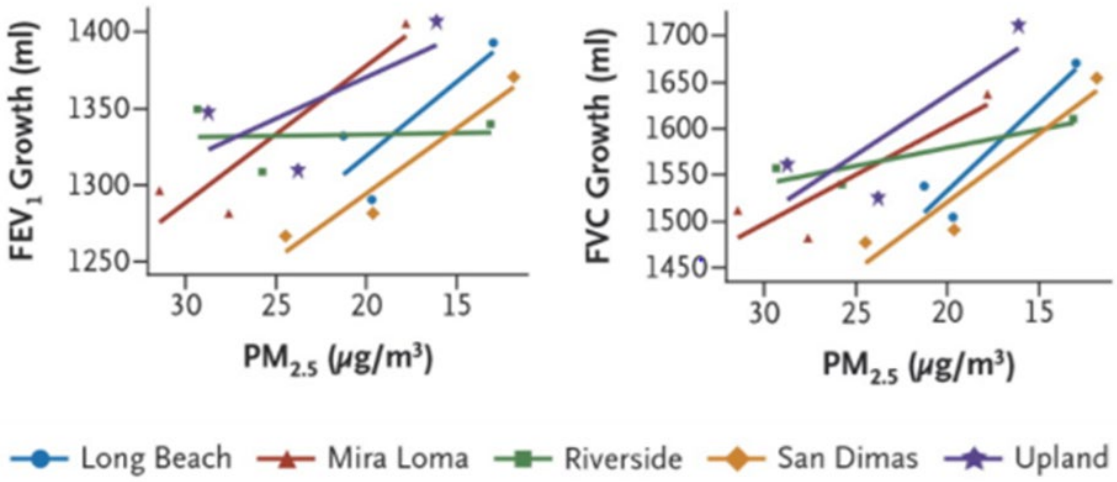


Source: Permission pending, Berhane et al. (2016).

Figure 5-36 Estimated bronchitic symptom prevalence at age 10 versus mean air pollutant concentrations among Children's Health Study (CHS) participants by asthma status.

5.2.11.2 Pulmonary Function

A recent study combined data obtained from three separate CHS cohorts to examine the association between long term reductions in air pollution and lung development in children between the ages of 11 and 15 (Gilliland et al., 2017; Gauderman et al., 2015). Study specific details, including results, are presented in Table 5-19 (Section 5.2.2.1). Briefly, the study sample included children recruited from three separate CHS cohorts spread out over a 20-year period. The analysis was restricted to the five study communities (Long Beach, Mira Loma, Riverside, San Dimas, and Upland) in which pulmonary function testing was performed in all three cohorts (n = 2,120). Significant improvements in lung-function growth were observed within and across communities as air quality improved over the study period (see Figure 5-37 for unadjusted relationship and Table 5-19 for fully-adjusted model results).



Note: The 4-year mean growth in forced expiratory volume in 1 second (FEV_1) and the mean growth in forced vital capacity (FVC) from 11 to 15 years of age are plotted against the corresponding levels of $PM_{2.5}$ for each community and cohort.
Source: Permission pending, Gauderman et al. (2015).

Figure 5-37 Mean 4-year lung-function growth versus the mean levels of $PM_{2.5}$.

A similar study examined the impact of improved air quality on lung function in adults (Boogaard et al., 2013). Boogaard et al. (2013) conducted a small population-based study in the Netherlands, aiming to describe the effect of traffic policy-related reductions in air pollution in 12 locations in the Netherlands (8 urban, 4 suburban). Study details and results are presented in Table 5-20 (Section 5.2.2.2). In summary, baseline lung function was measured in 746 participants prior to implementation of a low emission zone traffic policy. Lung function was measured again at follow-up, 2 years after policy implementation (87% follow-up). In adjusted analyses, 2-year declines in $PM_{2.5}$ were associated with increases in FVC and decreases in airway resistance, indicating improvements in lung function associated with reductions in $PM_{2.5}$.

5.2.11.3 Summary

Initial studies examining the relationship between improvements in air quality and whether this resulted in beneficial changes in respiratory effects observed a consistent relationship between decreasing $PM_{2.5}$ concentrations and improved respiratory health. These results provide corroborating evidence of an association between $PM_{2.5}$ and lung development (Section 5.2.2) and bronchitis (Section 5.2.5). Examination of potential copollutant confounding was limited, but there was evidence that the $PM_{2.5}$ effect was robust in models including O_3 (Berhane et al., 2016).

5.2.12 Associations Between $PM_{2.5}$ Components and Sources and Respiratory Effects

The 2009 PM ISA (U.S. EPA, 2009) did not include an organized discussion of the potential relationship between long-term exposure to $PM_{2.5}$ components and respiratory effects. The limited number of available studies found some evidence of an association between respiratory health and exposure to elemental and organic carbon (EC and OC), but no studies examining metals were available. In addition to constituting a small body of evidence, the EC and OC results did not adjust for $PM_{2.5}$ mass, which raises additional uncertainties considering that EC and OC are components within the complex mixture that is $PM_{2.5}$, and the generally high correlations ($r > 0.7$) between EC, OC, and $PM_{2.5}$. Since the completion of the 2009 PM ISA, a number of recent studies have further examined $PM_{2.5}$ components, including metals, and a limited number of these studies have attempted to control for potential confounding by $PM_{2.5}$ mass. In addition to studies of carbon fractions and metals, a recent study also examined respiratory health effects related to the oxidative potential (OP) of $PM_{2.5}$. Due to a limited number of studies for most individual components, and even fewer studies for any given endpoint, no single component is identified as having a stronger relationship with respiratory effects or one that clearly differs from that of $PM_{2.5}$ total mass. All of the studies presented in Table 5-27 are discussed in greater detail throughout this chapter, such that the discussion in this section will not focus on specific study details unless they are specifically relevant to interpretation of $PM_{2.5}$ component results.

Figure 5-38 charts the trend of results for $PM_{2.5}$ mass and individual $PM_{2.5}$ components studies detailed in Table 5-27. The focus of the figure and the ensuing discussion is on studies of lung function and asthma, for which there is evidence of an association with long-term exposure to $PM_{2.5}$. Where available, the chart reflects $PM_{2.5}$ mass-adjusted component results.

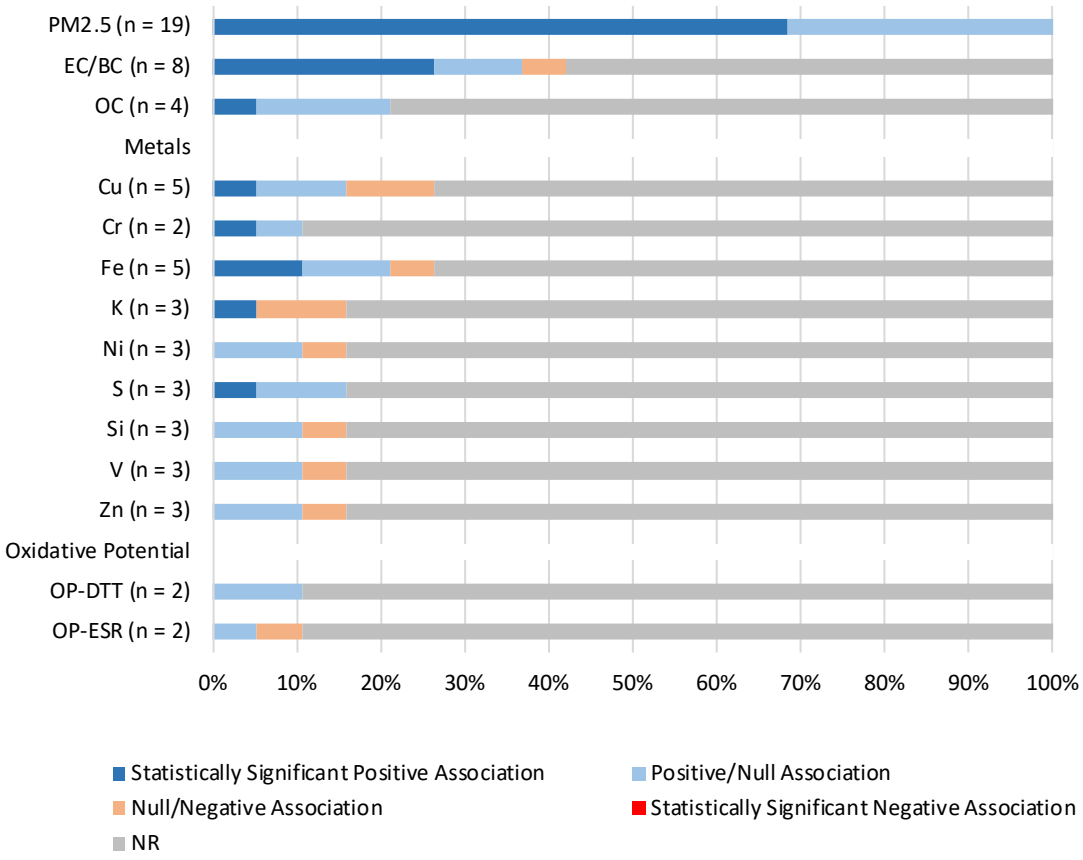
Table 5-27 Heat map of associations observed between long-term exposure $PM_{2.5}$ and $PM_{2.5}$ components and respiratory health.

Study	Endpoint	$PM_{2.5}$	EC/BC	OC	Cu	Cr	Fe	K	Ni	S	Si	V	Zn	OP^{DTT}	OP^{ESR}
Lung Function and Development															
Gauderman et al. (2004)	FEV_1 Growth														
†Breton et al. (2011)	FEV_1														
†Gehring et al. (2015a)	FEV_1														
†Eeftens et al. (2014)	FEV_1														
†Eeftens et al. (2014)‡	FEV_1														
†Yang et al. (2016)	FEV_1														
†Yang et al. (2016)‡	FEV_1														
†Boogaard et al. (2014)	FVC														
†Boogaard et al. (2014)	Airway Resistance														
Asthma															
Islam et al. (2007)	Asthma Incidence														
†Gehring et al. (2015a)	Asthma Incidence														
†Clark et al. (2013)	Asthma Incidence														
†Carlsten et al. (2011)	Asthma Incidence														
†Yang et al. (2016)	Asthma Incidence														
†Yang et al. (2016)‡	Asthma Incidence														
†Chiu et al. (2014)	Wheeze														
Other															
Kim et al. (2004)	Bronchitis														
McConnell et al. (2003)	Bronchitic Symptoms														
McConnell et al. (2003)‡	Bronchitic Symptoms														
†Fuertes et al. (2014)[a]	Pneumonia														
†Fuertes et al. (2014)[a]‡	Pneumonia														
†Karr et al. (2009)	Infant bronchiolitis														
†Gan et al. (2013)	COPD														

[a]$PM_{2.5}$ estimate came from a different study of the same cohort (Eeftens et al., 2014).

‡Associations adjusted for $PM_{2.5}$ mass.

Note: † $PM_{2.5}$ component studies published since the 2009 PM ISA. Dark blue = study reported statistically significant association between $PM_{2.5}$/component and impaired respiratory health outcome; light blue = study reported association between $PM_{2.5}$/component and impaired respiratory health outcome regardless of width of confidence intervals; light orange = study reported null or inverse association; red = study reported statistically significant association between $PM_{2.5}$/component and improved respiratory health outcome; gray = study did not examine individual component. Studies sorted by outcome.



Note: Bars represent the percentage of results for $PM_{2.5}$ mass or $PM_{2.5}$ components from lung function and asthma studies detailed in Table 5-27 that show statistically significant impaired respiratory health (dark blue), impaired respiratory health (light blue), null/improved respiratory health (light orange), or statistically significant improved respiratory health (red). n = number of estimates across the studies detailed in Table 5-27 for $PM_{2.5}$ mass or the individual $PM_{2.5}$ components. When available, this figure uses $PM_{2.5}$ mass-adjusted component associations. See Table 5-27 for more details.

Figure 5-38 Distribution of associations for $PM_{2.5}$ and $PM_{2.5}$ components examined in studies detailed in Table 5-27.

5.2.12.1 Elemental Carbon, Black Carbon, and Organic Carbon

As discussed in the 2009 PM ISA (U.S. EPA, 2009), Gauderman et al. (2004) examined the relationship between lung function growth and long-term exposure to EC and OC. The authors observed evidence of an association between EC and OC exposure and lung development in children, as measured by 8-year growth in FEV_1, FVC, and MMEF. In a recent, expanded CHS analysis examining an additional cohort, Breton et al. (2011) observed similar results to Gauderman et al. (2004). However, $PM_{2.5}$ effects were noted in both studies, and EC and OC were highly correlated with $PM_{2.5}$ ($r = 0.91$ for both components), adding uncertainty to the independent effect of either component. Results from a limited number of recent studies also suggest a potential link between EC and asthma incidence in children. However, the results are not as consistent as those for $PM_{2.5}$.

5.2.12.2 Metals

Elemental fractions of $PM_{2.5}$ were examined as predictors of lung function in two European cohort studies (Gehring et al., 2015a; Eeftens et al., 2014). In an ESCAPE project analysis of 6- to 8-year-old children in five European birth cohorts, Eeftens et al. (2014) reported small reductions in FEV_1, between 0.5 and 1.5%, associated with IQR increases in Cu, Fe, Ni, S, and V. However, after adjustment for $PM_{2.5}$ mass, all negative associations were null except for Fe and S. Similar single-pollutant results were noted in 8- to 12-year-old children in the PIAMA cohort (Gehring et al., 2015a), which was also included in the ESCAPE analysis. The authors did not report $PM_{2.5}$-mass adjusted results. Gehring et al. (2015a) also reported associations between all of the examined metals and asthma incidence (Cu, Fe, K, Ni, S, Si, V, and Zn).

As discussed previously for EC and OC, moderate to high correlations with $PM_{2.5}$, as well as negated effects in models adjusting for $PM_{2.5}$, indicate uncertainty about the independence of the observed associations between elemental fractions of $PM_{2.5}$ and respiratory health. Additionally, the ESCAPE cohorts, including PIAMA, implemented LUR models to estimate exposure to $PM_{2.5}$ components. The models predicted concentration variance with varying degrees of accuracy (R^2 = 0.53−0.79), potentially introducing more exposure measurement error for some components compared to others (de Hoogh et al., 2013). Overall, explained variance was generally higher for $PM_{2.5}$ mass compared to components, indicating greater confidence in the $PM_{2.5}$ concentrations as compared to components.

5.2.12.3 Oxidative Potential

Information from recent studies on the oxidative potential (OP) of $PM_{2.5}$ (i.e., the inherent capacity of PM to generate reactive oxygen species) is presented in a study of the PIAMA cohort in the Netherlands (Yang et al., 2016). The authors propose a link between oxidative potential of $PM_{2.5}$, $PM_{2.5}$ exposure, oxidative stress and inflammation, and respiratory health effects. Yang et al. (2016) reported associations with asthma incidence and lung function decrements (FEV_1 and FVC). Results were dependent on the methods used to quantify OP, with health effects observed with OP measured using the dithiothreitol assay, but null effects for OP measured using spin resonance assay. Results also differed by exposure period, with stronger associations generally observed between the aforementioned respiratory health effects and OP estimated (by LUR) for the concurrent period, compared to OP estimated at participants' birth address. Asthma and lung function associations with OP persisted with adjustment in two-pollutant models for $PM_{2.5}$, NO_2, and a number of $PM_{2.5}$ metals.

5.2.12.4 Summary

Overall, recent studies add evidence for respiratory effects related to long-term $PM_{2.5}$ component exposures. However, evidence remains limited for any component being more strongly associated with a specific respiratory effect compared to $PM_{2.5}$ mass. Additionally, due to generally high component correlations with $PM_{2.5}$ mass, it is uncertain whether the exposure estimates adequately represent exposure to the components rather than a marker for $PM_{2.5}$, which is more strongly associated with respiratory health effects across a large number of studies.

5.2.13 Summary and Causality Determination

The 2009 PM ISA (U.S. EPA, 2009) evaluated long-term $PM_{2.5}$ exposure and respiratory effects and concluded that a causal relationship is likely to exist between long-term $PM_{2.5}$ exposure and respiratory effects (U.S. EPA, 2009).[58] This conclusion was based mainly on epidemiologic evidence demonstrating associations between long-term $PM_{2.5}$ exposure and changes in lung function or lung function growth rate in children. Correlations of $PM_{2.5}$ concentrations with concentrations of other air pollutants, and a limited number of studies that examined potential copollutant confounding, made the interpretation of epidemiologic results more challenging. However, the consistency of findings across different locations supported an independent effect of $PM_{2.5}$. Biological plausibility was provided by a single animal toxicological study involving pre- and -post-natal exposure to $PM_{2.5}$ CAPs which found impaired lung development. Recent studies enhance the evidence base. The evidence for the relationship between long-term exposure to $PM_{2.5}$ and respiratory effects is summarized in Table 5-28, using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015).

[58] As detailed in the Preface , risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations unless otherwise noted.

Table 5-28 Summary of evidence for a likely to be causal relationship between long-term $PM_{2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Lung function and development			
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{2.5}$ concentrations	Studies provide evidence of decrements in lung function growth and for decrements in attained lung function in children in multiple cohorts.	Children: Gauderman et al. (2015); Gehring et al. (2015a); Gauderman et al. (2004)	Children: CHS community mean concentration range: 6−28 µg/m^3 PIAMA Cohort: 16.4 µg/m^3
	Associations are also observed for $PM_{2.5}$-related acceleration of lung function decline in adults.	Adults: Rice et al. (2015a) Adam et al. (2015) Section 5.2.2	Adults: Framingham: 10.8 µg/m^3 ESCAPE Range: 9.5−17.8 µg/m^3
	Supporting evidence is provided by improvements in lung function growth associated with declining $PM_{2.5}$ concentrations.	Gauderman et al. (2015) Boogaard et al. (2013) Section 5.2.11	
Limited evaluation of confounding by copollutants	Potential copollutant confounding for lung function growth is examined in a limited number of studies, with some evidence that associations remain robust in models with gaseous pollutants. However, there is uncertainty regarding studies in Asia due to high annual $PM_{2.5}$ concentrations.	Hwang et al. (2015) Gehring et al. (2013) Wang et al. (2015b)	
Limited evidence from toxicological studies at relevant concentrations	Pre- and post-natal exposure to ambient levels of urban particles impaired mouse lung development.	Mauad et al. (2008)	17 µg/m^3
Biological plausibility	Evidence from an animal toxicological study provides biological plausibility for epidemiologic findings for lung function growth.	Section 5.2.1	

Table 5-28 (Continued): Summary of evidence for a likely to be causal relationship between long term $PM_{2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Development of asthma			
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{2.5}$ concentrations	Longitudinal studies provide evidence of associations with asthma incidence in children.	Carlsten et al. (2011) Tétreault et al. (2016a) Gehring et al. (2015b) Section 5.2.3.1	5.2−16.5 μg/m^3
	Supporting evidence is provided by studies of asthma prevalence in children and by studies of childhood wheeze.	Chiu et al. (2014) Section 5.2.3.1	11.2 μg/m^3
Limited evaluation of confounding by copollutants	Potential copollutant confounding for asthma incidence in children is examined in a single study, with limited evidence that associations remain robust in models with NO_2.	MacIntyre et al. (2014a)	
Coherence in epidemiologic studies across the continuum of effects	Supporting evidence provided by associations with eNO, a marker of pulmonary inflammation.	Dales et al. (2008) Berhane et al. (2014)	
Limited evidence from toxicological studies at relevant concentrations	Results show the development of an allergic Th2 phenotype, increased bronchial obstruction, and collagen deposition in the lungs of DEP-exposed mice.	Kim et al. (2016a)	100 μg/m^3
Biological plausibility	Evidence from an animal toxicological study provides biological plausibility for epidemiologic findings for the development of asthma.	Section 5.2.3.3	
Respiratory effects in healthy populations			
Strong evidence from toxicological studies at relevant concentrations	Results show oxidative stress, inflammation, and morphologic changes in both the upper (nasal) and lower airways. Upregulation of the RAS was also found. Other results relevant to the development of asthma, allergic disease, and COPD and to impaired lung development are mentioned above.	Section 5.2.8	61−200 μg/m^3

Table 5-28 (Continued): Summary of evidence for a likely to be causal relationship between long term $PM_{2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Respiratory mortality			
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{2.5}$ concentrations	Cohort studies show associations for respiratory mortality and cause-specific respiratory mortality, including COPD and infection.	Thurston et al. (2015) Lipsett et al. (2011) Ostro et al. (2010) Hart et al. (2011) Pinault et al. (2016) Crouse et al. (2015) Turner et al. (2016) Pope et al. (2014) Lepeule et al. (2012)	10.2−13.6 μg/m^3 15.6 μg/m^3 17.0 μg/m^3 14.1 μg/m^3 6.3 μg/m^3 8.9 μg/m^3 12.6 μg/m^3 12.6μg/m^3 11.4−23.6 μg/m^3
Uncertainty regarding confounding by copollutants and exposure measurement error	Potential copollutant confounding is examined in a few studies with some evidence that associations remained robust in models with gaseous pollutants. Exposure measurement error is less likely for long-term $PM_{2.5}$ compared with shorter averaging times and other size fractions.	Section 5.2.10	
Some coherence with underlying causes of mortality	COPD evidence provides coherence with respiratory mortality.	Section 5.2.6	
Other respiratory endpoints			
Limited epidemiologic evidence from studies of allergic disease, severity of respiratory disease, and COPD development	Generally consistent evidence of an association for allergic sensitization. However, consistent associations with specific allergens have not emerged.	Gruzieva et al. (2014) Gehring et al. (2010) Weir et al. (2013) Section 5.2.4	12.7−16.9 μg/m^3
	Limited evidence of increased bronchitic symptoms and increased hospitalizations in children with asthma.	McConnell et al. (2003) Tétreault et al. (2016b) Section 5.2.7	9.9−13.8 μg/m^3
	Cohort studies provide some evidence of associations with COPD development.	Atkinson et al. (2015) Gan et al. (2013) To et al. (2015) Section 5.2.5	4.1−12.5 μg/m^3

Table 5-28 (Continued): Summary of evidence for a likely to be causal relationship between long term $PM_{2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Coherence of related effects across disciplines	Evidence from an animal toxicological study provides coherence with epidemiologic findings for the development of an allergic phenotype.	Kim et al. (2016a)	100 μg/m^3
	Exposure to DEP did not worsen the asthma phenotype.	Farraj et al. (2010)	2,000 μg/m^3
Other uncertainties	Studies of COPD development and severity of respiratory disease may not account for the potential effect of short-term exposures leading to these acute events.	Section 5.2.5 Section 5.2.7	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

Multiple cohort studies measuring lung function development over time continue to support the relationship between long-term $PM_{2.5}$ exposure and decrements in lung function growth, providing evidence for a robust and consistent association across study locations, exposure assessment methods, and time periods (Section 5.2.2). The relationship between $PM_{2.5}$ and lung function development is further supported by a recent study that related declining $PM_{2.5}$ concentrations to improvements in pulmonary function growth. Epidemiologic studies also examined asthma development in children (Section 5.2.3). A few recent prospective cohort studies in children found generally positive associations, but several are imprecise (i.e., reporting wide confidence intervals). Supporting evidence is provided by studies of asthma prevalence in children, by studies of childhood wheeze, and by studies of eNO, a marker of pulmonary inflammation. A recent animal toxicological study showing the development of an allergic phenotype and an increase in a marker of airway responsiveness provides biological plausibility for allergic asthma. One epidemiologic study reports a copollutant model with NO_2, in which the $PM_{2.5}$ effect persisted. Other epidemiologic studies focusing on lung function in adults and report a $PM_{2.5}$-related acceleration of lung function decline in adults, while improvement was observed with declining $PM_{2.5}$ concentrations (Section 5.2.11). Declining $PM_{2.5}$ concentrations are also associated with an improvement in chronic bronchitis symptoms in children in a recent longitudinal study, strengthening evidence reported in the 2009 PM ISA for a relationship between increased chronic bronchitic symptoms and long-term $PM_{2.5}$ exposure (Section 5.2.11).

A common uncertainty across the epidemiologic studies is the lack of examination of copollutants to assess the potential for confounding. While there is some evidence that associations remain robust in models with gaseous pollutants, a number of studies examining copollutant confounding are conducted in Asia, and thus have limited generalizability due to high annual pollutant concentrations. Exposure measurement error is less likely for long-term $PM_{2.5}$ compared with shorter averaging times and other size fractions (Section 3.4.5). Animal toxicological studies continue to provide evidence that long-term exposure to $PM_{2.5}$ results in a variety of respiratory effects. Recent studies show pulmonary oxidative stress, inflammation, and morphologic changes in the upper (nasal) and lower airways. Other results show changes consistent with the development of allergy and asthma and impaired lung development, which are mentioned above. **Overall, the collective evidence is sufficient to conclude that a causal relationship is likely to exist between long-term $PM_{2.5}$ exposure and respiratory effects.**

5.3 Short-Term $PM_{10-2.5}$ Exposure and Respiratory Effects

The 2009 PM ISA (U.S. EPA, 2009) concluded that the relationship between short-term exposure to $PM_{10-2.5}$ and respiratory effects is "suggestive of a causal relationship" (U.S. EPA, 2009), based on a limited number of epidemiologic studies supporting associations with some respiratory effects and a limited number of experimental studies that provide biological plausibility.[59] Epidemiologic findings were consistent for hospital admissions and ED visits for respiratory infection and respiratory-related diseases, but not for COPD. Evidence that short-term $PM_{10-2.5}$ exposure exacerbates asthma was inconsistent in epidemiologic studies. In addition, these studies were characterized by overall uncertainty in the exposure assignment approach. Limited information was available regarding potential copollutant confounding across the array of respiratory effects examined. Controlled human exposure studies of short-term $PM_{10-2.5}$ exposure found no lung function decrements and inconsistent evidence for pulmonary inflammation in healthy individuals or human subjects with asthma. Animal toxicological studies were limited to those using noninhalation (e.g., intra-tracheal instillation) routes of $PM_{10-2.5}$ exposure.

Recent epidemiologic findings more consistently link $PM_{10-2.5}$ to asthma exacerbation, and a recent controlled human exposure study in individuals with asthma found pulmonary inflammation and other alterations of the immune system following short-term exposure to $PM_{10-2.5}$ CAPs (Section 5.3.2). Recent animal toxicological studies use noninhalation routes of $PM_{10-2.5}$ exposure and demonstrate enhanced allergic responses in models of allergic airway disease, which share phenotypic features with asthma in humans. Recent epidemiologic findings are more consistent than previous findings for COPD exacerbation (Section 5.3.3), consistent with previous findings for respiratory-related diseases (Section 5.3.5), and somewhat inconsistent with previous findings for respiratory infection (Section 5.3.4). Respiratory effects related to short-term $PM_{10-2.5}$ exposure in healthy people remain

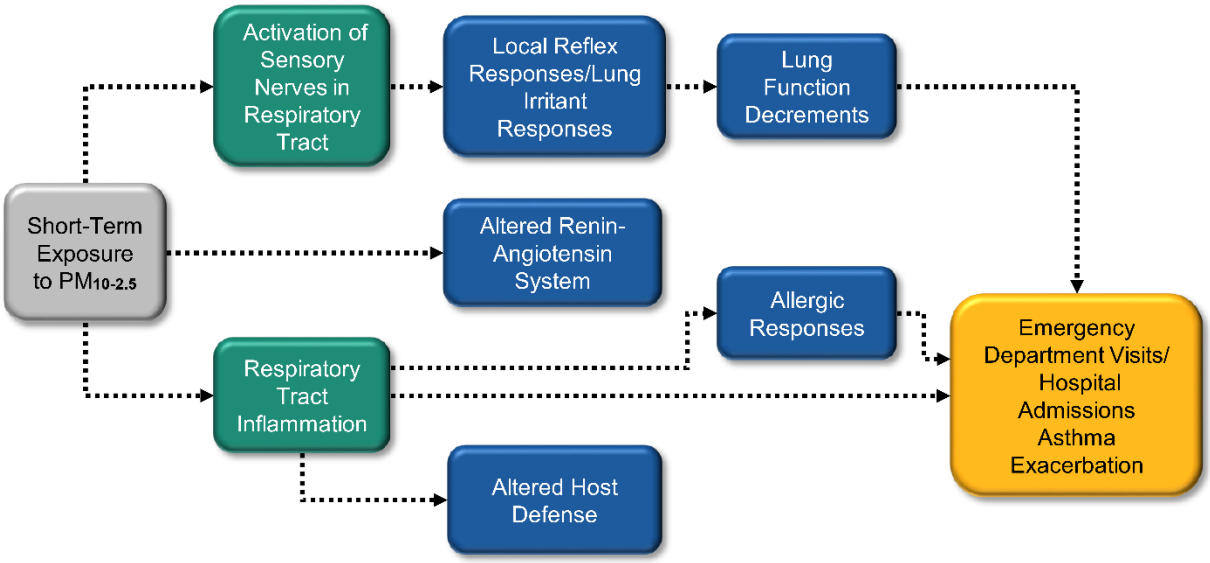
[59] As detailed in the Preface, risk estimates are for a 10 $\mu g/m^3$ increase in 24-hour average $PM_{10-2.5}$ concentrations unless otherwise noted.

uncertain (Section 5.3.6). Evidence from recent epidemiologic studies is inconsistent. A controlled human exposure study found no evidence for changes in lung function. In contrast, a few recent studies involving short-term inhalation exposure of rodents showed decreased lung function and increased pulmonary inflammation.

Previous epidemiologic studies using a single dichotomous $PM_{10-2.5}$ monitor or averaging across monitors to obtain an estimate for $PM_{10-2.5}$ concentration likely have more uncertainty in the exposure surrogate compared with $PM_{2.5}$, given spatiotemporal variability in ambient $PM_{10-2.5}$ concentrations (Section 3.3.1.1 and Section 3.4.2.2). Uncertainties were compounded for previous epidemiologic studies that estimate $PM_{10-2.5}$ concentration as the difference between PM_{10} concentration and $PM_{2.5}$ concentration from monitors that were not collocated. For asthma exacerbation, recent epidemiologic studies have improved exposure assessment with $PM_{10-2.5}$ measurements in subjects' microenvironments using personal samplers. However, across respiratory outcome groups, uncertainties remain regarding copollutant confounding.

5.3.1 Biological Plausibility

This section describes biological pathways that potentially underlie respiratory health effects resulting from short-term exposure to $PM_{10-2.5}$. Figure 5-39 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" short-term exposure to $PM_{10-2.5}$ may lead to respiratory health effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 5.3.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 5-39 Potential biological pathways for respiratory effects following short-term $PM_{10-2.5}$ exposure.

Once $PM_{10-2.5}$ deposits in the respiratory tract, it may be retained, cleared, or solubilized (see CHAPTER 4). Insoluble and soluble components of $PM_{10-2.5}$ may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate reactive oxygen species (ROS) and this capacity is termed "oxidative potential." Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see CHAPTER 4). Immune system responses due to the presence of particles in the interstitial space may contribute to respiratory health effects.

Evidence that short-term exposure to $PM_{10-2.5}$ may affect the respiratory tract generally informs two proposed pathways (Figure 5-39). The first pathway begins with injury, inflammation, and oxidative stress responses, which are difficult to disentangle. Inflammation generally occurs as a consequence of injury and oxidative stress, but it may also lead to further oxidative stress and injury due to secondary production of ROS by inflammatory cells. The second pathway begins with the activation of sensory

nerves in the respiratory tract that can trigger local reflex responses and transmit signals to regions of the central nervous system that regulate autonomic outflow.

Injury, Inflammation and Oxidative Stress

Experimental evidence that short-term exposure to $PM_{10-2.5}$ may affect the respiratory tract by inflammation-mediated pathways is provided by a limited number of inhalation studies. In healthy human subjects, some studies involving short-term exposure to $PM_{10-2.5}$ CAPs found inflammatory responses (Graff et al., 2009; Alexis et al., 2006), while others did not (Behbod et al., 2013; Jr et al., 2004). In human subjects with asthma, Alexis et al. (2014) found increased neutrophils in the BW, increased cytokines in BALF and BW, decreased expression of markers of innate immune and antigen presentation cell surface receptors, and increased expression of inflammatory cell surface receptors and the low-affinity IgE receptor. These changes indicate that alterations in innate host defense and allergic responses may occur. However, no increased markers of airway inflammation or changes in lung function were found by Jr et al. (2004) in humans with asthma. Variability in results of studies that involved short-term exposure to $PM_{10-2.5}$ CAPs may reflect differences in concentration and sources of $PM_{10-2.5}$ present in the airshed. Some epidemiologic studies linked short-term exposure to $PM_{10-2.5}$ to eNO, a marker of airway inflammation, in healthy individuals (Matt et al., 2016; Kubesch et al., 2015) and in children with asthma (Sarnat et al., 2012). Inflammatory and allergic responses in the context of asthma provide plausibility for epidemiologic findings of hospital admissions and ED visits for asthma (Section 5.3.2.1).

Two recent inhalation studies in rodents demonstrated inflammatory responses (Aztatzi-Aguilar et al., 2015; Amatullah et al., 2012). Increases in BALF total cells and macrophages and increased tissue IL-6 levels were observed following short-term exposure to $PM_{10-2.5}$ CAPs. Since rodents are obligatory nasal breathers (as opposed to humans who are oro-nasal breathers), deposition of inhaled $PM_{10-2.5}$ is expected to primarily occur in the extrathoracic airways (i.e., the nose) of rodents and to result in a much smaller fraction deposited in the lower respiratory tract compared with humans. Supportive evidence for respiratory tract effects is provided by animal toxicological studies involving noninhalation routes of exposure (i.e., oropharyngeal aspiration, intra-nasal instillation, subcutaneous injection). Pulmonary injury, oxidative stress, inflammation, and morphological changes were observed in healthy animals and in an animal model of cardiovascular disease (Section 5.3.6.3). In models of allergic airway disease, exposure to $PM_{10-2.5}$ by noninhalation routes enhanced allergic responses (Kurai et al., 2016; McGee et al., 2015; Kurai et al., 2014; He et al., 2012). The enhancement of allergic responses may underly exacerbation of asthma resulting from short-term exposure to $PM_{10-2.5}$ (Section 5.3.2).

Activation of Sensory Nerves

One of the recent inhalation studies in rodents involving short-term $PM_{10-2.5}$ CAPs exposure demonstrated changes in lung function (Amatullah et al., 2012). Baseline total respiratory resistance and

the maximum response to methacholine were increased and quasi-static compliance was decreased. The rapid nature of the lung function responses, which indicate airway obstruction, seen in the study by Amatullah et al. (2012) (i.e., immediately following the 4-hour exposure) indicates that activation of sensory nerves in the respiratory tract, possibly in the nasal airways, and the triggering of local reflex responses may have contributed to the effects of $PM_{10-2.5}$. Activation of sensory nerves in the respiratory tract can also transmit signals to regions of the central nervous system that regulate autonomic outflow and influence all the internal organs, including the heart. No changes in heart rate or heart rate variability were observed, indicating that altered autonomic outflow to the heart did not occur. Findings of lung function changes in this experimental study provide plausibility for epidemiologic findings related to asthma exacerbation.

Aztatzi-Aguilar et al. (2015) also found changes in components of the RAS. The RAS and the sympathetic nervous system, which is one arm of the ANS, are known to interact in a positive feedback fashion (Section 8.1.2) with important ramifications in the cardiovascular system. However, it is not known whether SNS activation or some other mechanism mediated the changes in the RAS observed in the respiratory tract in this study.

Summary

As described here, there are two proposed pathways by which short-term exposure to $PM_{10-2.5}$ may lead to respiratory health effects. One pathway involves respiratory tract inflammation and allergic responses, which are linked to asthma exacerbation. The second pathway involves the activation of sensory nerves in the respiratory tract leading to lung function decrements, which are also linked to asthma exacerbation. While experimental studies involving animals or human subjects contribute most of the evidence of upstream effects, epidemiologic studies found associations between short-term exposure to $PM_{10-2.5}$ and respiratory tract inflammation. Together, these proposed pathways provide biological plausibility for epidemiologic evidence of respiratory health effects and will be used to inform a causality determination, which is discussed later in the chapter (Section 5.3.8).

5.3.2 Asthma Exacerbation

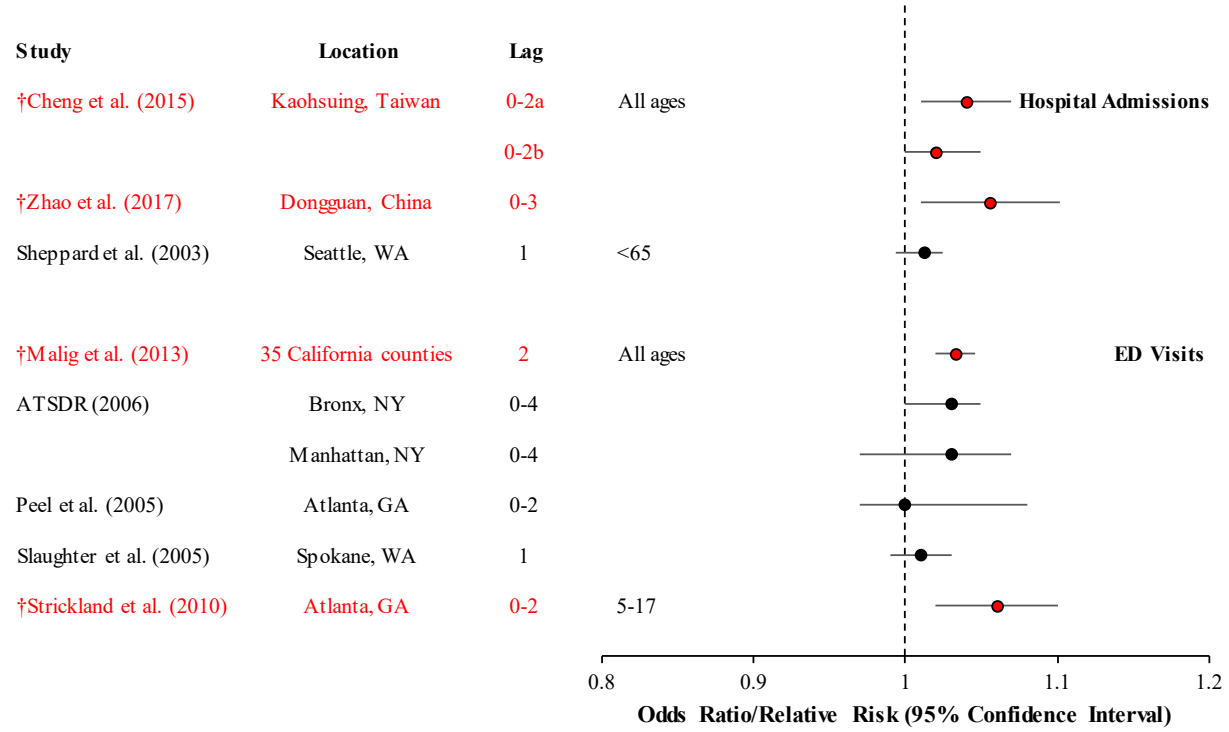
In the 2009 PM ISA (U.S. EPA, 2009), the evaluation of the relationship between short-term $PM_{10-2.5}$ exposure and asthma hospital admissions and ED visits was limited to single-city studies. These studies primarily focused on analyses of people of all ages, with a smaller number of studies examining associations in children and older adults. Across studies, there was inconsistent evidence of an association between short-term $PM_{10-2.5}$ exposure and asthma hospital admissions and between short-term $PM_{10-2.5}$ exposure and asthma ED visits, with some studies reporting evidence of a positive association while others did not. In addition, there was **limited epidemiologic evidence linking short-term $PM_{10-2.5}$ exposure and respiratory symptoms in children with asthma.** As detailed in Section 5.1.2, it is often

difficult to reliably diagnose asthma in children <5 years of age, potentially complicating the interpretation of results from studies that focus on $PM_{10-2.5}$ effects in children. **In the single controlled human exposure study which was evaluated, no evidence for decrements in pulmonary function or inflammation was found.**

5.3.2.1 Hospital Admissions and Emergency Department (ED) Visits

Recent epidemiologic studies continue to examine whether there is evidence of an association between short-term $PM_{10-2.5}$ exposure and asthma hospital admissions and ED visits, but the overall assessment remains limited to a small number of studies. Across studies, there is evidence of generally consistent, positive associations between $PM_{10-2.5}$ and asthma hospital admissions and between short-term $PM_{10-2.5}$ exposure and asthma ED visits (Figure 5-40). The results from asthma hospital admission and ED visit studies in children are supported by a study focusing on asthma physician visits in Atlanta, for the initial time period of the study, but this pattern of associations was not observed for the later time period at lag 3−5 days (Sinclair et al., 2010). However, as mentioned in Section 5.1.2.1, insurance type may dictate whether an individual visits the doctor or a hospital, making it difficult to readily compare results between studies focusing on physician visits versus hospital admissions and ED visits.

Across $PM_{10-2.5}$ studies, a remaining uncertainty is the varying methods employed to measure ambient $PM_{10-2.5}$ concentrations (Section 2.5.1.2.3) and the subsequent impact on exposure measurement error (Section 3.3.1.1). Similar to previous hospital admission and ED visit sections, the focus of this section is on those studies that address uncertainties and limitations in the evidence as detailed in the 2009 PM ISA (U.S. EPA, 2009), such as potential copollutant confounding and model specification. For each of the studies evaluated in this section, Table 5-29 presents the air quality characteristics of each city, or across all cities, the exposure assignment approach used, and information on copollutants examined in each asthma hospital admission and ED visit study. Other recent studies of asthma hospital admissions and ED visits are not the focus of this evaluation because they did not address uncertainties and limitations in the evidence previously identified. Additionally, many of these studies were conducted in small single-cities, encompassed a short study duration, or had insufficient sample size. The full list of these studies can be found in HERO: https://hero.epa.gov/hero/particulate-matter.



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 ISA. a = results for temperatures <25°C; b = results for temperatures ≥25°C. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-40 Summary of associations from studies of short-term $PM_{10-2.5}$ exposures and asthma hospital admissions and emergency department (ED) visits for a 10 μg/m³ increase in 24-hour average $PM_{10-2.5}$ concentrations.

Table 5-29 Epidemiologic studies of $PM_{10-2.5}$ and hospital admissions, emergency department (ED) visits and physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment/Measurement of $PM_{10-2.5}$ Concentrations	Mean (SD) Concentration µg/m^{3a}	Upper Percentile Concentrations µg/m^{3a}	Copollutant Examination
Hospital admissions				
Sheppard (2003) Seattle, WA 1987−1994 <65 yr	Average of two monitors $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at a collocated monitor.	16.2	90th: 29.0	Correlation (*r*): 0.43 $PM_{2.5}$, 0.73 PM_{10}, 0.19 O_3, 0.34 SO_2, 0.56 CO Copollutant models with: NR
†Zhao et al. (2016) Dongguan, China 2013−2015 All ages	Average of five monitors $PM_{10-2.5}$ estimated by calculating the difference between PM_{10} and $PM_{2.5}$ averaged across all monitors.	18.6	75th: 22.6 Max: 96.4	Correlation (*r*): 0.42 O_3, 0.58 SO_2, 0.60 NO_2 Copollutant models with: O_3, SO_2, NO_2
†Cheng et al. (2015) Kaohsiung, Taiwan 2006−2010 All ages	Average of six monitors $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at a collocated monitor.	31.7	75th: 42.1 Max: 490	Correlation (*r*): 0.64 $PM_{2.5}$, 0.89 PM_{10}, 0.24 O_3, 0.53 NO_2, 0.47 CO, 0.19 SO_2 Copollutant models with: O_3, NO_2, CO, SO_2
ED visits				
ATSDR (2006) Manhattan and Bronx, NY 1999−2000 5−18 yr; all ages	One monitor per borough $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at a collocated monitor.	Manhattan: 7.1 Bronx: 7.7	NR	Correlation (*r*): NR Copollutant models with: NR
Peel et al. (2005) Atlanta, GA 1998−2000 All ages	One monitor $PM_{10-2.5}$ directly measured by a dichotomous monitor (Van Loy et al., 2000).	9.7	90th: 16.2	Correlation (*r*): NR Copollutant models with: NR

Table 5-29 (Continued): Epidemiologic studies of $PM_{10-2.5}$ and hospital admissions, emergency department (ED) visits and physician visits for asthma.

Study, Location, Years, Age Range	Exposure Assessment/Measurement of $PM_{10-2.5}$ Concentrations	Mean (SD) Concentration µg/m^{3a}	Upper Percentile Concentrations µg/m^{3a}	Copollutant Examination
Slaughter et al. (2005) Spokane, WA 1995−1999 All ages	One monitoring site $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors.	ED visits	NR	Correlation (*r*): 0.31 $PM_{2.5}$, 0.94 PM_{10}, 0.32 CO Copollutant models with: NR
†Malig et al. (2013) 35 California counties 2005−2008 All ages	Difference of collocated PM_{10} and $PM_{2.5}$ concentration, assigned from the nearest monitoring station within 20 km of population-weighted zip code centroid.	5.6−34.4	NR	Correlation (*r*): 0.31 $PM_{2.5}$, 0.38 O_3, 0.14 CO Copollutant models with: $PM_{2.5}$, O_3, NO_2, CO, SO_2
†Strickland et al. (2010) Atlanta, GA 1993−2004 5−17 yr	Population-weighted average across monitoring site $PM_{10-2.5}$ directly measured by a dichotomous monitor (Van Loy et al., 2000).	9.0	NR	Correlation (*r*): Cold season = 0.29, 0.51, −0.05 O_3, 0.25 NO_2, 0.22 CO, 0.08 SO_2; warm season = 0.26, 0.49, 0.15 O_3, 0.36 NO_2, 0.32 CO, 0.13 SO_2 Copollutant models with: NR
Physician visits				
†Sinclair et al. (2010) Atlanta, GA 1998−2002 Children and adults	One monitor $PM_{10-2.5}$ directly measured by a dichotomous monitor (Van Loy et al., 2000).	Overall: 9.6 8/1998−8/2000: 9.7 9/2000−12/2002: 9.5	NR	Correlation (*r*): 0.43 CO warm season, 0.50 NO_2 cold season Copollutant models with: NR

CO = carbon monoxide, IQR = interquartile range, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, O_3 = ozone, $PM_{10-2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤10 µm and >2.5 µm, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, PM_{10} = particulate matter with a nominal mean aerodynamic diameter ≤10 µm, *r* = correlation coefficient, SD = standard deviation, SO_2 = sulfur dioxide.

[a]All data are for 24-h average unless otherwise specified.

†Studies published since the 2009 PM ISA.

Recent studies that examine the association between short-term $PM_{10-2.5}$ exposure and asthma hospital admissions were conducted in Taiwan (Cheng et al., 2015) and China (Zhao et al., 2016). Cheng et al. (2015), in a study conducted in Kaohsiung, Taiwan, focused on whether the association between short-term $PM_{10-2.5}$ exposure and asthma hospital admissions varied if the mean temperature of each day was above or below 25°C. The authors reported positive associations similar in magnitude for both temperature ranges (≥25°C: RR = 1.02 [95% CI: 1.00, 1.05]; <25°C: RR = 1.04 [95% CI: 1.01, 1.07]). Zhao et al. (2016), in a study conducted in Dongguan, China, also reported evidence of a positive association with $PM_{10-2.5}$ that was similar in magnitude (5.5% [95% CI: 1.0, 10.2]; lag 0−3). Both Cheng et al. (2015) and Zhao et al. (2016) examined potential copollutant confounding with gaseous pollutants (i.e., NO_2, SO_2, O_3, and CO). In both studies, moderate (r, >0.4 and <0.8) to low correlations (r < 0.4) were reported between $PM_{10-2.5}$ and all pollutants (Table 5-29). In Cheng et al. (2015), the results from copollutant analysis were similar to those reported in the single-pollutant analyses (≥25°C: Single-pollutant, RR = 1.02, copollutant, RR = 1.01 to 1.02; <25°C: Single-pollutant, RR = 1.04, copollutant RR = 1.02 to 1.04). Zhao et al. (2016) also reported that results remained relatively unchanged in copollutant models with SO_2 and O_3, but the association with NO_2 was attenuated and uncertain (1.8% [95% CI: −2.9, 6.8]).

A limited number of epidemiologic studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) examined asthma ED visits and short-term exposure to $PM_{10-2.5}$, and were limited to single-city studies. Recent studies of ED visits consist of studies conducted in the U.S. that collectively provide evidence of a positive association between asthma ED visits and $PM_{10-2.5}$. Malig et al. (2013), in a study of 35 California counties, observed positive associations across single-day lags ranging from 0 to 2 days, with the strongest association in terms of magnitude and precision at lag 2 (3.3% [95% CI: 2.0, 4.6]) in an analysis of people of all ages. This result was found to persist when excluding extreme (i.e., highest 5%) $PM_{10-2.5}$ concentrations. Additionally, Malig et al. (2013) provided some evidence that the association between asthma ED visits and $PM_{10-2.5}$ is larger in magnitude in the warm months (quantitative results not presented). The all-year results of Malig et al. (2013) are supported by Strickland et al. (2010) in a study conducted in Atlanta, GA that focused on pediatric asthma ED visits where the authors reported a RR = 1.06 (95% CI: 1.02, 1.1) for a 0−2-day lag. However, when examining seasonal associations, the authors reported evidence that contradicts Malig et al. (2013), with associations being larger in magnitude in the cold months (RR = 1.07 [95% CI: 1.02, 1.13]) compared to the warm months (RR = 1.04 [95% CI: 0.99, 1.10]). Of the ED visit studies only, Malig et al. (2013) examined potential copollutant confounding with $PM_{2.5}$ and reported that results were robust to the inclusion of $PM_{2.5}$ in the model (3.0% [95% CI: 1.8, 4.2], lag 2).

Across both asthma hospital admissions and ED visits studies there was a rather limited assessment of the influence of model specification on the relationship with $PM_{10-2.5}$, as well as the lag structure of associations. Zhao et al. (2016) examined whether varying the degrees of freedom (df) per year to account for temporal trends and increasing the df for the temperature covariate impacted the

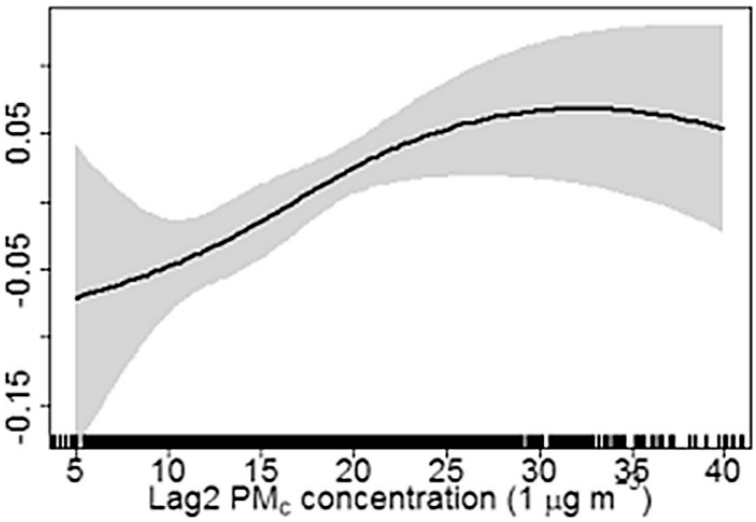
association between $PM_{10–2.5}$ and asthma hospital admission. In both cases, the authors reported results consistent with those observed in the main model (quantitative results not presented). Strickland et al. (2010) took a different approach to examining model misspecification by examining associations with asthma ED visits 1 day after the visit (lag −1 day), which can provide evidence of residual confounding. In an analysis limited to the warm season, the authors did not observe any evidence of potential residual confounding (RR = 1.01 [95% CI: 0.97, 1.04]). Overall, the limited association of model specification provides initial evidence indicating that models adequately account for temporal trends and the confounding effects of weather.

5.3.2.1.1 Concentration-Response Relationship

To date, very few studies have conducted analyses to examine the C-R relationship between short-term $PM_{10–2.5}$ exposure and respiratory-related hospital admissions and ED visits, including asthma. Recent studies provide a limited analysis of the C-R relationship and are limited to examining linearity without conducting a systematic evaluation of potential alternatives to linearity (Zhao et al., 2016; Malig et al., 2013), along with quintile analyses used to examine whether there is evidence that the risk of asthma ED visits changes at different $PM_{10–2.5}$ concentrations (Strickland et al., 2010).

Malig et al. (2013) examined the C-R relationship between short-term $PM_{10–2.5}$ and asthma ED visits in 35 California counties by focusing on model fit and whether replacing a linear term in the model with a squared term for $PM_{10–2.5}$ improved model fit. The authors reported no evidence of an improvement in model fit when allowing for the potential of nonlinearity in the $PM_{10–2.5}$-asthma ED visits relationship. The results of Malig et al. (2013) are consistent with Zhao et al. (2016) in a study conducted in Dongguan, China where there was evidence of a linear relationship when including a natural spline along the range of $PM_{10–2.5}$ concentrations where the data density is the highest (Figure 5-41).

Instead of examining the shape of the C-R curve, Strickland et al. (2010) conducted a quintile analysis to examine whether the association between $PM_{10–2.5}$ and asthma ED visits changed at different concentrations. For the warm season, the authors did not observe any evidence of an association when comparing each quintile to the referent (i.e., quintile 1). However, when examining the cold season, Strickland et al. (2010) reported evidence that the risk of an asthma ED visit increased as $PM_{10–2.5}$ concentrations increased, with the strongest associations observed for the 4th (RR = 1.05 [95% CI: 0.99, 1.10]) and 5th (RR = 1.08 [95% CI: 1.02, 1.14]) quintiles.



Source: Permission pending, Zhao et al. (2016).

Figure 5-41 Concentration-response relationship between short-term $PM_{10-2.5}$ exposure and asthma emergency department (ED) visits at lag 2 for a natural spline model with three degrees of freedom (df) for Dongguan, China.

5.3.2.2 Respiratory Symptoms and Medication Use

As discussed in Section 5.1.2.2, uncontrollable respiratory symptoms can lead people with asthma to seek medical care. Thus, studies examining the relation between $PM_{10-2.5}$ and increases in asthma symptoms may provide support for the observed increases in asthma hospital admissions and ED visits in children, as discussed in Section 5.3.2.1. A single U.S. study evaluated in the 2009 PM ISA (U.S. EPA, 2009) examined respiratory symptoms in people with asthma. Mar et al. (2004) reported $PM_{10-2.5}$-related increases across a number of self-reported symptoms in children, including wheeze, shortness of breath, cough, increased sputum, and runny nose. The authors did not observe associations in healthy adults.

Evidence from a limited number of recent panel studies further supports an association between $PM_{10-2.5}$ and respiratory symptoms in asthmatic children. Wheeze was associated with $PM_{10-2.5}$ in a panel study of children in Fresno, CA (Mann et al., 2010). The reported association was observed with 3-day lag $PM_{10-2.5}$ concentrations from a single monitor (OR: 1.07 [95% CI: 1.01, 1.14]), but the authors noted that the association was relatively stable across lags. Associations are also supported with $PM_{10-2.5}$ measured on the rooftops of two schools in El Paso, TX (Zora et al., 2013). 4-day average $PM_{10-2.5}$ concentrations measured outside of the schools were associated with poorer asthma control scores, which reflect symptoms and activity levels. The two schools included in the study differed in nearby traffic levels but varied similarly in outdoor $PM_{2.5}$ concentration over time (Section 3.4.3.1). Prieto-Parra et al. (2017) also observed associations between 7-day average coarse PM and cough and wheeze in Santiago,

Chile. Notably, the authors reported that $PM_{10–2.5}$ was associated with decreased bronchodilator use (Prieto-Parra et al., 2017).

5.3.2.3 Lung Function

There were no epidemiologic studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) that examined the association between $PM_{10–2.5}$ and lung function in populations with asthma. One recent study observed a decrease in FEV_1 in children associated with 4-day average $PM_{10–2.5}$ concentrations measured outside of two El Paso schools (Greenwald et al., 2013).

A single controlled human exposure study evaluated in the 2009 PM ISA (U.S. EPA, 2009) examined the effects of short-term exposure to $PM_{10–2.5}$ on lung function. Jr et al. (2004) did not observe significant decrements in pulmonary function in human subjects with asthma exposed to $PM_{10–2.5}$. Recently, Alexis et al. (2014) conducted a proof-of-concept study to confirm the assumption that $PM_{10–2.5}$, like other pollutants, can initiate deleterious responses in individuals with asthma at concentrations not observed in healthy individuals. This assumption is based on people with asthma having elevated levels of pre-existing inflammation and altered innate immune function compared to healthy individuals, which may enhance their susceptibility to $PM_{2.5–10}$-induced health effects. Alexis et al. (2014) exposed individuals with mild asthma for 2 hours to either $PM_{10–2.5}$ CAPs or filtered air collected from ambient air in Chapel Hill, NC (see Table 5-30 for study details). No measure of lung function (i.e., FEV_1 and FVC) was affected in $PM_{10–2.5}$-exposed subjects.

Table 5-30 Study-specific details from a controlled human exposure study of short-term $PM_{10-2.5}$ exposure and lung function in populations with asthma.

Study	Study Design	Disease Status; n; Sex; (Age)	Exposure Details (Concentration; Duration; Comparison Group)	Endpoints Measured
Alexis et al. (2014)	Single-blind cross-over	Mild to moderate individuals with asthma; n = 10; sex not stated (18−45 yr)	86.9 ± 17.4 μg/m^3 $PM_{10-2.5}$ for 2 hr with intermittent exercise (15 min of rest followed by 15 min of exercise on recumbent bicycle). Comparison group was clean air; a wash-out period of at least 4 weeks was used between exposures.	BAL and BW (24-hr post-exposure): Differential leukocyte counts, IL-6, IL-8, IL-1β, TNF-α, flow-cytometry to identify cell surface phenotypes Spirometry (24-hour post-exposure): FEV_1, FVC

BAL = bronchoalveolar lavage; BW = bronchial wash; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IL-6 = interleukin 6; IL-8 = interleukin 8; IL-1β = interleukin 1β; TNFα = tumor necrosis factor α.

5.3.2.4 Subclinical Effects Underlying Asthma Exacerbation

5.3.2.4.1 Epidemiologic Studies

No epidemiologic studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) examined the association between short-term exposure to $PM_{10-2.5}$ and subclinical respiratory effects in populations with asthma. Recent panel studies of schoolchildren in El Paso provide inconsistent evidence of an association between $PM_{10-2.5}$ and eNO, an indicator of pulmonary inflammation. Among children at four schools in the neighboring cities of El Paso, TX and Ciudad Juarez, Mexico, eNO was associated with 48-hour average outdoor $PM_{10-2.5}$ (Sarnat et al., 2012). While Sarnat et al. (2012) reported an association between 2-day average outdoor $PM_{10-2.5}$ concentrations and eNO in El Paso, a follow-up study of children in the same schools in El Paso observed a null association with 4-day average outdoor $PM_{10-2.5}$ concentrations (Greenwald et al., 2013). The associations observed by Sarnat et al. (2012) appear to have been driven largely by results from children in one school (Ciudad Juarez) with the highest mean $PM_{10-2.5}$ concentrations.

5.3.2.4.2 Controlled Human Exposure Studies

A single study evaluated in the 2009 PM ISA (U.S. EPA, 2009) investigated whether short-term exposure to $PM_{10–2.5}$ was associated with subclinical outcomes in individuals with asthma. Jr et al. (2004) did not observe changes in lung function or markers of airway inflammation in individuals with asthma who were exposed to $PM_{10–2.5}$. Recently, Alexis et al. (2014) exposed individuals with mild asthma for 2 hours to either $PM_{10–2.5}$ CAPs or filtered air collected from ambient air in Chapel Hill, NC. Differential leukocyte numbers and cell surface markers on recovered leukocytes were examined (see Table 5-31 for study details). The authors reported an increase in BW polymorphonuclear neutrophil concentration (8 vs. 13%, $p < 0.05$) and that this effect was different from effects observed when healthy subjects were exposed to a similar concentration of course PM (Graff et al., 2009). Levels of IL-1β and IL-8 were also elevated in both BW and bronchoalveolar lavage (BAL) samples ($p < 0.05$). Short-term exposure to $PM_{10–2.5}$ CAPs also induced decreased expression of innate immune (CD11b/CR3, CD64/FcγRI) and antigen presentation (CD40, CD86/B7.2) cell surface receptors, and increased expression of inflammatory cell surface receptors (CD16/FcγRIII) and the low-affinity IgE receptor (CD23). The up-regulation of the CD23/IgE receptor reported by Alexis et al. (2014) suggests an asthma-specific pathway induced by $PM_{10–2.5}$, a pathway not typically observed with other xenobiotics, such as O_3 or endotoxin. In summary, the observations reported by Alexis et al. (2014), namely that significant $PM_{10–2.5}$ CAPs-induced pulmonary inflammation, altered innate host defense response, and potentially enhanced IgE signaling, supports the hypothesis that individuals with asthma have greater sensitivity to the inflammatory and immune modifying effects of short-term $PM_{10–2.5}$ CAPs exposure. Furthermore, short-term $PM_{10–2.5}$ CAPs exposure may increase the airway responsiveness of individuals with allergic asthma to inhaled allergens and thereby enhancing the overall risk of asthma exacerbation.

Table 5-31 Study-specific details from a controlled human exposure study of short-term $PM_{10-2.5}$ exposure and subclinical effects underlying asthma.

Study	Study Design	Disease Status; n; Sex; (Age)	Exposure Details (Concentration; Duration; Comparison Group)	Endpoints Measured
Alexis et al. (2014)	Single-blind cross-over	Individuals with mild to moderate asthma; n = 10; sex not stated (18−45 yr)	86.9 ± 17.4 ug/m^3 $PM_{10-2.5}$ for 2 hr with intermittent exercise (15 min of rest followed by 15 min of exercise on recumbent bicycle). Comparison group was clean air; a wash-out period of at least 4 weeks was used between exposures	BAL and BW (24-hr post-exposure): Differential leukocyte counts, IL-6, IL-8, IL-1β, TNF-α, flow-cytometry to identify cell surface phenotypes Spirometry (24-hr post-exposure): FEV_1, FVC

BAL = bronchoalveolar lavage; BW = bronchial wash; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IL-6 = interleukin 6; IL-8 = interleukin 8; IL-1β = interleukin 1β; TNFα = tumor necrosis factor α.

5.3.2.4.3 Animal Toxicological Studies

There were no studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) that investigated the effects of short-term exposure to $PM_{10-2.5}$ in animal models of allergic airway disease, which share phenotypic features with asthma (see Section 5.1.2.4). Inhalation exposure of rodents to $PM_{10-2.5}$ is technically difficult since rodents are obligatory nasal breathers. A group of recent studies involving noninhalation routes of exposure (i.e., oropharyngeal aspiration, intra-nasal instillation, subcutaneous injection) provide biological plausibility for a role of $PM_{10-2.5}$ in enhancing allergic responses (Kurai et al., 2016; McGee et al., 2015; Kurai et al., 2014; He et al., 2012; Alberg et al., 2009).

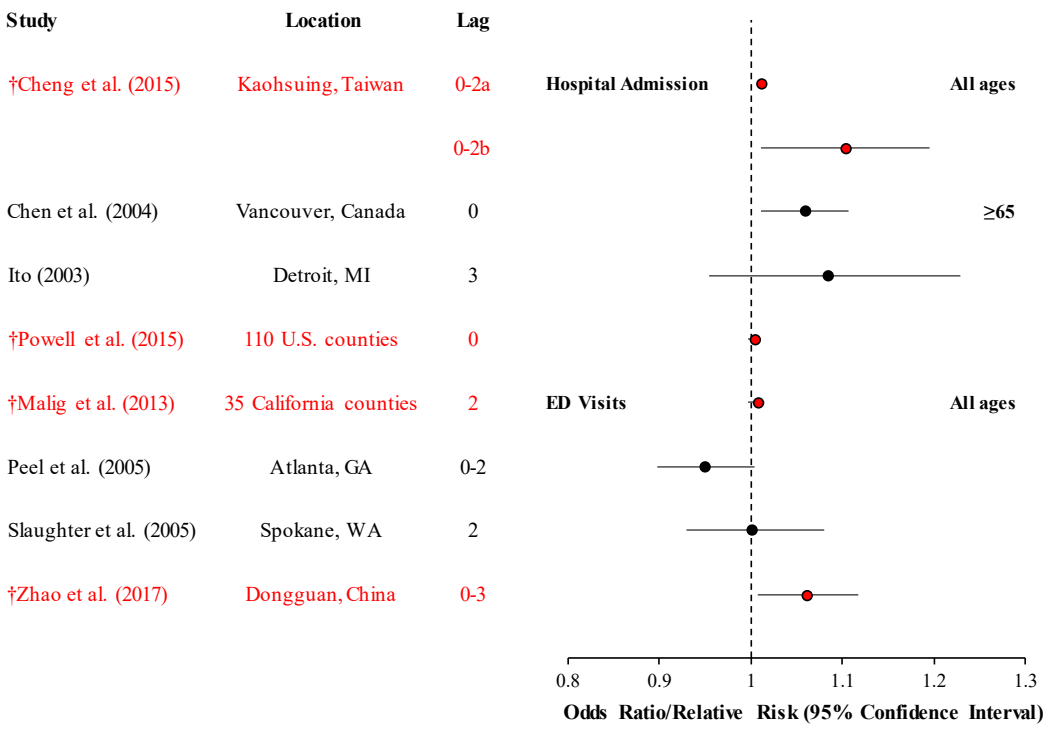
5.3.2.5 Summary of Asthma Exacerbation

Recent epidemiologic findings more consistently link $PM_{10-2.5}$ to asthma exacerbation than studies reported in the 2009 PM ISA. Studies of asthma hospital admission and ED visits include children older than 5 years. These findings are supported by epidemiologic studies observing respiratory symptoms in children, but coherence does not clearly extend to other asthma-related effects since associations were not observed between short-term $PM_{10-2.5}$ exposure and lung function and epidemiologic evidence for pulmonary inflammation was inconsistent. There is limited evidence that

associations remain robust in models with gaseous pollutants and $PM_{2.5}$. An uncertainty related to $PM_{10-2.5}$ measurements is how adequately the spatiotemporal variability is represented given that measurements are mainly based on subtraction of $PM_{2.5}$ from PM_{10} at different locations. Evidence for an independent effect of short-term $PM_{10-2.5}$ exposure was provided by a controlled human exposure study showing effects on inflammation and the immune system.

5.3.3 Chronic Obstructive Pulmonary Disease (COPD) Exacerbation

Among the few epidemiologic studies available for the 2009 PM ISA (U.S. EPA, 2009), short-term exposure to $PM_{10-2.5}$ were inconsistently associated with hospital admissions for COPD and lung function changes in adults with COPD. Recent studies are relatively limited in number but improve on previous studies with residential exposure assessment, additional outcomes, and analysis of potential copollutant confounding (Figure 5-42 and Table 5-32). Recent studies show associations of $PM_{10-2.5}$ with COPD hospital admissions, ED visits, respiratory symptoms, and pulmonary inflammation. However, the evidence overall is inconsistent across several U.S. and Canadian cities, for older adults, and for direct $PM_{10-2.5}$ measurements.



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-42 Summary of associations between short-term $PM_{10-2.5}$ exposures and chronic obstructive pulmonary disease (COPD) hospital admissions and emergency department (ED) visits for a 10 µg/m^3 increase in 24-hour average $PM_{10-2.5}$ concentrations.

Table 5-32 Epidemiologic studies of $PM_{10-2.5}$ and exacerbation of chronic obstructive pulmonary disease.

Study	Exposure Assessment	Outcome Assessment	Mean (SD) Concentration ($\mu g/m^3$)[a]	Upper Percentile Concentrations ($\mu g/m^3$)[a]	$PM_{10-2.5}$ Copollutant Model Results and Correlations
Direct $PM_{10-2.5}$ measurement by a dichotomous monitor					
Peel et al. (2005) Atlanta, GA 1998−2000	One monitor (Van Loy et al., 2000)	ED visits All ages	9.7 (4.7)	90th: 16.2	No copollutants examined
Ito (2003) Detroit, MI 1992−1994	One monitor	Hospital admissions Older adults, age NR	13 (SD NR)	75th: 17 95th: 28	Correlation (r) = 0.42 $PM_{2.5}$, 0.77 PM_{10} No copollutant model
†Sinclair et al. (2010) Atlanta, GA 1998−2002	One monitor	Outpatient visits for acute respiratory illness	9.6 (5.4)	NR	No copollutants examined
Difference of PM_{10} and $PM_{2.5}$ measurements					
†Malig et al. (2013) 35 California counties 2005−2008	Difference of collocated PM_{10} and $PM_{2.5}$ concentration, assigned from the nearest monitoring station within 20 km of population-weighted zip code centroid.	ED visits All ages	5.6 (3.1) to 34.4 (25.6)	NR	Correlation (r) = 0.31 $PM_{2.5}$, 0.30 O_3, 0.14 CO Copollutant models examined: $PM_{2.5}$
Chen et al. (2004) Vancouver, Canada 1995−1999	Concentrations averaged for 13 census divisions; authors did not state if PM_{10} and $PM_{2.5}$ monitors were collocated.	Hospital admissions Older adults ≥65 yr	5.6 (3.6)	75th: 7.3 Max: 24.6	Copollutant correlations NR Copollutant models examined: $PM_{2.5}$, O_3, NO_2, CO

Table 5-32 (Continued): Epidemiologic studies of $PM_{10-2.5}$ and exacerbation of chronic obstructive pulmonary disease.

Study	Exposure Assessment	Outcome Assessment	Mean (SD) Concentration ($\mu g/m^3$)[a]	Upper Percentile Concentrations ($\mu g/m^3$)[a]	$PM_{10-2.5}$ Copollutant Model Results and Correlations
†Zhao et al. (2016) Dongguan, China 2013−2015	Difference of collocated PM_{10} and $PM_{2.5}$ concentration, averaged over five monitoring sites.	Hospital clinic visits All ages	18.6 (9.2)	75th: 22.6 Max: 96.4	Correlation (r) = 0.42 O_3, 0.58 SO_2, 0.60 NO_2 Copollutant models examined: O_3, SO_2. NO_2
†Cheng et al. (2015) Kaohsiung, Taiwan 2006−2010	Difference of PM_{10} (β ray absorption) and $PM_{2.5}$ (TEOM) concentrations collocated, averaged across six monitoring sites.	Hospital admissions All ages	Median (IQR) 24.8 (24.4)	75th: 30.8 Max: 490	Correlation (r) = 0.64 $PM_{2.5}$, 0.89 PM_{10}, 0.24 O_3, 0.53 NO_2, 0.47 CO, 0.19 SO_2 Copollutant models examined: O_3, NO_2, CO, or SO_2
Slaughter et al. (2005) Spokane, WA 1995−1999	$PM_{10-2.5}$ concentration estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors at one site.	ED visits All ages	NR	NR	Correlation (r) = 0.31 $PM_{2.5}$, 0.94 PM_{10} No copollutant model
†Powell et al. (2015) 110 U.S. counties 1999−2010	Difference of PM_{10} and $PM_{2.5}$ concentrations collocated at one monitoring site for each county.	Hospital admissions Older adults ≥65 yr	Median (IQR) 12.78 (3.06)	75th: 15.84	No copollutants examined

CO = carbon monoxide, ED = emergency department, IQR = interquartile range, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, O_3 = ozone, $PM_{10-2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤10 μm and >2.5 μm, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 μm, PM_{10} = particulate matter with a nominal mean aerodynamic diameter ≤10 μm, r = correlation coefficient, SD = standard deviation, SO_2 = sulfur dioxide.

[a]All data are for 24-h average.

†Studies published since the 2009 PM ISA.

1

5.3.3.1 Hospital Admissions and Emergency Department (ED) Visits

The body of literature reviewed in the 2009 PM ISA (U.S. EPA, 2009) that examined the association between short-term $PM_{10-2.5}$ exposure and hospital admissions for COPD was small and consisted of single-city studies conducted in the U.S. and Canada. Across studies, there was inconsistent evidence of an association, with the strongest evidence for hospital admissions in adults over the age of 65 years. An initial assessment of the potential confounding effects of copollutants provided some evidence that COPD associations may be attenuated in models with NO_2. Similarly, an international single-city study reported an association between ED visits for COPD and asthma combined and $PM_{10-2.5}$, but the positive association was attenuated after adjustment for $PM_{2.5}$, NO_2 and CO. Similar to the 2009 PM ISA, the evidence base remains limited when examining the association between short-term $PM_{10-2.5}$ exposure and hospital admissions for COPD, but provides some additional evidence for a positive association (see Figure 5-42).

5.3.3.1.1 Hospital Admissions

In a study of 110 U.S. counties, Powell et al. (2015) assessed the relationship between $PM_{10-2.5}$ and COPD-related hospital admissions among residents older than 65 years of age. The authors reported a positive, but imprecise association with COPD hospital admissions in single pollutant models (0.31% [95% PI: −0.39, 1.01]) and copollutant models with same-day $PM_{2.5}$ (0.19% [95% PI: −0.54, 0.92]). COPD-related admissions were also not associated with short-term $PM_{10-2.5}$ exposures occurring during a 1−3-day lag (which would be indicative of a more delayed response) in either single pollutant or copollutant models. Moreover, Cheng et al. (2015) assessed the relationship between $PM_{10-2.5}$ and COPD-related hospital admissions in a case-crossover study in Kaohsuing, Taiwan. This study observed an increase in hospital admissions of 1.02% (95% CI: 1.01,1.03).

5.3.3.1.2 Emergency Department (ED) Visits

In a multicity study conducted in 35 California counties, Malig et al. (2013) examined the association between short-term $PM_{10-2.5}$ exposures and respiratory ED visits, including COPD visits. The authors reported positive associations between $PM_{10-2.5}$ and COPD ED visits at lag 2 days (0.67% [95% CI: −0.04, 1.38]). In a copollutant model with $PM_{2.5}$, the association was stronger (1.48%) and more precise (95% CI: 0.40, 2.56) [results presented in Figure 5-6 and supplemental data, (Malig et al., 2013)]. The COPD relationship at lag 2 remained elevated for those living closer to the monitor (within 10 km vs. 10−20 km), but it was not present among those farther away indicating potential exposure measurement error based on distance to monitor (Section 3.4.2.2).

5.3.3.2 Other Epidemiologic Studies

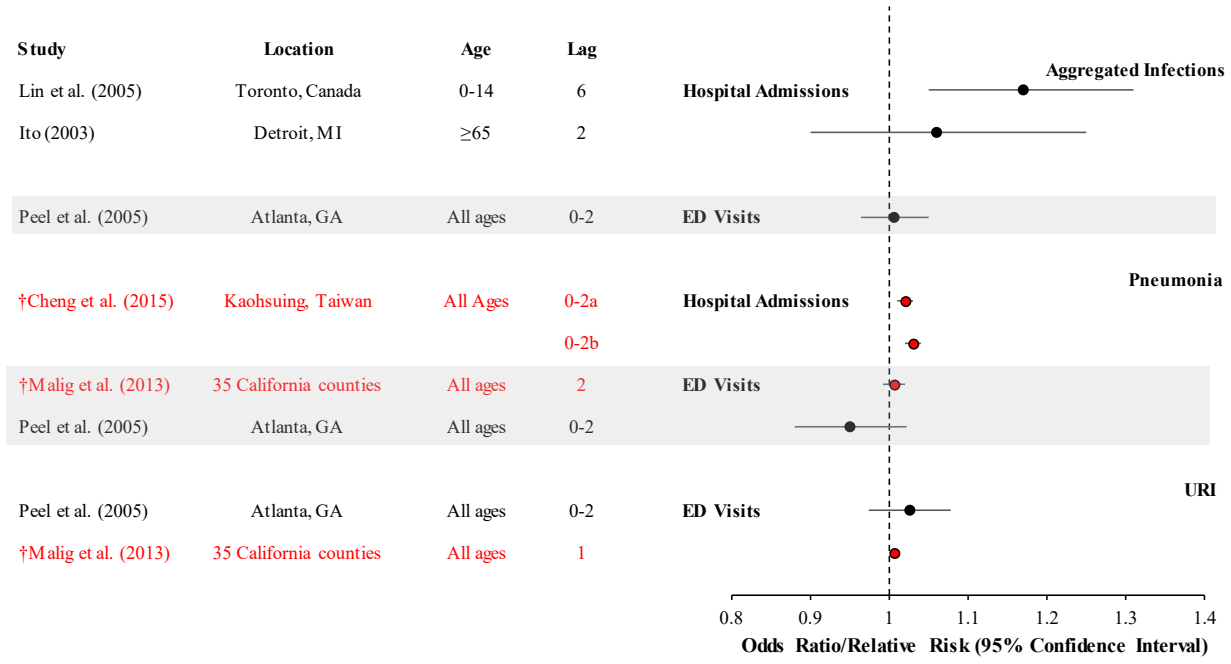
As discussed in the 2009 PM ISA (U.S. EPA, 2009), a limited number of previously evaluated studies provide contrasting evidence of an association between coarse PM and lung function changes in adults with COPD. Associations were not observed for $PM_{10-2.5}$ calculated from residential outdoor PM_{10} and $PM_{2.5}$ in Seattle (Trenga et al., 2006). Conversely, $PM_{10-2.5}$ exposure (24-hour average, lag 0) was associated with a decrease in FEV_1 in adults in Vancouver, Canada (Ebelt et al., 2005). $PM_{10-2.5}$ was calculated by estimating the ambient fractions of $PM_{2.5}$ and PM_{10} measured from personal monitors and subtracting $PM_{2.5}$ from PM_{10}. The $PM_{10-2.5}$ concentrations examined in Ebelt et al. (2005) were lower (mean = 2. $\mu g/m^3$) than those examined for COPD hospital admissions and ED visits (Table 5-9). Neither study examined other pollutants, so it is not clear whether the results reflect an independent association for $PM_{10-2.5}$. There are no recent studies available for review that examine the association between $PM_{10-2.5}$ and indicators of COPD exacerbation.

5.3.3.3 Summary of Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

Overall, the body of literature that examined the association between $PM_{10-2.5}$ and hospital admissions and ED visits for COPD is limited. Studies reported in the 2009 ISA (U.S. EPA, 2009) provided inconsistent evidence. Of the recent studies, there is some evidence of a positive association between short-term $PM_{10-2.5}$ exposure and COPD hospital admissions and ED visits, but evidence for other indicators of COPD exacerbation is inconsistent. In addition, there is a relative lack of information on potential copollutant confounding and the potential implications of exposure measurement error due to the different methods employed across studies to estimate $PM_{10-2.5}$ concentrations.

5.3.4 Respiratory Infection

The respiratory tract is protected from exogenous pathogens and particles through various lung host defense mechanisms that include mucociliary clearance, particle transport and detoxification by alveolar macrophages, and innate and adaptive immunity. Impairment of these defense mechanisms can increase the risk of respiratory infection. Previous epidemiologic studies consistently observed associations between short-term $PM_{10-2.5}$ exposure and hospital admissions, ED visits, or physician visits for aggregated respiratory infections or URI, but not pneumonia. In contrast, the few recent epidemiologic studies indicate associations with pneumonia, but not aggregated respiratory infections (Figure 5-43). The 2009 PM ISA (U.S. EPA, 2009) did not report any experimental studies of altered susceptibility to infectious agents following short-term exposure to $PM_{10-2.5}$ and no studies have become available since that time.



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-43 Summary of associations between short-term $PM_{10-2.5}$ exposures and respiratory infection hospital admissions and emergency department (ED) visits for a 10 μg/m³ increase in 24-hour average $PM_{10-2.5}$ concentrations.

5.3.4.1 Hospital Admissions and Emergency Department (ED) Visits

Although the body of literature was small, the few studies evaluated in the 2009 PM ISA reported inconsistent evidence of an association between $PM_{10-2.5}$ and hospital admissions and ED visits for respiratory infections. Some studies observed associations of respiratory infections with $PM_{10-2.5}$ among subjects younger than 15 years old, and others reported associations between $PM_{10-2.5}$ and outpatient visits for lower respiratory tract infections. The recent literature adds to the evidence base and provides some support for an association between short-term $PM_{10-2.5}$ exposure and hospital admissions/ED visits for pneumonia and respiratory infections considered in aggregate (see Figure 5-43). For each of the studies evaluated in this section, Table 5-33 presents the air quality characteristics of each city, or across all cities, the exposure assignment approach used, and information on copollutants examined in each asthma hospital admission and ED visit study.

In 110 U.S. counties Powell et al. (2015) reported a positive, but uncertain, association between short-term $PM_{10-2.5}$ exposure and respiratory infection hospital admissions among residents older than

65 years in single pollutant models (0.07% [95% PI: −0.46, 0.61]; lag 0). This association was attenuated in a copollutant model with $PM_{2.5}$ (−0.02% [95% PI: −0.59, 0.55]; lag 0). Respiratory infection-related admissions were also not associated with $PM_{10–2.5}$ exposures occurring 1−3 days prior to admission in either single pollutant or copollutant models. Cheng et al. (2015) assessed the relationship between $PM_{10–2.5}$ and pneumonia-related hospital admissions among residents older than 65 years of age in a case-crossover study in Kaohsuing, Taiwan between 2006−2010. This study observed a small positive association, with an increase in hospital admissions of 1.02% (95% CI: 1.01, 1.03) per 10-$\mu g/m^3$ increase in $PM_{10–2.5}$. This association was consistent after model adjustment for SO_2, NO_2, CO, and O_3 and was slightly stronger on colder days below 25°C (1.03% [95% CI: 1.02, 1.04]).

In a multicity study conducted in 35 California counties, Malig et al. (2013) reported no association between short-term $PM_{10–2.5}$ exposures at single-day lags 0−2 days and ED visits due to acute respiratory infection [RR 1.007, 95% CI: 1, 1.01]. This study also reported a very weak association between short-term $PM_{10–2.5}$ exposures at single-day lags 0−2 days for pneumonia visits RR 1.006 [95% CI: 0.99, 1.02].

Table 5-33 Epidemiologic studies of $PM_{10-2.5}$ and respiratory infections.

Study	Exposure Assessment	Outcome Assessment	Mean (SD) Concentration µg/m^{3a}	Upper Percentile Concentrations µg/m^{3a}	$PM_{10-2.5}$ Copollutant Model Results and Correlations
Direct $PM_{10-2.5}$ measurement by a dichotomous monitor					
Peel et al. (2005) Atlanta, GA 1998−2000	One monitor	ED visits URI, pneumonia All ages	9.7 (4.7)	90th: 16.2	No copollutant model Copollutant correlations NR
Sinclair et al. (2010) Atlanta, GA 1998−2002	One monitor	Physician visits URI, LRI All ages	Aug 1998−Aug 2000: 9.7 (4.7) Sep 2000−Dec 2002: 9.6 (5.4)	NR	Correlation (r) = 0.43 CO warm season, 0.50 NO_2 cold season No copollutant model
Ito (2003) Detroit, MI 1992−1994	One monitor	Hospital admissions Type of infection NR Older adults	13 (SD NR)	75th: 17 95th: 28	Correlation (r) = 0.42 $PM_{2.5}$, 0.77 PM_{10} No copollutant model
Difference of PM_{10} and $PM_{2.5}$ measurements					
†Malig et al. (2013) 35 California counties 2005−2008	Nearest monitor Within 25 km of population-weighted zip code centroid. Difference of collocated PM_{10} and $PM_{2.5}$ concentration, assigned from the nearest monitoring station within 20 km of population-weighted zip code centroid.	ED visits URI, pneumonia All ages	5.6 (3.1) to 34.4 (25.6)	NR	Correlation (r) = 0.31 $PM_{2.5}$, 0.30 O_3, 0.14 CO

Table 5-33 (Continued): Epidemiologic studies of $PM_{10-2.5}$ and respiratory infections.

Study	Exposure Assessment	Outcome Assessment	Mean (SD) Concentration µg/m³[a]	Upper Percentile Concentrations µg/m³[a]	$PM_{10-2.5}$ Copollutant Model Results and Correlations
†Cheng et al. (2015) Kaohshing, Taiwan 2006−2010	Difference of PM_{10} (β ray absorption) and $PM_{2.5}$ (TEOM) concentrations collocated, averaged across six monitoring sites.	Hospital admissions Pneumonia All ages	Median (IQR) 24.8 (24.4)	75th: 30.8 Max: 490	Correlation (*r*) = 0.64 $PM_{2.5}$, 0.89 PM_{10}, 0.24 O_3, 0.53 NO_2, 0.47 CO, 0.19 SO_2
Lin et al. (2005) Toronto, Canada 1998−2001	Difference of average PM_{10} (β ray absorption) and average $PM_{2.5}$ (TEOM) concentrations across four monitoring sites.	Hospital admissions URI + pneumonia Children <15 yr	10.9 (5.4)	75th: 13.5 Max: 45	Correlation (*r*) = 0.33 $PM_{2.5}$, 0.76 PM_{10}, 0.30 O_3, 0.40 NO_2, 0.06 CO, 0.29 SO_2 No copollutant model

CO = carbon monoxide, ED = emergency department, IQR = interquartile range, max = maximum, LRI = lower respiratory infection, NO_2 = nitrogen dioxide, NR = not reported, O_3 = ozone, $PM_{10-2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤10 µm and > 2.5 µm, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, PM_{10} = particulate matter with a nominal mean aerodynamic diameter ≤10 µm, *r* = correlation coefficient, SD = standard deviation, SO_2 = sulfur dioxide, URI = upper respiratory infection.

[a]All data are for 24-h average unless otherwise specified.

†Studies published since the 2009 PM ISA.

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5.3.4.2 Outpatient and Physician Visit Studies

In Atlanta, GA, Sinclair et al. (2010) compared air pollutant concentrations and relationships for acute respiratory visits for the 25-month time-period examined in a previous study (August 1998−August 2000) and an additional 28-month time-period of available data from the Atlanta Aerosol Research Inhalation Epidemiology Study (ARIES) (September 2000−December 2002). Across the two time periods, $PM_{10–2.5}$ mass concentrations (measured from ARIES) were essentially stable with only a 3% difference between the two study periods (9.6 μg/m^3 overall average). Unlike $PM_{2.5}$ mass, $PM_{10–2.5}$ mass did not change significantly across warm or cold seasons. A comparison of the two time periods indicated that associations for $PM_{10–2.5}$ tended to be larger in the earlier 25-month period compared to the later 28-month period. Associations with URI for lag 3−5 in the 25-month time period represented the highest finding (4.2% [95% CI: 0.75, 7.8]). For LRI in the 25-month period, associations were positive for all lags, with the largest for lag 3−5 (13.2% [95% CI: 3.2, 24.4]). As noted in Section 5.1.2.1, several factors may dictate whether an individual visits the doctor or a hospital, making it difficult to readily compare results between studies focusing on physician visits versus hospital admissions and ED visits.

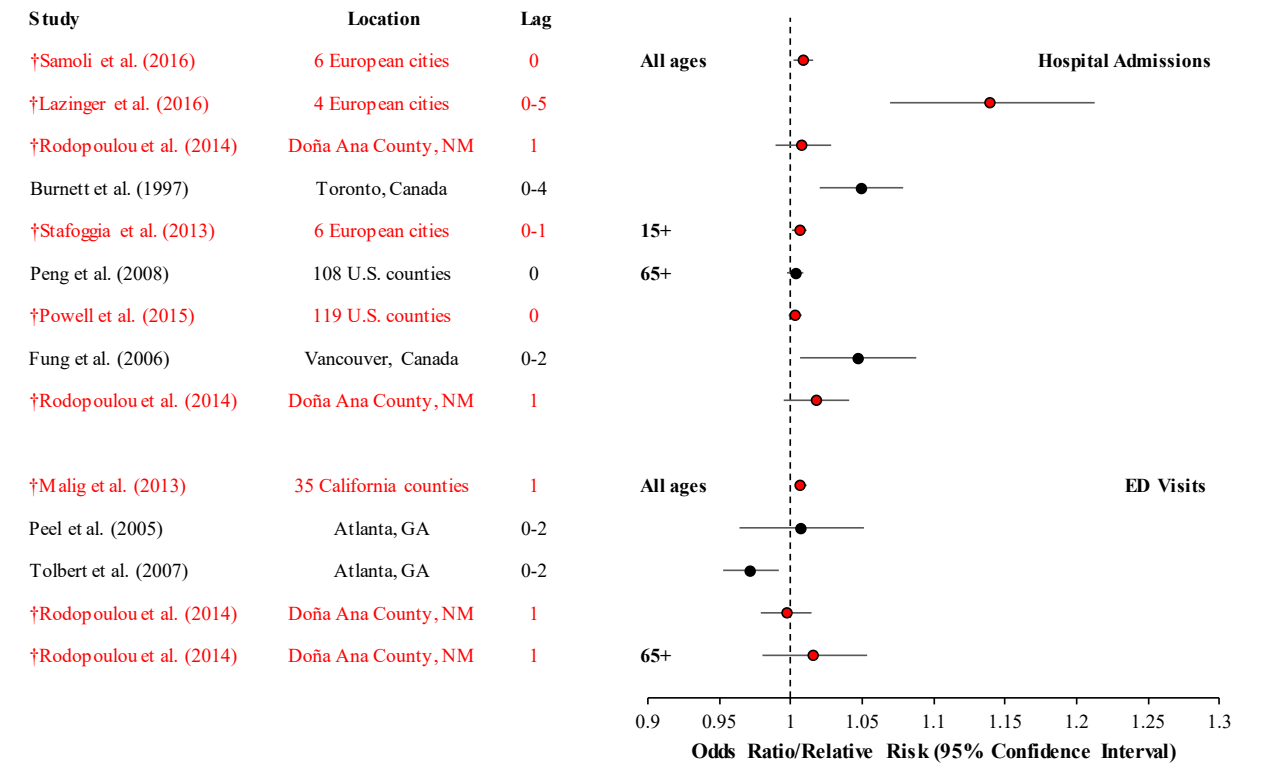
5.3.4.3 Summary of Respiratory Infection

The body of literature that examined the association between $PM_{10–2.5}$ and hospital admissions and ED visits for respiratory infection hospital admissions expanded since the 2009 PM ISA (U.S. EPA, 2009), but remains limited. Previous studies reported associations between $PM_{10–2.5}$ and both acute respiratory infection and a combination of respiratory infection, but not pneumonia. Recent studies are generally indicative of associations for both acute respiratory infection and pneumonia, but not the combination of respiratory infections. A multicity study conducted in the U.S. and several single-city studies in the U.S. and internationally report positive associations between $PM_{10–2.5}$ and hospital admissions/ED visits for pneumonia or acute respiratory infection. Despite some inconsistency between previous and recent findings, the evidence overall is supportive of a link between short-term $PM_{10–2.5}$ exposure and respiratory infection. However, previous and recent findings have similar uncertainties in exposure measurement error in $PM_{10–2.5}$ concentrations, particularly when PM_{10} and $PM_{2.5}$ concentrations that were not collocated were differenced to estimate $PM_{10–2.5}$ concentrations. Previous and recent findings also have uncertainties in limited examination of copollutant confounding and limited information from experimental studies to assess biological plausibility.

5.3.5 Combinations of Respiratory-Related Hospital Admissions and Emergency Department (ED) Visits

In the 2009 PM ISA (U.S. EPA, 2009), the evaluation of the relationship between short-term $PM_{10-2.5}$ exposure and hospital admissions and ED visits for respiratory-related diseases was limited to a rather small number of studies. Across hospital admissions studies, there was evidence of positive associations that varied in terms of the magnitude and precision of the estimates, while the evidence for ED visits was inconsistent. Of the studies evaluated in the 2009 PM ISA, the majority consisted of single-city studies, and different approaches were used to estimate ambient $PM_{10-2.5}$ concentrations. Across studies, there was limited to no information on potential copollutant confounding or other assessments of the relationship between short-term $PM_{10-2.5}$ exposure and hospital admissions and ED visits for respiratory-related diseases, such as model specification, lag structure of associations, or the C-R relationship.

Recent multi- and single-city studies that examine short-term $PM_{10-2.5}$ exposure and hospital admissions and ED visits for respiratory-related diseases add to the body of evidence detailed in the 2009 PM ISA (U.S. EPA, 2009). Consistent with the studies evaluated in the 2009 PM ISA, recent hospital admissions studies provide evidence of positive associations that are similar in magnitude and precision, while recent ED visits studies provide inconsistent evidence of an association (Figure 5-44). Similar to the studies evaluated in Section 5.1.6, the studies that examined combinations of respiratory-related diseases encompassed all respiratory-related diseases or only a subset, which can complicate the interpretation of results across studies. As described in preceding sections, the evidence for association with $PM_{10-2.5}$ is more consistent for asthma (Section 5.3.1) than for COPD (Section 5.3.2) or for respiratory infection (Section 5.3.4). For each of the studies evaluated in this section, Table 5-34 (summary table of studies) presents the air quality characteristics of each city, or across all cities, the exposure assignment approach used, and information on copollutants examined in each study. Other recent studies of hospital admissions and ED visits for respiratory-related diseases that did not address uncertainties and limitations in the evidence previously identified are not the focus of this evaluation. Additionally, many of these other studies were conducted in small single cities, encompassed a short study duration, or had insufficient sample size. The full list of these other studies can be found in HERO: https://hero.epa.gov/hero/particulate-matter.



Note: †Studies published since the completion of the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-44 Summary of associations from studies of short-term $PM_{10-2.5}$ exposures and respiratory-related hospital admissions and emergency department (ED) visits for a 10 μg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations.

Table 5-34 Epidemiologic studies of $PM_{10-2.5}$ and respiratory-related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment/Measurement of $PM_{10-2.5}$ Concentrations	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m^3	Upper Percentile Concentrations µg/m^3	Copollutant Examination
Hospital admissions					
Peng et al. (2008) 108 U.S. counties 1999−2005 ≥65 yr	Average across sites in a county $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at a collocated monitor.	464−466, 480−487; 490−492	9.8	75th: 15.0	Correlation (*r*): NA Copollutant models with: NA
Fung et al. (2006) Vancouver, Canada 1995−1999 ≥65 yr	Average across sites monitors $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at a collocated monitor.	460−519	5.6	Max: 27.1	Correlation (*r*): −0.03 O_3, 0.36 NO_2, 0.23 CO, 0.42 SO_2, 0.34 $PM_{2.5}$ Copollutant models with: NA
Burnett et al. (1997) Toronto, Canada 1992−1994, summers only All ages	One monitor $PM_{10-2.5}$ directly measured by a dichotomous monitor.	464−466; 490; 480−486; 491−494, 496	10a	75th: 23 95th: 40 Max: 66	Correlation (*r*): 0.32 O_3, 0.45 NO_2, 0.42 CO, 0.49 SO_2, 0.72 $PM_{2.5}$ Copollutant models with: O_3, CO, NO_2, SO_2
†Powell et al. (2015) 119 U.S. counties 1999−2010 ≥65 yr	Average of across sites in each county $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors.	464−466, 480−487; 490−492	12.8a	75: 15.8	Correlation (*r*): NA Copollutant models with: NA

Table 5-34 (Continued): Epidemiologic studies of $PM_{10-2.5}$ and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment/Measurement of $PM_{10-2.5}$ Concentrations	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
†Samoli et al. (2016a) Five European cities 2001−2011 All ages	Average across sites in each city $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at a collocated monitor.	466, 480−487; 490−492, 494, 496; 493	5.7−12.2	NR	Correlation (*r*): NA Copollutant models with: NA
†Lanzinger et al. (2016b)[b] Four European cities (UFIREG) 2011−2014 All ages	Average across sites in each city $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors.	J00−J99	4.7−9.8	Max: 21.6−44.6	Correlation (*r*): 0.40−0.61 $PM_{2.5}$, 0.58−0.78 PM_{10}, 0.37−0.43 NO_2 Copollutant models with: NA
†Stafoggia et al. (2013)[c] Six European cities (MED-PARTICLES) 2003−2013 ≥15 yr	Average across sites in each city $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors.	460−519	9.3−17.5	NR	Correlation (*r*): ≥0.5 $PM_{2.5}$ Madrid, Milan, Emilia-Romagna, 0 other cities, >0.60 with NO_2 Copollutant models with: $PM_{2.5}$, NO_2, O_3
†Atkinson et al. (2010) London, U.K. 2000−2005 0−14 yr, All ages	One monitor $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors.	J00−J99	7.0a	75th: 10.0 Max: 36.0	Correlation (*r*): 0.22 $PM_{2.5}$, 0.52 PM_{10} Copollutant models with: NR
†Alessandrini et al. (2013) Rome, Italy 2001−2004 All ages	One monitor $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at a collocated monitor.	460−519	No Saharan dust days: 14.6 Saharan dust days: 20.7	NR	Correlation (*r*): 0.25 $PM_{2.5}$, 0.81 PM_{10} Copollutant models with: $PM_{2.5}$, O_3

Table 5-34 (Continued): Epidemiologic studies of $PM_{10-2.5}$ and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment/Measurement of $PM_{10-2.5}$ Concentrations	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m^3	Upper Percentile Concentrations µg/m^3	Copollutant Examination
ED visits					
Peel et al. (2005) Atlanta, GA 1993−2000 All ages	One monitor Direct measurement of $PM_{10-2.5}$ concentration by a dichotomous monitor (Van Loy et al., 2000).	460−466, 477; 480−486; 491, 492, 496; 493, 786.09	19.2	90th: 32.3	Correlation (*r*): 0.55−0.68, CO, NO_2 Copollutant models with: NA
Tolbert et al. (2007) Atlanta, GA 1993−2004 All ages	One monitor Direct measurement of $PM_{10-2.5}$ concentration by a dichotomous monitor (Van Loy et al., 2000).	460−465, 460.0, 477; 480−486; 491, 492, 496; 493, 786.07, 786.09; 466.1, 466.11, 466.19	17.1	75th: 21.9 90th: 28.8 Max: 65.8	Correlation (*r*): 0.62 O_3, 0.47 NO_2, 0.47 CO, 0.17 SO_2, 0.47 $PM_{10-2.5}$ Copollutant models with: NA
†Malig et al. (2013) 35 California counties 2005−2008 All ages	Difference of collocated PM_{10} and $PM_{2.5}$ concentrations, assigned from the nearest monitoring station within 20 km of population-weighted zip code centroid.	460−519	5.6−34.4	NR	Correlation (*r*): 0.31 $PM_{2.5}$, 0.38 O_3, 0.14 CO Copollutant models with: $PM_{2.5}$, O_3, NO_2, CO, SO_2

Table 5-34 (Continued): Epidemiologic studies of $PM_{10-2.5}$ and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment/Measurement of $PM_{10-2.5}$ Concentrations	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m^3	Upper Percentile Concentrations µg/m^3	Copollutant Examination
Hospital admissions and ED visits, separately					
†Rodopoulou et al. (2014) Doña Ana County, NM 2007−2010 ≥18 yr	Three monitors $PM_{10-2.5}$ concentration estimated by calculating difference between PM_{10} and $PM_{2.5}$ concentrations; not clearly stated if $PM_{10-2.5}$ concentrations were averaged across monitors, if assignment came from the nearest monitor, or if PM_{10} and $PM_{2.5}$ monitors were collocated.	460−465, 466, 480−486, 490−493, 496	10.9	75th: 13 Max: 55.6	Correlation (*r*): −0.05 O_3 Copollutant models with: NA

CMAQ = Community Multi-Scale Air Quality model; MED-PARTICLES = particles size and composition in Mediterranean countries: geographical variability and short-term health effects; UFIREG = ultrafine particles—an evidence-based contribution to the development of regional and European environmental and health policy.

[a]Median concentration

[b]Only four of the five cities had $PM_{10-2.5}$ data.

[c]Only six of the eight cities had $PM_{10-2.5}$ data.

†Studies published since the 2009 PM ISA.

Recent multicity studies (Lanzinger et al., 2016b; Samoli et al., 2016a; Powell et al., 2015; Stafoggia et al., 2013) and single-city studies (Rodopoulou et al., 2014; Alessandrini et al., 2013; Atkinson et al., 2010) conducted in the U.S. and Europe that examined the association between short-term $PM_{10-2.5}$ exposure and respiratory-related hospital admissions provide evidence of positive associations that vary in terms of magnitude and precision (Figure 5-44), particularly in analyses of people of all ages. In a limited assessment of potential copollutant confounding, associations were often attenuated, but remained positive in copollutant models with $PM_{2.5}$, NO_2, and O_3 (Powell et al., 2015; Alessandrini et al., 2013; Stafoggia et al., 2013). The positive associations reported across these studies is supported by a meta-analysis focusing on $PM_{10-2.5}$ and respiratory hospital admissions that reported a RR = 1.01 (95% CI: 1.00, 1.02) (Adar et al., 2014). Additional analyses conducted by Adar et al. (2014) to assess potential copollutant confounding by $PM_{2.5}$ did not observe a consistent pattern in $PM_{10-2.5}$ associations as the correlation with $PM_{2.5}$ increased or when evaluating studies that examined associations with both $PM_{2.5}$ and $PM_{10-2.5}$.

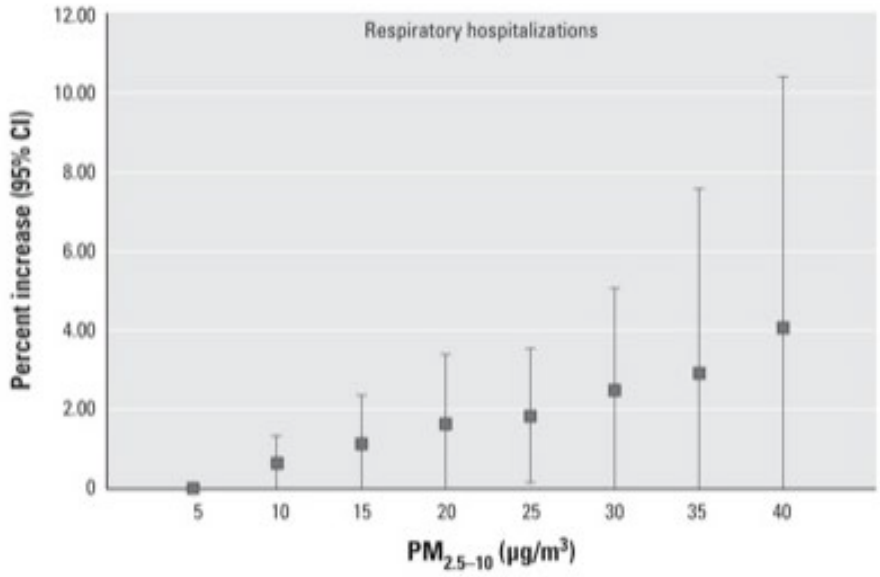
Additional single-city studies conducted in London, U.K. (Atkinson et al., 2010) and Rome, Italy, (Alessandrini et al., 2013) also contribute to the total body of evidence for respiratory-related hospital admissions. Atkinson et al. (2010) when examining a number of urban particles, examined associations with $PM_{10-2.5}$ and across single-day lags ranging from 0 to 6 days. The authors reported evidence of a positive association at lag 1 in an all ages analysis, but there was no evidence of an association for the other lags examined (quantitative results not presented). Instead of focusing on urban particles, Alessandrini et al. (2013) examined the role of Saharan dust on the relationship between short-term $PM_{10-2.5}$ exposure and respiratory-related hospital admissions. Across the entire study duration, the authors reported a 4.4% increase (95% CI: −0.53, 9.60) in hospital admissions at lag 0−5 days. However, when differentiating between Saharan and non-Saharan dust days, Alessandrini et al. (2013) observed that the overall association reported was primarily attributed to the Saharan dust days (13.5%) compared to the non-Saharan dust days (−0.30%).

Across the hospital admissions studies evaluated, a few of the studies conducted sensitivity analyses to examine the lag structure of associations and model specification. Both Stafoggia et al. (2013) and Lanzinger et al. (2016b) examined whether there is evidence of immediate (lag 0−1), delayed (lag 2−5), or prolonged (lag 0−5) effects of $PM_{10-2.5}$ on respiratory-related hospital admissions. In both studies, positive associations were observed across each of the lags, with the association largest in magnitude at lag 0−5, indicating a potential prolonged effect [(Stafoggia et al., 2013): lag 0−1, 1.0% [95% CI: 0.10, 1.8]; lag 2−5: 1.2% [95% CI: −1.1, 3.6]; lag 0−5: 2.0% [95% CI: −0.51, 4.5]; (Lanzinger et al., 2016b): lag 0−1, 7.4% [95% CI: 1.9, 12.7]; lag 2−5: 10.7% [95% CI: 4.7, 16.9]; lag 0−5: 13.9% [95% CI: 6.9, 21.3]]. However, in Stafoggia et al. (2013), as the lag days increased, the confidence intervals did as well, resulting in more uncertain estimates. The results of Stafoggia et al. (2013) and Lanzinger et al. (2016b) are supported by Samoli et al. (2016a) when examining single-day lags ranging from 0 to 10 days where positive associations were observed through lag Day 4, but the strongest

association in terms of magnitude and precision was a lag 1 (quantitative results not presented). Stafoggia et al. (2013) and Powell et al. (2015) both examined the influence of alternative approaches to account for temporal trends and the confounding effects of weather and found that results were relatively unchanged.

Similar to the 2009 PM ISA (U.S. EPA, 2009), compared to studies that examined short-term $PM_{10-2.5}$ exposure and respiratory-related hospital admissions, fewer studies focused on ED visits with the evidence primarily limited to single-city studies. In analyses of all ages, there is no evidence of an association when examining the results from single-city studies. Rodopoulou et al. (2014) in a study conducted in Doña Ana County, NM reported a positive association for older adults, but no evidence of an association for an all ages analysis, which is consistent with the single-city studies evaluated in the 2009 PM ISA (Figure 5-44). However, Malig et al. (2013), in a study of 35 California counties, reported positive associations at lags 1 and 2 days, with the strongest association in terms of magnitude and precision at lag 1 (0.7% [95% CI: 0.3, 1.1]). The association with $PM_{10-2.5}$ was found to remain positive in copollutant models with O_3, NO_2, CO, SO_2, and $PM_{2.5}$. Additionally, associations were found to be slightly elevated in the warm compared to cold season, and robust to the exclusion of extreme $PM_{10-2.5}$ values (the highest and lowest 5% of calculated coarse particle levels) from the analysis. Rodopoulou et al. (2014) also examined the influence of season and extreme $PM_{10-2.5}$ concentrations and reported contradictory results to Malig et al. (2013), i.e., associations larger in magnitude in the cold season and that the $PM_{10-2.5}$ association increased in magnitude when excluding high $PM_{10-2.5}$ concentrations. Uncertainties in how $PM_{10-2.5}$ concentration was estimated in Rodopoulou et al. (2014) complicates the comparison between studies.

Recent studies of respiratory-related hospital admissions and ED visits provide an initial assessment of the C-R relationship, but is limited by the studies not conducting extensive empirical evaluations of alternatives to linearity, and whether there is evidence of a threshold below which effects are not observed. Malig et al. (2013) provides initial evidence of a linear relationship through an analysis where the inclusion of a squared term for $PM_{10-2.5}$ into the statistical model to account for possible nonlinearity did not improve the goodness of fit over the initial model that assumed linearity. Stafoggia et al. (2013) examined whether there was evidence of a threshold in a study of six European cities, which is similar the threshold analysis detailed for $PM_{2.5}$ (Section 5.1.10.6). As depicted in Table 5-45, the authors examined the percent increase in hospital admissions at various concentrations across the distribution of $PM_{10-2.5}$ concentrations, up to 40 $\mu g/m^3$, relative to 5 $\mu g/m^3$, and reported no evidence a threshold.



Source: Permission pending, Adapted from Stafoggia et al. (2013).

Figure 5-45 Concentration-response relationship between short-term $PM_{10-2.5}$ exposure and respiratory-related hospital admissions, lag 0−5, relative to 5 µg/m^3.

5.3.6 Respiratory Effects in Healthy Populations

The 2009 PM ISA (U.S. EPA, 2009) evaluated a limited number of studies that examined the effects of short-term exposure to $PM_{10-2.5}$ on respiratory effects in healthy populations. No epidemiologic studies were available on $PM_{10-2.5}$ exposure and respiratory effects in healthy populations. Null findings were reported for lung function in populations of children, but their health status was not reported (Dales et al., 2008; Moshammer et al., 2006). Evidence for inflammation was inconsistent in controlled human exposure studies. Alexis et al. (2006) found evidence of pulmonary inflammation, as well as innate immune responses of airway macrophages, and increased levels of eotaxin in healthy individuals. Some of these responses were reduced by biological inactivation (i.e., heat-treatment of $PM_{10-2.5}$) implicating a role for endotoxin. Additionally, short-term exposure to $PM_{10-2.5}$ particles was also shown to elicit increases in polymorphonuclear leukocytes and inflammatory cytokines in healthy adults (Graff et al., 2009). However, Jr et al. (2004) reported no effect of short-term $PM_{10-2.5}$ exposure on markers of airway inflammation in healthy subjects. Animal toxicological studies employed noninhalation routes of exposure since inhalation exposure of rodents to $PM_{10-2.5}$ is technically difficult given that rodents are obligatory nasal breathers. A number of studies of involving noninhalation routes of exposure (i.e., oropharyngeal aspiration, intra-tracheal instillation) support a potential role of short-term $PM_{10-2.5}$ exposure in pulmonary oxidative stress and inflammation (Gilmour et al., 2007; Happo et al., 2007; Dick et al., 2003). Evidence for pulmonary injury, oxidative stress, inflammation, and morphological changes

was also provided by Gerlofs-Nijland et al. (2007); Gerlofs-Nijland et al. (2005) in studies involving intra-tracheal instillation of $PM_{10–2.5}$ and an animal model of cardiovascular disease.

5.3.6.1 Epidemiologic Studies

Recent studies have used scripted exposures of healthy adults alternating between rest and exercise in high- and low-pollution locations. These studies minimize uncertainty in the $PM_{10–2.5}$ exposure metric by measuring personal ambient $PM_{10–2.5}$ at the site of exposure (calculated as the difference between PM_{10} and $PM_{2.5}$). In Utrecht, the Netherlands, $PM_{10–2.5}$ exposure of 5 hours was associated with a decrease in FVC and an increase in eNO (Strak et al., 2012). However, the observed associations were small in magnitude and the authors did not report confidence intervals or other measures of precision. Two-hour $PM_{10–2.5}$ exposure was also associated with increased eNO, but not with any of the number of lung function metrics measured in a study of healthy adults in Barcelona, Spain (Kubesch et al., 2015). In a follow-up study using a similar design, Matt et al. (2016) reported FEV_1, FVC, and PEF decrements associated with $PM_{10–2.5}$. Results appeared to be transient, as associations were observed immediately after exposure, but not 7 hours later during a follow-up spirometry test (Matt et al., 2016). Inconsistent associations among the vast number of pollutants and outcomes analyzed within studies is a limitation of all the reviewed studies.

There is limited evidence in healthy children in Chile, Sweden, and Taiwan for associations with 24-hour average $PM_{10–2.5}$ concentrations (difference between PM_{10} and $PM_{2.5}$ measured at monitors). Repeated measures of respiratory symptoms and eNO were associated with $PM_{10–2.5}$ concentrations at a monitor within 1.5 or 3 km of home or school (Prieto-Parra et al., 2017; Carlsen et al., 2016). In a cross-sectional analysis, $PM_{10–2.5}$ averaged across city monitors were associated with decreases in FEV_1, FVC, MMEF, FEV_1/FVC, and MMEF/FVC (Chen et al., 2015a). Cross-sectional measurements are generally less informative than repeated measures study designs because they do not establish a temporal relationship between the exposure and outcome of interest. Other findings in children are inconsistent, but do not provide insight into the respiratory effects of $PM_{10–2.5}$ exposure in healthy people because they are for a population with 66% prevalence of asthma or allergy (Chen et al., 2012; Chen et al., 2011a) or infants on cardiorespiratory monitors who may not spend much time outdoors away from home (Peel et al., 2011).

5.3.6.2 Controlled Human Exposure

In a recent study, Behbod et al. (2013) exposed subjects to $PM_{10–2.5}$ CAPs and measured multiple markers of airway inflammation, but relative to filtered air, no significant airway (sputum) responses were found (Table 5-35).

Table 5-35 Study-specific details from a controlled human exposure study of short-term $PM_{10-2.5}$ exposure and respiratory effects in a healthy population.

Study	Study Design	Disease Status; n; Sex; (Age)	Exposure Details (Concentration; Duration; Comparison Group)	Endpoints Measured
Behbod et al. (2013)	Double-blind, randomized cross-over block design	Healthy nonsmokers; n = 35; 11 M, 12 F (18−60 yr)	234.7 μg/m^3 $PM_{2.5}$ (IQR: 52.4 μg/m^3) for 130 min (120-min exposure + 10 min to complete tests) at rest. Comparison groups were either (1) filtered air or (2) medical air; a minimum 2-week washout period was used between exposures.	Sputum (pre- and 24-hour post-exposure): Total cell and neutrophil counts

BAL = bronchoalveolar lavage; IL-6 = interleukin-6, IL-8 = interleukin-8, IQR = interquartile range.

5.3.6.3 Animal Toxicological Studies

Recent studies involving intra-tracheal instillation confirm previous results showing that $PM_{10-2.5}$ collected during different seasons and from different locations exhibits variable potency in terms of pulmonary injury, inflammation, and morphologic changes (Lippmann et al., 2013a; Mirowsky et al., 2013; Halatek et al., 2011). In addition, two recent animal inhalation studies provide evidence for respiratory effects in healthy populations resulting from short-term exposure to $PM_{10-2.5}$. Amatullah et al. (2012) found that a 4-hour inhalation exposure of BALB/c mice to $PM_{10-2.5}$ CAPs in Toronto increased baseline total respiratory resistance ($p < 0.05$) and maximum response to methacholine ($p < 0.01$) immediately after exposure. In addition, quasi-static compliance was decreased ($p < 0.01$) and quasi-static elastance was increased ($p < 0.01$). These changes indicate airway obstruction. Amatullah et al. (2012) also found increased total cells and macrophages in the bronchoalveolar lavage fluid (BALF) ($p < 0.05$). Aztatzi-Aguilar et al. (2015) showed that multiday inhalation exposure of Sprague Dawley rats to $PM_{10-2.5}$ CAPs in Mexico City resulted in increased IL-6 protein in lung tissue ($p < 0.05$). In addition, a reduction in angiotensin converting enzyme was observed ($p < 0.05$). Angiotensin converting enzyme is a component of the RAS and regulates levels of the potent vasoconstrictor angiotensin II. Since deposition of inhaled $PM_{10-2.5}$ is expected to primarily occur in the extrathoracic airways (i.e., the nose) of rodents, recent animal toxicological studies links deposition in the nose to changes in pulmonary function including increased airway responsiveness, inflammation in the lower airways, and changes in the RAS. Additional study details for these recent toxicological studies are found in Table 5-36.

Table 5-36 Study-specific details from animal toxicological studies of short-term $PM_{10-2.5}$ exposure and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
Amatullah et al. (2012) Species: Mouse Sex: Female Strain: BALB/c Age/Weight: 6−8 weeks, 18 g	$PM_{10-2.5}$ CAPs Toronto Particle size: $PM_{10-2.5}$ Control: HEPA-filtered air	Route: Nose-only inhalation Dose/Concentration: $PM_{10-2.5}$ 793 µg/m³, duration: 4 h Time to analysis: At end of exposure Modifier: Baseline ECG	Pulmonary function—airways resistance, quasi-static elastance BALF cells
Aztatzi-Aguilar et al. (2015) Species: Rat Sex: Male Strain: Sprague Dawley	$PM_{10-2.5}$ CAPs Mexico City Particle size: $PM_{10-2.5}$ Control: Filtered air	Route: Inhalation Dose/Concentration: $PM_{10-2.5}$ 32 µg/m³ Duration: Acute 5 h/day, 3 days Time to analysis: 24 h	Gene and protein expression in lung tissue • IL-6 • Components of RAS and kalikrein-kinin endocrine system • Heme oxygenase-1

BALF = bronchoalveolar lavage fluid; ECG = electrocardiogram; IL-6 = interleukin 6; RAS = renin-angiotensin system.

5.3.6.4 Summary of Respiratory Effects in Healthy Populations

Epidemiologic and controlled human exposure studies examining healthy populations do not consistently support a relationship between $PM_{10-2.5}$ and lung function or pulmonary inflammation. Animal toxicological studies provide evidence for decrements in lung function, inflammation, oxidative stress, and upregulation of the RAS system following short-term inhalation exposure to $PM_{10-2.5}$. Support for some of these findings in animals are provided by studies using noninhalation routes of exposure.

5.3.7 Respiratory Mortality

Studies that examine the association between short-term $PM_{10-2.5}$ exposure and cause-specific mortality outcomes, such as respiratory mortality, provide additional evidence for $PM_{10-2.5}$-related respiratory effects, specifically whether there is evidence of an overall continuum of effects. In the 2009 PM ISA (U.S. EPA, 2009), only a few studies examined the association between short-term $PM_{10-2.5}$ exposure and respiratory mortality, with only one U.S. based multicity study (Zanobetti and Schwartz, 2009). Across studies, there was evidence of generally positive associations with respiratory mortality even though studies used a variety of approaches to estimate $PM_{10-2.5}$ concentrations, but confidence intervals were wide in the single-city studies evaluated. Overall, there was limited evaluation of the

potential confounding effects of gaseous pollutants and the influence of model specification on the associations observed.

Recent multicity epidemiologic studies that examined associations between short-term $PM_{10-2.5}$ exposure and respiratory mortality provide evidence of positive associations in some locations, but not in others (Figure 11-27). However, a meta-analysis (Adar et al., 2014) indicates a $PM_{10-2.5}$ association similar in magnitude as the multicity U.S. based study (Zanobetti and Schwartz, 2009) evaluated in the 2009 PM ISA (U.S. EPA, 2009). Unlike the studies evaluated in the 2009 PM ISA, some recent studies have also further evaluated the $PM_{2.5}$-respiratory mortality relationship by examining cause-specific respiratory mortality outcomes (i.e., COPD, pneumonia, and LRTI) (Samoli et al., 2014; Janssen et al., 2013). Overall, the results reported in the studies that examine cause-specific respiratory mortality outcomes are generally consistent with the results for all respiratory mortality, but the smaller number of mortality events observed results in estimates with larger uncertainty. As a result, this section focuses on studies that examine all respiratory mortality outcomes and address uncertainties and limitations in the relationship between short-term $PM_{10-2.5}$ exposure and respiratory mortality, specifically: potential copollutant confounding, lag structure of associations, and effect modification by season and temperature.

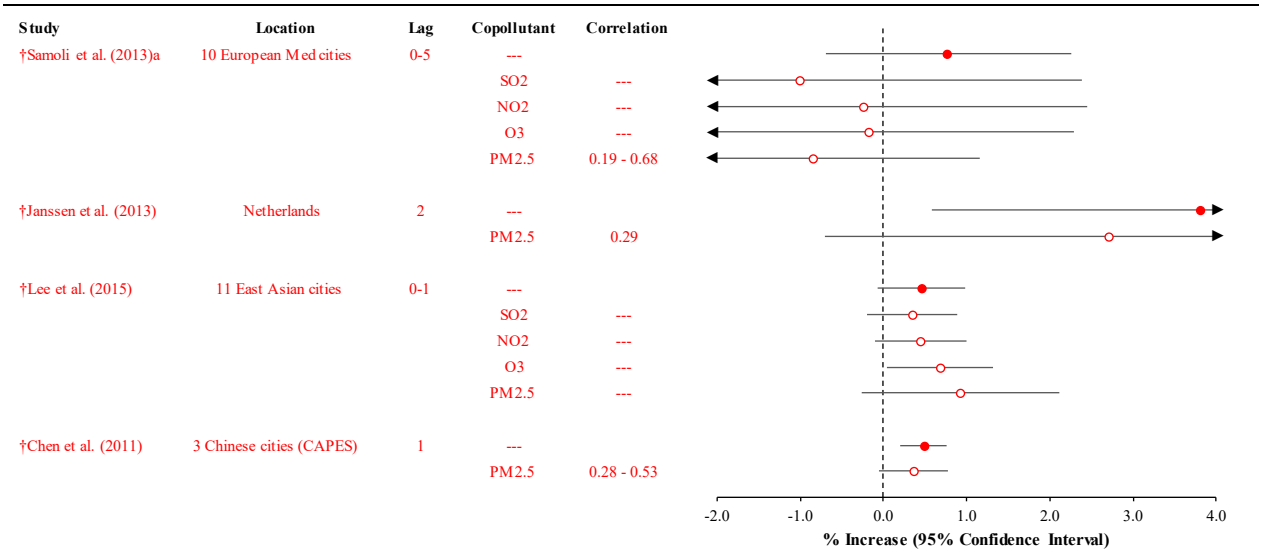
5.3.7.1 Characterizing the $PM_{10-2.5}$-Respiratory Mortality Relationship

Recent epidemiologic studies conducted additional analyses that address some of the uncertainties and limitations of the relationship between short-term $PM_{10-2.5}$ exposure and respiratory mortality identified in the 2009 PM ISA (U.S. EPA, 2009). Specifically, recent studies provide additional information on copollutant confounding, lag structure of associations, and seasonal associations. However, similar to those studies evaluated in the 2009 PM ISA, the approaches used to estimate $PM_{10-2.5}$ concentrations varies across studies and it remains unclear if the level of exposure measurement error varies by each approach (Table 11-9). Overall, these studies provide initial evidence that: $PM_{10-2.5}$-respiratory mortality associations remain positive but may be attenuated in copollutant models; $PM_{10-2.5}$ effects on respiratory mortality tend to occur within the first few days of exposure (i.e., lags 0 to 2 days); and it remains unclear if there are seasonal differences in associations.

5.3.7.1.1 Copollutant Confounding

Consistent with the evaluation of total (nonaccidental) mortality, the studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) provided limited information on the potential confounding effects of gaseous pollutants and $PM_{2.5}$ on the relationship between short-term $PM_{10-2.5}$ exposure and respiratory mortality. Recent multicity studies (Lee et al., 2015; Janssen et al., 2013; Samoli et al., 2013; Chen et al., 2011b) and a meta-analysis (Adar et al., 2014) provide additional information concerning the role of copollutants on the $PM_{10-2.5}$-respiratory mortality relationship.

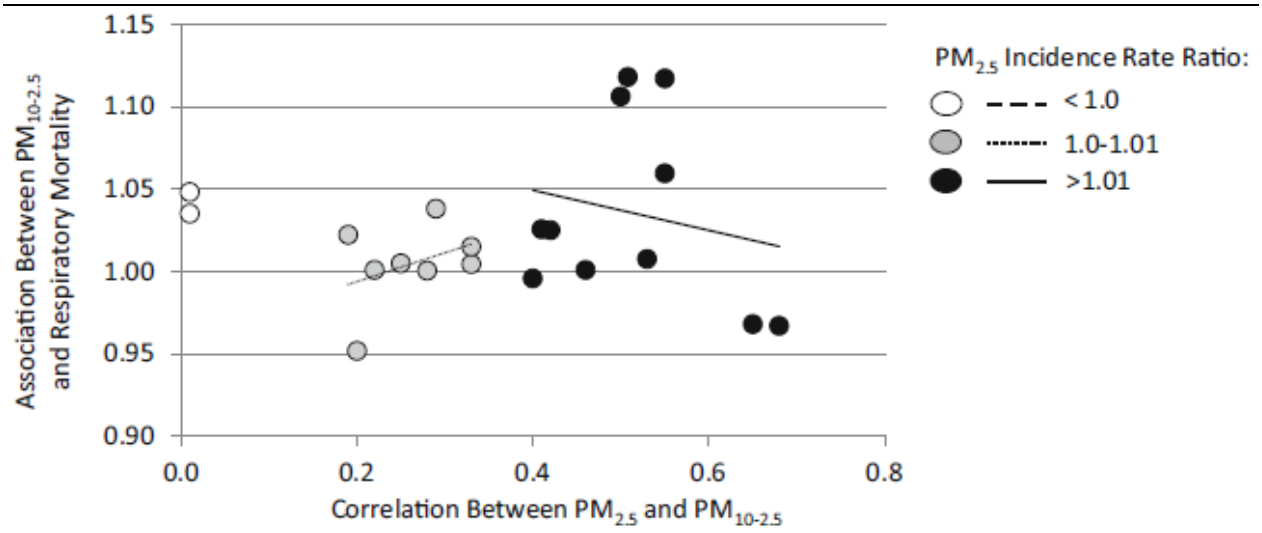
When focusing on potential copollutant confounding of the $PM_{10-2.5}$-respiratory mortality relationship by $PM_{2.5}$, there is evidence that the association generally remains positive (Figure 5-46). However, Samoli et al. (2013) in a study of 10 European Mediterranean cities within the MED-PARTICLES project did not find any evidence of $PM_{10-2.5}$-respiratory mortality association in copollutant models with $PM_{2.5}$. Unlike the other studies evaluated, the authors only presented copollutant model results for lag 0−5 days, which is a lag structure that is longer and inconsistent with the larger body of evidence (Section 5.3.7.1.2).



Note: †Studies published since the 2009 PM ISA. a = copollutant results only presented for a lag of 0−5 days. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-46 Percent increase in respiratory mortality for a 10 μg/m^3 increase in 24-hour average $PM_{10-2.5}$ concentrations in single- and copollutant models.

The studies that provide evidence of a $PM_{10-2.5}$-respiratory mortality association that remains positive in copollutant models with $PM_{2.5}$ are supported by analyses conducted by Adar et al. (2014) in the context of a meta-analysis. When examining studies that conducted copollutant models with $PM_{2.5}$, Adar et al. (2014) observed that the $PM_{10-2.5}$-respiratory mortality association was similar in magnitude to that observed in single-pollutant models (quantitative results not provided). The results from copollutant models were further supported when stratifying $PM_{10-2.5}$-mortality estimates by the correlation with $PM_{2.5}$ (low, $r < 0.35$; medium, $r = 0.35$ to <0.5; high, $r > 0.5$). The authors observed evidence of positive associations for the medium and high correlation categories that were similar in magnitude, but had wide confidence intervals. However, there was no evidence of an association for the low correlations. Adar et al. (2014) further examined potential copollutant confounding by $PM_{2.5}$ through an analysis focusing on whether $PM_{10-2.5}$-mortality associations were present when the correlation between $PM_{2.5}$ and $PM_{10-2.5}$ increased and when $PM_{2.5}$ was also associated with mortality. As highlighted in Figure 5-47, there was evidence of positive $PM_{10-2.5}$-respiratory mortality associations at both low and high correlations as well as low and high magnitudes of the $PM_{2.5}$-respiratory mortality association (Figure 5-47).



Source: Permission pending, Adar et al. (2014).

Figure 5-47 Associations between short-term $PM_{10-2.5}$ exposure and respiratory mortality as a function of the correlation between $PM_{10-2.5}$ and $PM_{2.5}$ stratified by strength of the association with $PM_{2.5}$.

Across the studies that examined potential copollutant confounding, only a few examined gaseous pollutants (Lee et al., 2015; Samoli et al., 2013) and the results contradict one another (see Figure 5-46).

As a result, it remains unclear whether gaseous copollutants confound the $PM_{10-2.5}$-respiratory mortality association.

Collectively, the recent epidemiologic studies that examined potential copollutant confounding provide initial evidence that $PM_{10-2.5}$-respiratory mortality associations remain generally positive in copollutant models particularly with $PM_{2.5}$. However, the lack of information on the correlations among the pollutants examined and the limited analyses of gaseous pollutants complicates the interpretation of the copollutant model results.

5.3.7.1.2 Lag Structure of Associations

Multicity epidemiologic studies that examined cause-specific mortality in the 2009 PM ISA (U.S. EPA, 2009) observed immediate effects on respiratory mortality attributed to short-term $PM_{10-2.5}$ exposure, with consistent positive associations observed at lags ranging from 0 to 2 days. However, the majority of these studies either examined single-day lags or selected lags a priori. Recent multicity studies have conducted more extensive examinations of the lag structure of associations by examining multiple sequential single-day lags or examining whether there is evidence of immediate (i.e., lag 0−1 days), delayed (i.e., lag 2−5 days), or prolonged (i.e., lag 0−5 days) effects of short-term $PM_{10-2.5}$ exposure on respiratory mortality.

Across the studies that examined single-lag days, most of the studies focused on lags within the range of 0 to 2 days. Although a few studies extended out to a longer duration, collectively the studies provided evidence that was generally in agreement with one another. Janssen et al. (2013), in a study conducted in the Netherlands, examined single-day lags of 0 to 3 days and reported no evidence of an association at lag 0 and 1 day. The largest association in terms of magnitude and precision was for lag 2 days (3.8% [95% CI: 0.6, 7.2]). Chen et al. (2011b), within the CAPES study, reported evidence of an immediate effect between short-term $PM_{10-2.5}$ exposure and respiratory mortality by observing evidence of a positive association at lag 1 and no evidence of an association at lag 0 and 2 days. Stafoggia et al. (2017), in a study of eight European cities, examined single-day lags ranging from 0 to 10 days also reported evidence of an immediate effect with positive associations at lags 0 and 1 day. However, the authors found evidence of positive associations at longer lags (i.e., lag 4 and 5), but confidence intervals were wide. The results across the studies that examined a series of single-day lags is further supported by the meta-analysis by Adar et al. (2014) where an examination of single-day lag risk estimates across studies found positive associations across lags ranging from 0 to 2 days with the strongest association in terms of magnitude and precision occurring at lag 1.

Although the studies that examined a series of single-day lags tend to support a $PM_{10-2.5}$-respiratory mortality association within the first few days after exposure, Samoli et al. (2013), in the MED-PARTICLES project, did not provide further support for this lag structure of associations. The authors examined both a series of multiday lags as well as single-day lags through a polynomial

distributed lag over 0−7 days. In the multiday lag analysis, Samoli et al. (2013) reported the strongest evidence of an association for a delayed effect (i.e., lag 2−5 days) (0.72% [95% CI: −0.31, 1.8]), with no evidence of an association at lag 0−1 days. This observation was confirmed when examining the polynomial distributed lag provided evidence of positive associations only at lags 3,4, and 5 (quantitative results not presented).

Overall, studies that examined the lag structure of associations generally support that short-term $PM_{10-2.5}$ exposure contributes to respiratory mortality effects within the first few days after exposure, ranging from 0−2 days. However, there is initial evidence that the $PM_{10-2.5}$-respiratory mortality association may be more delayed.

5.3.7.1.3 Effect Modification

Season

An examination of potential seasonal differences in associations between short-term $PM_{10-2.5}$ exposure and respiratory mortality in the 2009 PM ISA (U.S. EPA, 2009) was limited to one U.S. multicity study (Zanobetti and Schwartz, 2009) that provided initial evidence of associations being larger in magnitude in the spring and summer. Although still limited in number, some recent multicity studies conducted an examination of potential seasonal differences in associations (Lee et al., 2015; Samoli et al., 2013).

Samoli et al. (2013), in the MED-PARTICLES project, only examined warm (April−September) and cold months (October−March). In analyses focusing on lag 0−5 days, the authors observed evidence of positive associations in both seasons, with associations larger in magnitude during the warm season (1.21% [95% CI: −2.0, 4.6]) compared to the cold season (0.30% [95% CI: −1.8, 2.5]), but confidence intervals were wide. Lee et al. (2015), in a study conducted in 11 east Asian cities, observed a different pattern of seasonal associations. The authors reported larger associations in the cold season (1.2% [95% CI: 0.16, 2.3]) compared to the warm (0.42% [95% CI: −0.30, 1.2]). It is unclear why these results differ from the other studies, but mean $PM_{10-2.5}$ concentrations and mean temperature tended to be higher across the cities in Lee et al. (2015) compared to the cities in the other studies evaluated in this section. Overall, the inconsistent evidence across studies does not provide additional information on the seasonal pattern of associations between short-term $PM_{10-2.5}$ exposure and respiratory mortality.

Temperature

In addition to examining whether there is evidence that warm temperatures modify the $PM_{10-2.5}$-respiratory mortality relationship by conducting seasonal analyses, a recent study also examined whether there is evidence that high temperature days modify the $PM_{10-2.5}$-respiratory mortality

relationship. Although in all-year analyses, Pascal et al. (2014) reported no evidence of an association between short-term $PM_{10–2.5}$ exposure and respiratory mortality, the authors examined whether temperature modified the relationship. Pascal et al. (2014) examined the impact of temperature on the $PM_{10–2.5}$-respiratory mortality relationship across nine French cities by comparing associations on warm and nonwarm days, where warm days were defined as those days where the mean temperature exceeded the 97.5th percentile of the mean temperature distribution. When calculating the interaction ratio, which estimated the extra PM effect due to warm days, the authors observed no evidence of a positive modifying effect of warm days on respiratory mortality.

5.3.8 Summary and Causality Determination

Based on a small number of epidemiologic studies observing associations with some respiratory effects and limited evidence from experimental studies to support biological plausibility, the 2009 PM ISA (U.S. EPA, 2009) concluded that the relationship between short-term exposure to $PM_{10–2.5}$ and respiratory effects is suggestive of a causal relationship. Epidemiologic findings were consistent for respiratory infection and combined respiratory-related diseases, but not for COPD. Studies were characterized by overall uncertainty in the exposure assignment approach and limited information regarding potential copollutant confounding. Controlled human exposure studies of short-term $PM_{10–2.5}$ exposure found no lung function decrements and inconsistent evidence for pulmonary inflammation in healthy individuals or human subjects with asthma. Animal toxicological studies were limited to those using noninhalation (e.g., intra-tracheal instillation) routes of $PM_{10–2.5}$ exposure. Recent studies strengthen the evidence base for asthma exacerbation and respiratory mortality, but they do not rule out chance and confounding. The evidence for the relationship between short-term exposure to $PM_{2.5}$ and effects on the respiratory system is summarized in Table 5-37, using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015).

Table 5-37 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10–2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10–2.5}$ Concentrations Associated with Effects[c]
Asthma exacerbation			
Consistent epidemiologic evidence from a limited number of multiple, high quality studies at relevant $PM_{2.5}$ concentrations	Increases in asthma-related hospital admissions and ED visits. Evidence mostly from single-city studies conducted in the U.S.	Section 5.3.2.1	9.7−16.2 μg/m^3

Table 5-37 (Continued): Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10-2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Uncertainty regarding confounding by copollutants	Potential copollutant confounding for asthma-related hospital admissions and ED visits is examined in a few studies, with some evidence that associations remain robust in models with gaseous pollutants and $PM_{2.5}$.	Section 5.3.2.1	
Uncertainty regarding exposure measurement error	Uncertainty in using $PM_{10-2.5}$ concentrations, estimated by differencing PM_{10} and $PM_{2.5}$ concentrations, as exposure surrogates, is not addressed.		
Limited coherence in epidemiologic studies across the continuum of effects	Providing support for asthma exacerbation are findings of associations for respiratory symptoms in children. There is no evidence for association with lung function decrements, and inconsistent evidence for eNO.	Section 5.3.2.2 Section 5.3.2.3 Section 5.3.2.4	
Inconsistent evidence from controlled human exposure studies	In adults with asthma, measures of lung function are unaffected. Results for pulmonary inflammation were inconsistent, with one study finding many effects on immune function.	Section 5.3.2.4.2 Alexis et al. (2014)	90 µg/m^3
Biological plausibility	Evidence from one controlled human exposure study provides biological plausibility with epidemiologic findings for allergic asthma, the most common asthma phenotype in children.		
Respiratory mortality			
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{10-2.5}$ concentrations	Associations are observed in single and multicity studies, with effects tending to occur between 0−2 days.	Section 5.3.7	
Uncertainty regarding confounding by copollutants and exposure measurement error	Potential copollutant confounding is examined in a few studies, with some evidence that associations remain robust in models with $PM_{2.5}$.	Section 5.3.7	
Uncertainty regarding exposure measurement error	Uncertainty in using $PM_{10-2.5}$ concentrations, estimated by differencing PM_{10} and $PM_{2.5}$ concentrations, as exposure surrogates, is not addressed.	Section 3.3.1	

Table 5-37 (Continued): Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10-2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Some coherence with underlying causes of mortality	COPD and respiratory infection evidence provide some coherence.	Section 5.3.3 Section 5.3.4	
Exacerbation of COPD, respiratory infection and combined respiratory-related diseases			
Limited epidemiologic evidence and uncertainty regarding $PM_{10-2.5}$ independent effects	Generally positive associations for COPD-related hospital admissions in a limited number of studies conducted in the U.S., Canada, and Asia. Evidence is inconsistent for COPD ED visits.	Section 5.3.3.1	5.6−24.8 μg/m^3
	Generally positive associations ED visits for acute respiratory infection, pneumonia, and combinations of respiratory infections in a limited number of studies in the U.S., Canada, and Asia.	Section 5.3.4.1	5.6−24.8 μg/m^3
	Generally positive associations are observed for combined respiratory-related disease hospital admissions in single-city and multicity studies conducted in the U.S., Canada, and Europe. Evidence is inconsistent for combined respiratory-related disease visits.	Section 5.3.5	
Respiratory effects in healthy populations			
Inconsistent evidence from epidemiologic studies	A limited number of panel studies in healthy adults reported inconsistent evidence of associations with lung function and pulmonary inflammation.	Section 5.3.6.1	
Inconsistent evidence from controlled human exposure studies	Evidence is inconsistent for pulmonary inflammation.	Section 5.3.6.2 Behbod et al. (2013)	235 μg/m^3
Some evidence from toxicological studies at relevant concentrations	Results show altered lung function and pulmonary inflammation in rodents exposed by inhalation to $PM_{10-2.5}$ CAPs.	Amatullah et al. (2012) Aztatzi-Aguilar et al. (2015)	32−793 μg/m^3

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

Recent epidemiologic findings more consistently link $PM_{10–2.5}$ to asthma exacerbation than studies reported in the 2009 PM ISA (U.S. EPA, 2009). These studies of hospital admission and ED visits include children older than 5 years. These findings are supported by epidemiologic studies observing respiratory symptoms in children and by a controlled human exposure study showing PM-related effects on inflammation and the immune system. There is limited evidence that associations remain robust in models with gaseous pollutants and $PM_{2.5}$. Recent, but limited, epidemiologic findings are also more consistent for COPD exacerbation and combined respiratory-related diseases compared with studies reported in the 2009 PM ISA. However, the evidence for COPD hospital admissions is inconsistent across several U.S. cities and for direct $PM_{10–2.5}$ measurements. Recent epidemiologic findings for respiratory infection differ than findings reported in the 2009 ISA in that they indicate associations with pneumonia, but not combinations of respiratory infections. The respiratory effects related to short-term $PM_{10–2.5}$ exposure in healthy individuals remain inconsistent, although some controlled human exposure and animal toxicological studies show effects. The evidence base for respiratory mortality is expanded since the 2009 PM ISA (U.S. EPA, 2009) and is generally supportive of associations with short-term exposure to $PM_{10–2.5}$. Studies provide initial evidence that $PM_{10–2.5}$-respiratory mortality associations remain positive but may be attenuated in copollutant models. In addition, $PM_{10–2.5}$ effects on respiratory mortality tend to occur within the first few days of exposure (i.e., lags 0 to 2 days). Across most of these respiratory outcome groups, copollutant confounding remains uncertain. An uncertainty spanning all epidemiologic studies examining associations with $PM_{10–2.5}$ is the lack of a systematic evaluation of the various methods used to estimate $PM_{10–2.5}$ concentrations and the resulting uncertainty in the spatial and temporal variability in $PM_{10–2.5}$ concentrations compared to $PM_{2.5}$ (Section 2.5.1.2.3 and Section 3.3.1.1). **Overall, the collective evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10–2.5}$ exposure and respiratory effects.**

5.4 Long-Term $PM_{10–2.5}$ Exposure and Respiratory Effects

The 2009 PM ISA concluded that the evidence was inadequate to assess the relationship between long-term exposure to $PM_{10–2.5}$ and respiratory effects (U.S. EPA, 2009).[60] At that time, the evidence consisted of a single epidemiologic study. Some recent epidemiologic findings link $PM_{10–2.5}$ to lung function metrics (Section 5.4.2), the development of asthma (Section 5.4.3), and respiratory infection (Section 5.4.5) in children. However, there is little or no evidence for the development of allergic disease (Section 5.4.4), severity of asthma (Section 5.4.6), or respiratory effects in healthy populations (Section 5.4.7). In all recent studies, $PM_{10–2.5}$ concentrations were estimated by LUR models, dispersion models, or by subtracting monitored $PM_{2.5}$ concentrations from monitored PM_{10} concentrations. The major uncertainties for these studies involve the potential for exposure measurement error, especially

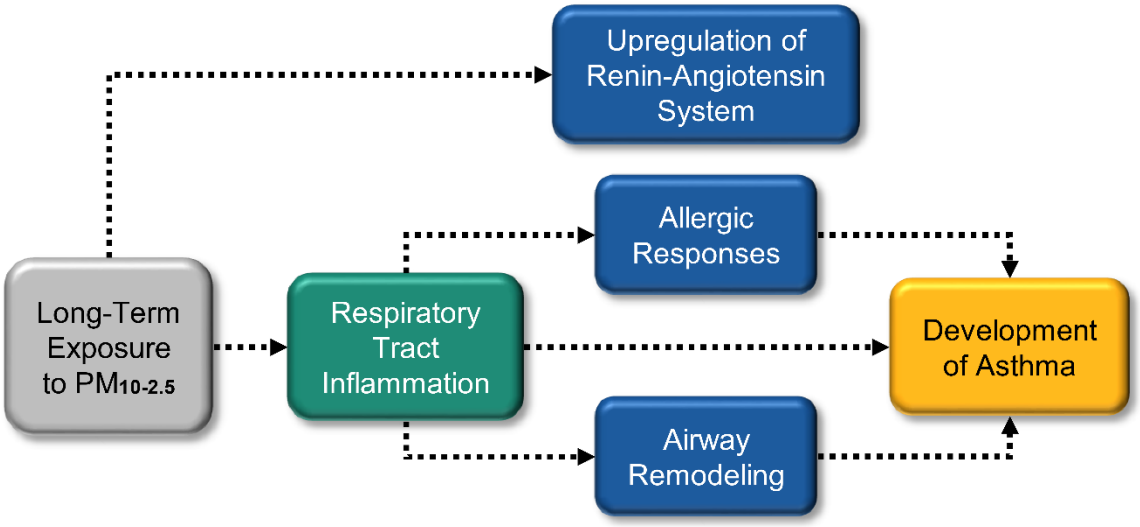
[60] As detailed in the Preface, risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{10-2.5}$ concentrations unless otherwise noted.

relating to the errors due to subtracting $PM_{2.5}$ concentration from PM_{10} concentration, notably when the monitors are not collocated, and the potential for confounding related to copollutants. Experimental evidence is limited to a single inhalation exposure in healthy animals, although additional studies using noninhalation routes of exposure provide biological plausibility for a relationship between long-term exposure to $PM_{10–2.5}$ and asthma severity.

5.4.1 Biological Plausibility

This section describes biological pathways that potentially underlie respiratory health effects resulting from long-term exposure to $PM_{10–2.5}$. Figure 5-48 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" long-term exposure to $PM_{10–2.5}$ may lead to respiratory health effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 5.4.

Once $PM_{10–2.5}$ deposits in the respiratory tract, it may be retained, cleared, or solubilized (see CHAPTER 4). Insoluble and soluble components of $PM_{10–2.5}$ may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate reactive oxygen species (ROS) and this capacity is termed "oxidative potential." Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see CHAPTER 4). Immune system responses due to the presence of particles in the interstitial space may contribute to respiratory health effects.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 5-48 Potential biological pathways for respiratory effects following long-term $PM_{10-2.5}$ exposure.

Evidence that long-term exposure to $PM_{10-2.5}$ may affect the respiratory tract generally informs one proposed pathway (Figure 5-48). It begins with respiratory tract inflammation and leads to allergic responses and airway remodeling that may underly the development or worsening of asthma. Epidemiologic evidence links long-term exposure to $PM_{10-2.5}$ and eNO, a marker of airway inflammation (Dales et al., 2008). Supportive evidence is provided by several animal toxicological studies involving intra-tracheal instillation (Liu et al., 2014; He et al., 2013a; He et al., 2013b). In these studies, multiple exposures to dust storm-associated $PM_{10-2.5}$ resulted in allergic inflammation and airway remodeling in nonallergic mice and enhanced allergen-induced responses in allergic mice. These findings are supportive of a link between long-term $PM_{10-2.5}$ exposure and incident asthma (Section 5.4.3). This proposed pathway provides biological plausibility for epidemiologic evidence of respiratory health effects and will be used to inform a causality determination, which is discussed later in the chapter (Section 5.4.9).

In addition, a study of long-term $PM_{10-2.5}$ exposure in animals (Aztatzi-Aguilar et al., 2015) found decreases in tissue levels of heme oxygenase-1 and IL-6, markers of oxidative stress and inflammation, respectively. Increases in mRNA and protein levels of angiotensin receptor Type 1 and mRNA levels of angiotensin converting enzyme, which are components of the RAS, were also observed. Angiotensin receptor Type 1 mediates the effects of angiotensin II, which is a potent vasoconstrictor and mediator in the vasculature. Deposition of inhaled $PM_{10-2.5}$ is expected to primarily occur in the extrathoracic airways

(i.e., the nose) of rodents and to result in a much smaller fraction deposited in the lower respiratory tract compared with humans. This study links deposition of $PM_{10–2.5}$ in the nose to increased activity of the RAS and to a possible dampening of oxidative stress and inflammation in the lung.

5.4.2 Lung Function and Lung Development

As evaluated in the 2009 PM ISA (U.S. EPA, 2009), a cross-sectional analysis of 1,613 schoolchildren in Windsor, Ontario reported that a 5 ug/m^3 increase in $PM_{10–2.5}$ was not associated with percent predicted FEV_1 (0.26 [95% CI: −4.22, 4.74]) and was associated with small, imprecise (i.e., wide 95% CIs) increase in percent predicted FVC: (1.10 [95% CI: −8.11, 10.39]) (Dales et al., 2008). Recent analyses of European birth cohorts have observed consistent associations between $PM_{10–2.5}$ and an array of lung function metrics. In the PIAMA cohort, $PM_{10–2.5}$ estimated at children's current addresses was associated with decreases in FEV_1, FVC, and $FEF_{25–75}$ measures collected at age 8 and 12 (Gehring et al., 2015a). Similarly, in an ESCAPE project analysis of five European cohorts, $PM_{10–2.5}$ estimates at both birth address and current address were negatively associated with FEV_1 measured at ages 6 and 8, but the effect was stronger when current address was used in the exposure assignment (Gehring et al., 2013). $PM_{10–2.5}$ at current address was also associated with higher odds of FEV_1 <85% of predicted values (OR: 1.81 [95% CI: 0.94, 3.47]), a clinically significant indicator of impaired lung function.

Cross-sectional studies of schoolchildren in 24 Taiwanese provinces (Chen et al., 2015a) and 9−10-year olds participating in the Child Heart and Health Study in England (Barone-Adesi et al., 2015) provided inconsistent evidence of an association between $PM_{10–2.5}$ and lung function. While Chen et al. (2015a) reported reductions of 102 ml (95% CI: 16, 189 ml) in FEV_1 and 121 ml (95% CI: 15, 227 ml) in FVC per 5 μg/m^3 increase in $PM_{10–2.5}$ over the past 2 months, Barone-Adesi et al. (2015) did not observe any associations between annual $PM_{10–2.5}$ exposure and the same lung function metrics. Additionally, it is unclear whether Chen et al. (2015a) estimated $PM_{10–2.5}$ using collocated PM_{10} and $PM_{2.5}$ monitors.

In addition to studies conducted among children, one epidemiologic study evaluated the effects of long-term exposure to $PM_{10–2.5}$ on pulmonary function in adults. Results for the various indices of pulmonary function were inconsistent among adults participating in the ESCAPE project (Adam et al., 2015). $PM_{10–2.5}$ was associated with decrements in FEV_1 and FVC in a cross-sectional analysis, but an increase in FEV_1 in longitudinal analyses. Due to the strengths of a longitudinal study design compared to a cross-sectional design, it's possible that the negative association may have been the result of unmeasured confounding in the cross-sectional analysis.

5.4.3 Development of Asthma

There were no studies examining the association between long-term exposure to $PM_{10–2.5}$ and the development of asthma available for inclusion in the 2009 PM ISA (U.S. EPA, 2009). A few recent studies report associations between $PM_{10–2.5}$ and asthma incidence. In the PIAMA cohort in the Netherlands (Gehring et al., 2015a) and a pooled analysis of four European birth cohorts (Gehring et al., 2015b), asthma incidence was associated with $PM_{10–2.5}$ concentrations outside birth residences. The associations were attenuated, but still positive when $PM_{10–2.5}$ concentrations were assigned at the address of the participant at the time of follow-up. This indicates the potential importance of early life exposures.

Studies examining asthma prevalence in children reported contrasting evidence. The Gehring et al. (2015b) pooled analysis, discussed above, observed inconsistent evidence of an association across cohorts, and reported a null association in a meta-analysis combining results from all cohorts. Another ESCAPE project analysis of five European birth cohorts estimated $PM_{10–2.5}$ at participants' birth addresses and addresses at age 4 and age 8 (Mölter et al., 2014). Birth and current address $PM_{10–2.5}$ was not associated with higher odds of prevalent asthma at age 4. However, $PM_{10–2.5}$ estimated at both birth and current address was associated with an increase in odds of asthma by age 8. Contrary to the results for asthma incidence, the association was higher in magnitude and more precise when asthma prevalence was related to current address $PM_{10–2.5}$ concentrations (OR: 1.16 [95% CI: 0.93, 1.44]) rather than birth address exposure (1.10 [0.72, 1.69]).

No recent studies have examined subclinical effects underlying the development of asthma in association with long-term exposure to $PM_{10–2.5}$. A cross-sectional analysis of 1,613 schoolchildren in Windsor, Ontario, reviewed in the 2009 PM ISA (U.S. EPA, 2009), reported a null association between $PM_{10–2.5}$ and Ln(eNO) (Dales et al., 2008). Results from a prior CHS analysis (Bastain et al., 2011) showed that elevated eNO was associated with increased risk of new onset asthma.

In addition to studies conducted among children, one epidemiologic study evaluated the effects of long-term $PM_{10–2.5}$ exposure in adults. An ESCAPE project analysis also examined associations between $PM_{10–2.5}$ and incident asthma (Jacquemin et al., 2015). In a meta-analysis of all cohorts, annual $PM_{10–2.5}$ was not associated with higher odds of incident asthma (OR: 0.99 [95% CI: 0.87, 1.14]).

Animal toxicological studies related to the development of asthma are typically conducted in nonallergic animal models. Inhalation exposure of rodents to $PM_{10–2.5}$ is technically difficult since rodents are obligatory nasal breathers. A group of recent studies examined the effects of long-term $PM_{10–2.5}$ using Asian sand dust and noninhalation routes of exposure (i.e., intra-tracheal instillation). Results provide biological plausibility for a potential role of $PM_{10–2.5}$ in allergic inflammation and airway remodeling (Liu et al., 2014; He et al., 2013a; He et al., 2013b).

5.4.4 Development of Allergic Disease

There were no studies examining the association between long-term exposure to $PM_{10-2.5}$ and the development of allergic disease available for inclusion in the 2009 PM ISA (U.S. EPA, 2009). A small number of recent epidemiologic studies examined the association between long-term exposure to $PM_{10-2.5}$ and allergic disease. The relation between early-life exposure to $PM_{10-2.5}$ and allergic sensitization at age 4 and 8 years was examined in the ESCAPE pooled analysis of five European cohorts (Gruzieva et al., 2014). There were no clear associations between $PM_{10-2.5}$ concentrations estimated at birth address and sensitization at age 4 or age 8. Similarly, another European birth cohort pooled analysis did not observe an association between $PM_{10-2.5}$ and rhinoconjunctvitis (Gehring et al., 2015b). The PIAMA cohort reported on associations between $PM_{10-2.5}$ and allergic outcomes (Gehring et al., 2015a) noting that $PM_{10-2.5}$ was associated with increases in self-reported hay fever, rhinitis and allergic sensitization during the first 11 years of life (ORs ranging from 1.3 to 1.6 per 5 $\mu g/m^3$ increase). In a 2006 U.S. National Health Interview Survey (NHIS) cross-sectional analysis, $PM_{10-2.5}$ was examined as a potential predictor of allergy in children aged 3−17 years living within 20 miles of an air-quality monitor (Parker et al., 2009). $PM_{10-2.5}$ was not associated with respiratory allergy/hay fever.

5.4.5 Respiratory Infection

There were no studies examining the association between long-term exposure to $PM_{10-2.5}$ and respiratory infection available for inclusion in the 2009 PM ISA (U.S. EPA, 2009). Recently, an ESCAPE project study examined respiratory infections in relation to $PM_{10-2.5}$ (MacIntyre et al., 2014b). $PM_{10-2.5}$ estimated at birth residence was associated with an imprecise increase in odds of pneumonia in the first 36 months of life (OR: 1.24 [95% CI: 1.03, 1.5] per 5 ug/m^3 increase), but was not associated with increased odds of otitis media or croup. A sensitivity analysis looking at alternative outcome windows showed the strongest association between long-term $PM_{10-2.5}$ and pneumonia diagnosed in the first year of life (OR: 1.46 [95% CI: 1.11, 1.92]). The association between $PM_{10-2.5}$ and pneumonia at 36 months was attenuated, but still positive in a two-pollutant model adjusting for NO_2 (1.13 [0.72, 1.76]; $r = 0.34-0.93$).

5.4.6 Severity of Asthma

There were no studies examining the association between long-term exposure to $PM_{10-2.5}$ and severity of asthma available for inclusion in the 2009 PM ISA (U.S. EPA, 2009). Recent studies are limited in number. In an epidemiologic study conducted in northern California, Balmes et al. (2014) examined the association between annual $PM_{10-2.5}$ and symptomatic asthma in a cross-sectional cohort study of adults with both asthma and allergies. The middle and highest tertiles of annual $PM_{10-2.5}$ exposure (10.68−12.68 and ≥12.71 $\mu g/m^3$, respectively) were not associated with increased odds of asthma symptoms compared to the lowest tertile of exposure (<10.68 $\mu g/m^3$).

Animal toxicological studies related to asthma severity are typically conducted in allergic animal models, which share phenotypic features with asthma (see Section 5.1.2.4). Inhalation exposure of rodents to $PM_{10–2.5}$ is technically difficult since rodents are obligatory nasal breathers. A group of recent studies examined the effects of long-term $PM_{10–2.5}$ using Asian sand dust and noninhalation routes of exposure (i.e., intra-tracheal instillation). Results provide biological plausibility for a potential role of $PM_{10–2.5}$ in enhancing allergic responses (Liu et al., 2014; He et al., 2013a; He et al., 2013b).

5.4.7 Subclinical Effects in Healthy Populations

Animal toxicological and epidemiologic studies provide evidence for subclinical effects potentially underlying the development of respiratory disease in healthy populations. As reported in the 2009 PM ISA (U.S. EPA, 2009), Dales et al. (2008) found a positive association between long-term exposure to $PM_{10–2.5}$ and eNO, a marker of inflammation, in an epidemiologic study among children living in Windsor, ON. In a recent animal toxicological study, Aztatzi-Aguilar et al. (2015) evaluated pulmonary oxidative stress and inflammatory responses in Sprague Dawley rats exposed for 8 weeks to $PM_{10–2.5}$ CAPs in Mexico City. A decrease in lung tissue heme oxygenase-1 activity was found ($p < 0.05$), but there was no change in γ-glutamyl cysteine synthetase catalytic subunit, another index of oxidative stress. Long-term exposure to $PM_{10–2.5}$ CAPs also resulted in a decrease in IL-6 protein ($p < 0.05$) and changes in the RAS. An increase in angiotensin receptor Type 1 protein was observed along with a decrease in its mRNA levels in lung tissue ($p < 0.05$). Angiotensin receptor Type 1 mediates the effects of angiotensin II, which is a potent vasoconstrictor and mediator in the vasculature. Protein and mRNA levels of angiotensin converting enzyme, which catalyzes the conversion of angiotensin I to angiotensin II, increased following long-term exposure to $PM_{10–2.5}$ CAPs ($p < 0.05$). Since deposition of inhaled $PM_{10–2.5}$ is expected to primarily occur in the extrathoracic airways (i.e., the nose) of rodents, this study links deposition in the nose to increased activity of the RAS and to a possible dampening of oxidative stress and inflammation in the lower airways. Additional study details are found in Table 5-38.

Table 5-38 Study-specific details from an animal toxicological study of long-term exposure to $PM_{10-2.5}$ and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
Aztatzi-Aguilar et al. (2015) Species: Rat Sex: Male Strain: Sprague Dawley Age/Weight:	$PM_{10-2.5}$ CAPs Mexico City Particle size: $PM_{10-2.5}$ Control: Filtered air	Route: Inhalation Dose/Concentration: Coarse $PM_{10-2.5}$ 32 µg/m^3 Duration: Acute 5 h/day, 3 days Subchronic 5 h/day, 4 days/week, 8 weeks Time to analysis: 24 h	Gene and protein expression in lung tissue • IL-6 • Components of RAS and kalikrein-kinin endocrine system • Heme oxygenase-1

IL-6 = interleukin 6; RAS = renin-angiotensin system.

5.4.8 Respiratory Mortality

Two recent European cohort studies evaluated the association between long-term $PM_{10-2.5}$ exposure and mortality and observed inconsistent results. In a pooled analysis of 22 cohorts from 13 European cohorts, Dimakopoulou et al. (2014) observed a null association with respiratory mortality in the ESCAPE cohort. In a French cohort, Bentayeb et al. (2015) observed a positive association between long-term $PM_{10-2.5}$ exposure and respiratory mortality. Both studies used statistical models to predict area-wide PM_{10} and $PM_{2.5}$ concentrations and used the subtraction method to estimate $PM_{10-2.5}$ concentrations, which contributes to uncertainty regarding exposure measurement error.

5.4.9 Summary and Causality Determination

Based on limited epidemiologic evidence demonstrating associations with some respiratory effects and a lack of evidence from experimental studies to support biological plausibility, the 2009 PM ISA (U.S. EPA, 2009) concluded that evidence was inadequate to assess the relationship between long-term exposure to $PM_{10-2.5}$ and respiratory effects. The evidence characterizing the relationship between long-term exposure to $PM_{10-2.5}$ and respiratory effects is detailed below (Table 5-39), using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015). A limited number of recent epidemiology studies expand the evidence base for decrements in lung function, the development of asthma, and respiratory infection in children. Uncertainty regarding copollutant confounding and exposure measurement error results in an inability to rule out chance and confounding. An animal toxicological study examined the potential for inhalation of $PM_{10-2.5}$ to affect the respiratory

system and found upregulation of the RAS and a dampening of oxidative stress and inflammation in the lung. Several animal toxicological studies involving noninhalation routes of exposure found allergic inflammation and airway remodeling, which provides biological plausibility for the development of asthma. Overall, **the evidence is inadequate to infer the presence or absence of a causal relationship between long-term $PM_{10-2.5}$ exposure and respiratory effects.**

Table 5-39 Summary of evidence that is inadequate to infer the presence or absence of a causal relationship between long-term $PM_{10-2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Limited epidemiologic evidence from multiple, high quality studies at relevant $PM_{10-2.5}$ concentrations	Decrements in attained lung function in children consistently observed in a limited number of cohort studies.	Gehring et al. (2013) Gehring et al. (2015a)	7.6−8.4 µg/m^3
	Increases in asthma incidence in children in a limited number of cohort studies. Supporting evidence from studies of asthma prevalence in children are inconsistent.	Gehring et al. (2015b) Gehring et al. (2015a)	8.4 µg/m^3
Coherence provided by epidemiologic studies of airway inflammation	Results from a single study show an association with eNO in children.	Dales et al. (2008)	7.3 µg/m^3
Uncertainty regarding confounding by copollutants	Potential copollutant confounding is not addressed.		
Uncertainty regarding exposure measurement error	Studies rely on subtraction method to estimate exposure to $PM_{10-2.5}$ adding uncertainty to the interpretation of effect estimates.	Section 3.3.1	
Biological plausibility	Evidence from a few animal toxicological studies involving intra-tracheal exposure provides biological plausibility for limited epidemiologic findings of the development of asthma.	Section 5.4.1	
Limited evidence from a toxicological study at relevant concentrations	Results from a single inhalation study in rodents show respiratory effects.	Aztatzi-Aguilar et al. (2015)	32 µg/m^3

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

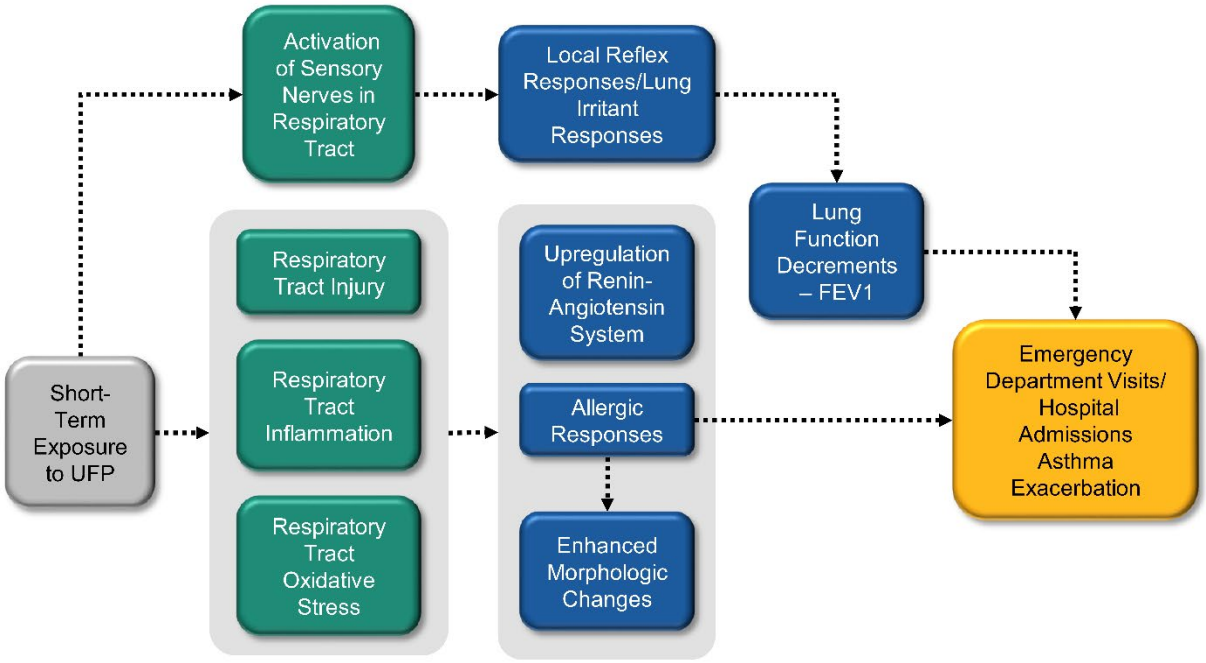
5.5 Short-Term UFP Exposure and Respiratory Effects

The 2009 PM ISA concluded that the relationship between short-term exposure to UFP and respiratory effects is "suggestive of a causal relationship" (U.S. EPA, 2009). This conclusion was based on limited, but supporting, epidemiologic evidence indicating associations with hospital admissions or ED visits for respiratory-related diseases, respiratory infection, and asthma exacerbation. Also providing support, personal ambient UFP exposure from time spent in high- and low-traffic areas was associated with lung function decrements in adults with asthma. The few available experimental studies provided limited coherence with epidemiologic findings for asthma exacerbation. Experimental studies of healthy human subjects and animals were also limited in number. Despite some evidence indicating a relationship between UFP exposure and respiratory effects, there was substantial uncertainty due to the small evidence base, a heterogeneous array of respiratory endpoints examined, indeterminate adequacy of UFP measurements, and limited biological plausibility.

For many respiratory outcomes, recent studies have not changed the overall evidence base. For asthma exacerbation, there continues to be some epidemiologic evidence, which is not entirely consistent, as well as some animal toxicological evidence (Section 5.5.2). Epidemiologic evidence continues to be consistent for respiratory-related diseases (Section 5.5.5) and inconsistent for COPD exacerbation (Section 5.5.3). Unlike findings reported in the 2009 PM ISA (U.S. EPA, 2009), recent findings are inconsistent for respiratory infection (Section 5.5.4). Recent experimental findings in healthy populations and animal models of cardiovascular disease show that short-term UFP exposure affects some respiratory responses in rodents (Section 0 and Section 5.5.7). Epidemiologic findings in healthy populations are inconsistent, including those for personal ambient exposures (Section 0). Evidence for respiratory mortality is limited (Section 5.5.8). Information on confounding by traffic-related copollutants continues to be limited, and inference about an independent effect of UFP exposure is limited because of uncertainty in the representativeness of UFP measurements, assessed mostly at fixed-site monitors.

5.5.1 Biological Plausibility

This section describes biological pathways that potentially underlie respiratory effects resulting from short-term exposure to UFP. Figure 5-49 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" short-term exposure to UFP may lead to respiratory effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 5.5.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 5-49 Potential biological pathways for respiratory effects following short-term UFP exposure.

Once UFP deposits in the respiratory tract, it may be retained, cleared, or solubilized (see CHAPTER 4). UFP and its soluble components may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate ROS and this capacity is termed "oxidative potential." Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see CHAPTER 4). Immune system responses due to the presence of particles in the interstitial space may contribute to respiratory health effects.

Although all size fractions of PM may contribute to oxidative stress, UFPs may contribute disproportionately more as a function of their mass due to their large surface/volume ratio. The relative enrichment of redox active surface components, such as metals and organics, per unit mass may translate

to a relatively greater oxidative potential of UFPs compared with larger particles with similar surface components. In addition, the greater surface per unit volume may deliver relatively more adsorbed soluble components to cells. These components may undergo intra-cellular redox cycling following cellular uptake. Furthermore, per unit mass, UFPs may have more opportunity to interact with cell surfaces due to their greater surface area and their greater particle number compared with larger PM. These interactions with cell surfaces may lead to ROS generation, as described in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). Recent studies have also demonstrated that UFPs have the capacity to cross cellular membranes by nonendocytic mechanisms involving adhesive interactions and diffusion, as described in CHAPTER 4. This may allow UFPs to interact with or penetrate intra-cellular organelles.

Evidence that short-term exposure to UFP may affect the respiratory tract generally informs two proposed pathways (Figure 5-49). The first pathway begins with injury, inflammation, and oxidative stress responses, which are difficult to disentangle. Inflammation generally occurs as a consequence of injury and oxidative stress, but it may also lead to further oxidative stress and injury due to secondary production of ROS by inflammatory cells. The second pathway begins with the activation of sensory nerves in the respiratory tract that can trigger local reflex responses and transmit signals to regions of the central nervous system that regulate autonomic outflow.

Injury, Inflammation, and Oxidative Stress

Experimental evidence that short-term exposure to UFP affects the respiratory tract is provided by numerous studies and supports a role for injury, inflammation, and oxidative stress. A few studies demonstrate markers of injury (i.e., decreased CC16 protein) and oxidative stress (4-hydroxynoneal, 3-nitrotyrosine, Ym1) (Cheng et al., 2016; Li et al., 2010; Kooter et al., 2006). Seagrave et al. (2008) exposed rats to GE containing UFP and found increased lung tissue chemiluminescence that was not present when GE was filtered, indicating that the particulate fraction played a role in the oxidative stress response. In the study by Cheng et al. (2016), a time-course analysis demonstrated oxidative stress in olfactory epithelium after a single exposure of 5 hours, as well as after multiple exposures over 3 weeks. Inflammatory responses were seen in some studies (Cheng et al., 2016; Aztatzi-Aguilar et al., 2015), but not others (Tyler et al., 2016; Amatullah et al., 2012). In Tyler et al. (2016), evidence for inflammation was found in a model of cardiovascular disease but not in healthy animals. In Cheng et al. (2016), time course analysis showed that inflammatory responses occurred concomitantly with oxidative stress responses.

Inflammation was not seen in human subjects with asthma following short-term exposure to UFP (Gong et al., 2008). However, supportive evidence for enhancement of allergic responses is provided by a study in human subjects with allergic asthma who were exposed to ultrafine carbon (Schaumann et al., 2014). Enhancement of allergic responses was also found in two studies in animals (Li et al., 2010; Kleinman et al., 2005). In Li et al. (2010), intra-nasal cosensitization with OVA and UFP was required for exacerbation of responses to inhaled UFP and OVA. These responses included increased BALF

eosinophils and neutrophils, upregulation of Th2 and Th17 cytokines, increased plasma OVA-specific IgE, and enhanced morphologic changes that extended to more distal parts of the lung. These results are consistent with some epidemiologic evidence of asthma-related hospital admissions and ED in association with UFP concentrations (Section 5.5.2.1).

Activation of Sensory Nerves

Short-term exposure to UFP did not alter pulmonary function in animal studies (Amatullah et al., 2012; Seagrave et al., 2008). However, in human subjects with asthma, decreases in FEV_1 and oxygen saturation were observed (Gong et al., 2008). Although lung irritant responses can sometimes result in decreased FEV_1, it is not clear whether inhalation of $PM_{2.5}$ led to FEV_1 changes by this pathway or whether it was mediated by inflammation. Epidemiologic panel studies conducted in people with asthma also found associations with lung function decrements (Mirabelli et al., 2015; McCreanor et al., 2007). These results are also consistent with some epidemiologic evidence of asthma-related hospital admissions and ED in association with UFP concentrations (Section 5.5.2.1).

Another study found upregulation of the RAS, as indicated by an increase in mRNA for angiotensin receptor Type 1 and angiotensin converting enzyme, in the lung (Aztatzi-Aguilar et al., 2015). Angiotensin receptor Type 1 mediates the effects of angiotensin II, which is a potent vasoconstrictor and mediator in the vasculature. The SNS and the RAS are known to interact in a positive feedback fashion (Section 8.1.2) with important ramifications in the cardiovascular system. However, it is not known whether SNS activation or some other mechanism mediated the changes in the RAS observed in the respiratory tract in this study.

Summary

As described here, there are two proposed pathways by which short-term UFP exposure may lead to respiratory health effects. One pathway involves respiratory tract inflammation and allergic responses, which are linked to asthma exacerbation. The second pathway involves the activation of sensory nerves in the respiratory tract leading to lung function decrements, which are also linked to asthma exacerbation. While experimental studies involving animals or human subjects contribute most of the evidence of upstream effects, epidemiologic studies found associations between short-term UFP exposure and lung function decrements. Together, these proposed pathways provide biological plausibility for epidemiologic evidence of respiratory health effects and will be used to inform a causality determination, which is discussed later in the chapter (Section 5.5.9).

5.5.2 Asthma Exacerbation

In the 2009 PM ISA (U.S. EPA, 2009), the evaluation of the relationship between short-term UFP exposure and asthma exacerbation consisted of a limited number of epidemiologic, controlled human exposure, and animal toxicological studies. Epidemiologic studies provided some evidence of an association between short-term UFP exposure and asthma exacerbation. Evidence for decrements in pulmonary function was found in subjects with asthma in the controlled human exposure study. Evidence for enhanced allergic responses was found in the animal toxicological study in a model of allergic airway disease that shares phenotypic features with asthma.

5.5.2.1 Epidemiologic Studies

In the 2009 PM ISA (U.S. EPA, 2009), studies of hospital admissions, ED visits (Andersen et al., 2008b; Halonen et al., 2008), and physician visits (Sinclair and Tolsma, 2004) reported evidence of associations across a range of lags, as well as for different UFP concentration metrics (i.e., number concentration [NC] and surface area [SA]). In panel studies of asthma symptoms in adults with asthma, supporting evidence of asthma exacerbation was observed across size fractions from $NC_{10–100}$ nm to $NC_{500–2,500}$ nm (Mar et al., 2004; von Klot et al., 2002). Supporting evidence was also provided by a study of lung function in adults with asthma in which $NC_{10–100}$ nm was associated with decrements in FEV_1, FVC, $FEF_{25–75\%}$, but not with increases in eNO after walking on a high-traffic road or in a park (McCreanor et al., 2007). This study of scripted exposure minimized uncertainty in the UFP exposure metric by measuring personal ambient UFP at the site of exposure. The evidence across studies was not entirely consistent, as associations between UFP exposure and ED visits for asthma were not observed in the Atlanta-based SOPHIA study (Peel et al., 2005). Additionally, the overall interpretation of results from epidemiologic studies that examined UFP exposures, including those focusing on asthma exacerbation, is complicated by the spatial variability in UFP concentrations, the correlation between UFPs and other traffic-related pollutants, and the various size fractions and concentration metrics used as UFP exposure surrogates.

A few recent epidemiologic studies add to those from the 2009 PM ISA (U.S. EPA, 2009) and continue to provide some, but not entirely consistent, support for associations between increases in short-term UFP concentrations exposure and asthma exacerbation. The supporting evidence comes from an array of outcomes related to asthma exacerbation, including hospital admissions, ED visits, and physician visits for asthma to asthma symptoms and medication use. Additional evidence from studies in adults with asthma using personal ambient UFP exposures via scripted exposures in high-traffic locations is more consistent for lung function decrements than pulmonary inflammation. The relatively small body of recent studies of asthma hospital admissions, ED visits, and physician visits examined a range of UFP size fractions, which complicates the interpretation of results across studies. Several studies examined $NC_{10–100}$ nm exposure among older children (>3 years), in whom the ascertainment of asthma is more

reliable. All the recent studies used NC to represent UFP exposure; and as detailed in the Preface, when examining the size distribution of particles 67 to 90% of NC contains particles <0.1 µm. Samoli et al. (2016a) reported no association with asthma hospital admissions in a study of five European cities. In contrast, Iskandar et al. (2012) reported an association with $NC_{10–700}$ nm in a study conducted in Copenhagen, Denmark. Across studies, a similar array of lags was examined and no particular lag was identified as having a stronger association with asthma hospital admissions, but many results support associations with UFP concentrations with a lag of 1 to 5 days or averaged over 3 to 6 days (Table 5-40). While the examination of the relationship between short-term UFP exposure and asthma hospital admissions focused on studies that examined daily changes in UFP concentrations and hospital admissions (e.g., time-series, case-crossover analyses), the assessment of the relationship with ED visits was limited to a study that focused on asthma exacerbations that led to an ED visit (Evans et al., 2014). In a group of children with asthma enrolled in the School-Based Asthma Therapy trial, Evans et al. (2014) examined whether exposure to traffic-related pollutants, including UFPs, resulted in an asthma exacerbation that lead to an ED visit over multiday averages up to 0−7 days. There was some evidence of an association for lag 0−3 days (OR = 1.3 [95% CI: 0.90, 1.8] for a 2,088 increase in UFPs per cm^{-3}); however, the association was more evident in children receiving preventative medication at school compared to at home. A recent study examined the association between UFP exposure and lung function and subclinical effects in adults with asthma. In this panel study of 18 adults in Atlanta, GA, NC_{total} was associated with increased eNO and decreased FEV_1 (Mirabelli et al., 2015). Personal NC_{total} was measured during two morning commutes through rush-hour traffic, resulting in higher exposure levels. The observed associations with FEV_1 were consistent across spirometry test conducted 0, 1, 2, and 3 hours post-commute, while increased eNO was only associated with UFP exposure in adults with below-median asthma control.

Table 5-40 Epidemiologic studies of UFP and asthma hospital admissions, emergency department (ED) visits, and physician visits.

Study, Location, Years, Age Range	Exposure Assessment	UFP Concentration (particles/cm^3)[a]	Single Pollutant Effect Estimate (95% CI)	Copollutant Examination
Hospital admissions				
Andersen et al. (2008b) Copenhagen, Denmark 2001−2004 5−18 yr	NC_{10-100} nm, NC total and NC with median diameters 12, 23, 57, 212 nm One monitor, within 15 km of hospitals, mean 6 km. *r* for NC_{total} = 0.62 with roadside monitor 3 km away, 0.80 with rural monitor	NC_{10-100} nm Mean: 6,847 99th: 16,189 NC_{total} Mean: 8,116 99th: 19,895	RR per 3,259 Lag 0−4 NC_{10-100} nm 1.06 (0.97, 1.16) RR per 3,907 NC_{total} 1.07 (0.98, 1.17)	Correlation (*r*): 0.61 NO_2, 0.48 CO, 0.40 $PM_{2.5}$ Copollutant models with: NO_2, CO
†Iskandar et al. (2012) Copenhagen, Denmark 2001−2008 0−18 yr	NC_{10-700} nm One monitor, within 15 km of hospitals, mean 6 km	Mean: 6,398 75th: 7,951	OR per 7,004 Lag 0−4 1.06 (0.98, 1.14)	Correlation (*r*): 0.51 NO_2, 0.45 NO_X, 0.26 $PM_{2.5}$ Copollutant models with: NO_2, NO_X, $PM_{2.5}$
†Samoli et al. (2016a) Five European cities 2001−2011 All ages	Barcelona: $NC_{5-1,000}$ nm Copenhagen: NC_{6-700} nm Helsinki: NC_{10-100} nm Rome and Stockholm: $NC_{7-3,000}$ nm One or two sites per city. All urban background sites except for traffic site in Rome	Means Barcelona: 19,554 Copenhagen: 5,105 Helsinki: 7,951 Rome: 34,043 Stockholm: 9,128	Percent increase per 10,000 Lag 1 2.1 (−0.28, 4.6)	Correlation (*r*): 0.38−0.69 NO_2, 0.07−0.67 CO, 0.09−0.57 $PM_{2.5}$ Copollutant models with: NR

Table 5-40 (Continued): Epidemiologic studies of ultrafine particle (UFP) and asthma hospital admissions, emergency department (ED) visits, and physician visits.

Study, Location, Years, Age Range	Exposure Assessment	UFP Concentration (particles/cm^3)[a]	Single Pollutant Effect Estimate (95% CI)	Copollutant Examination
ED visits				
Peel et al. (2005) Atlanta, GA 1998−2000 All ages	NC_{10-100} nm 1 monitor, near city center	Mean: 38,000 90th: 74,600	RR per 30,000 Lag 0−2 1.00 (0.98, 1.02)	Correlation (*r*): NR Copollutant models with: NR
†Evans et al. (2014) Rochester, NY 2006−2009 3−10 yr	NC_{10-100} nm 1 monitor 1.6−11 km from school, within 15 km of home, 1.5 km of highway.	Mean: 5,151 75th: 6,449 95th: 9,575	OR per 2,008 Lag 0−3 1.27 (0.90, 1.79)	Correlation (*r*): Warm season = 0.57 O_3 Copollutant models with: CO, O_3
Physician visits				
Sinclair and Tolsma (2004) Atlanta, GA 1998−2000 All ages	SC_{10-100} nm 1 monitor, near city center	Mean: 249 μm^2/cm^2	RR per 244 Lag 3−5 1.22 (95 CI NR)	Correlation (*r*): NR Copollutant models with: NR

CO = carbon monoxide, CI = confidence interval, NC = number concentration, NO_2 = nitrogen dioxide, NO_X = sum of NO_2 and nitric oxide, NR = not reported, O_3 = ozone, OR = odds ratio, RR = relative risk, SC = surface area concentration, SD = standard deviation, SO_2 = sulfur dioxide, UFP = ultrafine particles.

[a]All data are for 24-hour average.

†Studies published since the 2009 PM ISA.

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The epidemiologic studies of short-term exposure to UFP and asthma hospital admissions each have 1 to 2 monitors per study, covering a 15-km radius in some cases (Table 5-40). Spatial variability in UFP concentration may not be captured over this area, introducing some uncertainty in the exposure surrogate (Section 2.5; Section 3.4.2.2). It is possible that associations are related to similarities in temporal variability of UFP sources throughout study areas, as Sarnat et al. (2010) observed for spatially-variable NO_2, but this remains an uncertainty since spatiotemporal variability across cities has not been well characterized. In addition to major uncertainties regarding the spatial variability in UFP and the various size fractions and concentration metrics used as UFP exposure surrogates, confounding by traffic-related pollutants also remains a concern, as studies have not thoroughly examined potential copollutant confounding. Studies evaluated in the 2009 PM ISA (U.S. EPA, 2009), which focused on both asthma hospital admissions (Andersen et al., 2008b) and lung function changes (McCreanor et al., 2007) in people with asthma, provided initial evidence that UFP associations persisted after adjustment for NO_2 or CO even when UFP was moderately correlated with copollutants [e.g., $r = 0.58$ for personal ambient UFP and NO_2 exposures (McCreanor et al., 2007)]. Recent results show robust UFP associations to adjustment for CO and O_3, but null associations with adjustment for NO_2 or NO_X (Table 5-40).

5.5.2.2 Controlled Human Exposure

Only one study evaluated in the 2009 PM ISA (U.S. EPA, 2009) investigated the effects of short-term UFP exposure and respiratory effects in individuals with asthma. In this study, Gong et al. (2008) reported decreases in pulmonary function (oxygen saturation and FEV_1) following a 2-hour exposure to 100 $\mu g/m^3$ UFP CAPs (less than 0.18 µm aerodynamic diameter). No changes in pulmonary inflammation were found.

5.5.2.3 Animal Toxicological Studies

As described in the 2009 ISA for PM (U.S. EPA, 2009), Kleinman et al. (2005) found that a multiday exposure to roadway ultrafine PM (UFP) CAPs in Los Angeles enhanced allergic responses in OVA-sensitized and challenged BALB/c mice, and that this effect was dependent on proximity to the PM source. Recently, Li et al. (2010) extended these observations in OVA-sensitized and challenged BALB/c mice. A hybrid exposure to Los Angeles UFP CAPs was conducted by intra-nasal cosensitization with OVA and UFP (Days 1, 2, and 4), followed 2 weeks later with inhalation exposures to concentrated UFP (Days 18, 19, 22, 23 and 24) that overlapped with intra-nasal OVA challenge (Days 23 and 24). Only mice that were cosensitized with UFP responded to secondary OVA challenges with increases in lavaged eosinophils, plasma OVA-specific IgE, and pulmonary expression of eotaxin, IL-5, IL-13, and Muc5ac ($p < 0.05$). Inhalation exposure to UFP during the challenge phase enhanced these allergic responses compared to filtered air exposed mice ($p < 0.05$). Similarly, UFP exposure during OVA challenge

enhanced neutrophil influx and pulmonary expression of IL-17 and Ym1, a marker of oxidative stress, in mice which were cosensitized with UFP and OVA ($p < 0.05$). These results demonstrate that short-term UFP exposure exacerbated the effects of allergen and suggest the involvement of Th2 and Th17 helper cells in the response. Pulmonary histopathology revealed that UFP inhalation during the OVA challenge extended allergic inflammation to more distal regions of the lung (i.e., the proximal alveolar duct and adjacent alveolar parenchyma). Their small size may have allowed UFPs to evade phagocytosis and deposit in the deep lung due to diffusion, as well as to stick to the airways walls due to Van der Waal's forces. The oxidative potential of urban UFP (Li et al., 2009) may have also contributed to inflammatory responses. It should be noted that in the recent study by Li et al. (2010) PM and allergens were coinstilled during sensitization prior to the inhalation challenge. This study design more clearly demonstrates the exacerbation of allergic responses than adjuvant activity. Short-term exposure to UFP may also promote allergic sensitization and additional experiments employing different study designs are needed to show this effect. Additional study details are found in Table 5-41.

Table 5-41 Study-specific details from an animal toxicological study of short-term exposure to UFP and subclinical effects underlying asthma exacerbation in a model of allergic airway disease.

Study/Study Population	Pollutant	Exposure	Endpoints
Li et al. (2010) Species: Mouse Sex: Female Strain: BALB/c Age/Weight: 8−10 weeks	Ultrafine—ambient Los Angeles OVA Particle size: <0.18 µm Particle mass: 101.3 ± 5.1 µg/m^3	Route: Intra-nasal sensitization with PM and OVA (2 days) Inhalation of PM on days of OVA challenge Dose/Concentration: 4 h/day for 5 days	PM characterization Serum IgE, IgG1 BALF cells BALF cytokines Histopathology—lung

IgE = immunoglobulin E; IgG1 = immunoglobulin G1; BALF = bronchoalveolar lavage fluid; OVA = ovalbumin.

5.5.3 Chronic Obstructive Pulmonary Disease (COPD) Exacerbation

The 2009 PM ISA (U.S. EPA, 2009) evaluated a small body of literature examining the association between UFP and hospital admissions and ED visits for COPD. The studies evaluated in the 2009 PM ISA, limited to single-cities, provided inconsistent evidence of associations with UFPs. There are a few recent studies of UFP exposure and COPD exacerbation, but the evidence base remains small and does not clearly support a relationship. This applies to COPD hospital admissions and ED visits (Table 5-42), which can result from uncontrollable respiratory symptoms that are hallmarks of COPD

exacerbation such as cough, sputum production, and shortness of breath. The uncertain adequacy of the UFP concentration metrics used for exposure surrogates is a major limitation in the evidence base overall.

Recently, some studies examined associations with COPD, but they are limited to studies of hospital admissions and again are conducted in individual cities. Recent studies examine COPD hospital admissions in Europe and observe an association in Rome, Italy (Belleudi et al., 2010) but not a multicity study that includes Rome (Samoli et al., 2016a) (Table 5-42). UFP concentrations were averaged over 24 hours, and all studies examined an array of lags (up to 10 days). In Rome, Italy, (Belleudi et al., 2010) found evidence of a positive association between UFP and COPD hospital admissions at 0−1-day distributed lag among adults aged 35 years and older (0.95 [95% CI: −0.8, 2.73]). Adjustment for PM_{10} or for $PM_{2.5}$ did not alter the association of COPD (lag 0) with particle NC (1.9% [95% CI: 0.1, 3.8] and 1.3% [95% CI: 0.8, 3.5%], per 10,000 particles/cm^3, respectively). There was some evidence that associations were stronger in terms of magnitude and precision in the spring and fall season (3.72% [95% CI: 0.81, 6.70]). Additionally, in a study conducted in Helsinki, Finland, Halonen et al. (2009b) reported an association between COPD hospital admissions in the nucleation mode (<0.03 μm), with an 0.8% (95% CI: −2.28, 3.97) increase in hospital admissions for a 3,583-count increase in the nucleation mode, and a 0.82% (95% CI: −1.51, 3.20) increase in hospital admissions for a 2,467-count increase in the Aitken mode (0.03−0.1 μm) (lag 3). Among adults with COPD in Erfurt, Germany, $NC_{10–100}$ nm was not associated with blood levels of the proinflammatory cells neutrophils and eosinophils or most markers of blood coagulation that are linked to cardiovascular effects rather than COPD (Bruske et al., 2010; Hildebrandt et al., 2009).

Epidemiologic studies examining respiratory infection are limited by their UFP exposure assessment, because they relied on data from one or two monitors and thus could not capture the spatial variability in UFP concentrations across study locations (Section 2.5.1, Section 3.4.2.2). Additionally, the limited assessment of potential copollutant confounding complicates the interpretation of results and understanding whether UFPs are independently associated with COPD exacerbations or may be serving as an indicator of highly correlated copollutants.

Table 5-42 Epidemiologic studies of UFP and exacerbation of chronic obstructive pulmonary disease.

Study	Exposure Assessment	Outcome Assessment	UFP Concentration particles/cm^{3a}	Single Pollutant Effect Estimate 95% CI	UFP Copollutant Model Results and Correlations
Peel et al. (2005) Atlanta, GA 1998−2000	NC_{10-100} nm One monitor, near city center	ED visits All ages Visits concentrated in city center	Mean: 38,000 SD: 40,700 90th: 74,600	RR per 30,000 Lag 0−2 0.98 (0.94, 1.02)	No copollutant model Copollutant correlations NR
†Belleudi et al. (2010) Rome, Italy 2001−2005	NC_{total} Condensation Particle Counter One monitor, 2 km from city center	Hospital admissions Adults ≥35 yr	Mean: 37,456 SD: 21,394 75th: 47,995	RR per 9,392 Lag 0 1.02 (1.00, 1.03)	No copollutant model No copollutants examined r = 0.55 $PM_{2.5}$.
†Samoli et al. (2016a) Barcelona, Spain; Copenhagen, Denmark; Helsinki, Finland; Rome, Italy; Stockholm, Sweden 2001−2011 across cities	Barcelona: $NC_{5-1,000}$ nm Copenhagen: NC_{6-700} nm Helsinki: NC_{10-100} nm Rome and Stockholm: $NC_{7-3,000}$ nm One or two sites per city. All urban background sites except for traffic site in Rome	Hospital admissions All ages	Means Barcelona: 19,554 Copenhagen: 5,105 Helsinki: 7,951 Rome: 34,043 Stockholm: 9,128	RR per 10,000 Lag 0 0.99 (0.96, 1.02)	No copollutant model r = 0.38−0.69 NO_2, 0.07−0.67 CO, 0.09−0.57 $PM_{2.5}$.

CO = carbon monoxide, CI = confidence interval, ED = emergency department, NC = number concentration, NO_2 = nitrogen dioxide, NR = not reported, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, r = correlation coefficient, RR = relative risk, SD = standard deviation, ultrafine particles.

aAll data are for 24-hour average.

†Studies published since the 2009 PM ISA.

5.5.4 Respiratory Infection

Regarding the association between UFP and hospital admissions/ED visits for respiratory infections, the body of literature reviewed in the 2009 PM ISA (U.S. EPA, 2009) was very small and provided no evidence of associations with respiratory infections and was limited to single-city studies. Consistent with the 2009 PM ISA, recent studies are limited in number and focus on examining associations between short-term UFP exposure and respiratory infections in individual cities. In Rome, Italy, Belleudi et al. (2010) found no evidence of an association between UFP (UFPs were measures using particle NC from a single monitor) and lower respiratory tract infection hospital admissions at any lag among adults aged 35 years and older. The effect was positive, but imprecise at lag 2 and lag 3 (0.19% [95% CI: −1.48, 1.90] and 0.29% [95% CI: −1.37, 1.98], per 10,000 particles/cm^3, respectively). In a study of UFPs and respiratory hospital admissions in five European cities in 2001−2011, Samoli et al. (2016a) found no overall association using city-specific estimates to obtain pooled estimates but did identify a positive association with hospital admissions during warm months of April−September of 4.27% (95% CI 1.68−6.92) for an increase in 10,000 particles/cm^3 (lag 2). This effect estimate was robust to inclusion of CO and NO_2 in the statistical model. Halonen et al. (2009b), in a study conducted in Helsinki, Finland, reported no associations for pneumonia hospital admissions in the nucleation mode (<0.03 μm), but observed a 1.5% (95% CI: −0.72, 3.77) increase in hospital admissions for a 2,467-count increase in the Aitken mode (0.03−0.1 μm) (lag 3). Some similarity of the effect estimates was expected by the authors due to the high correlation between these particle fractions.

The body of literature that studied the association between UFPs and hospital admissions/ED visits for respiratory infection hospital admissions expanded since the 2009 PM ISA (U.S. EPA, 2009) but remains somewhat limited. The available evidence suggests small associations between UFPs and respiratory infections, though the distinct size fractions under analysis in each study make cross-study comparisons difficult. The limited evidence from previous and recent studies does not clearly link short-term UFP exposure to increases in respiratory infection, based largely on hospital admissions, ED visits, and physician visits for URI, pneumonia, or LRI, which combines pneumonia and bronchitis (Table 5-43). There is little information to assess the biological plausibility for the supporting findings. Host defense mechanisms that protect the respiratory tract from pathogens such as mucociliary clearance, alveolar macrophage clearance, or innate and adaptive immunity were not assessed in relation to short-term UFP exposure. For the supporting evidence, information also is lacking on sources of heterogeneity, C-R, and the influence of other traffic-related pollutants.

Table 5-43 Epidemiologic studies of UFP and respiratory infection.

Study	Exposure Assessment	Outcome Assessment	UFP Concentration Particles/cm^{3}[a]	Single Pollutant Effect Estimate 95% CI	UFP Copollutant Model Results and Correlations
Peel et al. (2005) Atlanta, GA 1998−2000	NC_{10-100} nm One monitor, near city center	ED visits URI and pneumonia All ages Visits concentrated in city center	Mean: 38,000 SD: 40,700 90th: 74,600	RR per 30,000 Lag 0−2 URI 0.99 (0.97, 1.01) Pneumonia 0.98 (0.95, 1.00)	No copollutant model Copollutant correlations NR
Sinclair et al. (2010) Atlanta, GA 1998−2000	SC_{10-100} nm One monitor, near city center	Physician visits URI and LRI All ages HMOs in city outskirt	Mean: 249 $\mu m^2/cm^2$ SD: 244	RR per 244 URI, Lag 3−5 1.04 (95% CI NR) LRI, Lag 0−2 1.10 (95% CI NR)	No copollutant model Copollutant correlations NR
Halonen et al. (2009b) Helsinki, Finland 1998−2004	NC_{30-100} nm One monitor	Hospital admissions Pneumonia Older adults	Median: 3,628 IQR: 1,309 75th: 4,937	RR per 1,309 Lag 0−4 1.04 (1.00, 1.08)	No copollutant model r = 0.48 $PM_{2.5}$, 0.65 NO_2, 0.41 CO, 0.72 traffic $PM_{2.5}$
†Belleudi et al. (2010) Rome, Italy 2001−2005	NC_{total} One monitor, 2 km from city center	Hospital admissions LRI Adults ≥35 yr	Mean: 37,456 SD: 21,394 75th: 47,995	RR per 9,392 Age 35−74 yr, lag 0 1.03 (1.00, 1.07)	No copollutant model r = 0.55 $PM_{2.5}$.

Table 5-43 (Continued): Epidemiologic studies of ultrafine particle (UFP) and respiratory infection.

Study	Exposure Assessment	Outcome Assessment	UFP Concentration Particles/cm^{3}[a]	Single Pollutant Effect Estimate 95% CI	UFP Copollutant Model Results and Correlations
†Samoli et al. (2016a) Barcelona, Spain; Copenhagen, Denmark; Helsinki, Finland; Rome, Italy; Stockholm, Sweden 2001−2011 across cities	Barcelona: $NC_{5-1,000}$ nm Copenhagen: NC_{6-700} nm Helsinki: NC_{10-100} nm Rome/Stockholm: $NC_{7-3,000}$ nm One or two monitors per city	Hospital admissions LRI All ages	Means Barcelona: 19,554 Copenhagen: 5,105 Helsinki: 7,951 Rome: 34,043 Stockholm: 9,128	RR per 10,000 Lag 1 0.99 (0.98, 1.01)	No copollutant model r = 0.38−0.69 NO_2, 0.07−0.67 CO, 0.09−0.57 $PM_{2.5}$.

CO = carbon monoxide, CI = confidence interval, ED = emergency department, HMO = health maintenance organization, LRI = lower respiratory infection, NC = number concentration, NO_2 = nitrogen dioxide, NR = not reported, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 μm, r = correlation coefficient, RR = relative risk, SD = standard deviation, UFP = ultrafine particles, URI = upper respiratory infection.

[a]All data are for 24-hour average.

†Studies published since the 2009 PM ISA.

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5.5.5 Combinations of Respiratory-Related Hospital Admissions and Emergency Department (ED) Visits

The evidence more consistently links increases in UFP concentration to increases in respiratory-related diseases broadly than to asthma, COPD, or respiratory infections. Recent findings not only add consistency for hospital admissions or ED visits, but they also indicate lung function changes among adults with asthma or COPD. As is observed with asthma exacerbation (Section 5.5.2), distinguishing an association for UFP and respiratory-related diseases independent of NO_2 remains uncertain. As noted previously, studies of respiratory-related diseases examine either all respiratory-related diseases or only a subset, which can complicate the interpretation of results across studies.

There is considerable variation across studies in the size fractions examined and, in the fraction, most strongly associated with hospital admissions and ED visits for respiratory-related diseases (Table 5-44). Associations were consistently observed for NC up to 100 nm (Lanzinger et al., 2016b; Samoli et al., 2016b; Leitte et al., 2011; Andersen et al., 2008b; Halonen et al., 2008). In Beijing, China, associations were observed with UFP NC and SC (Leitte et al., 2011). Results also are consistent with NC with an upper bound that included larger particles (Table 5-44); however, as detailed in CHAPTER 1, it has been demonstrated that 67−90% of NC represents particles <0.1 μm although the upper bound of the UFP size distribution measured by NC may include larger size particles. In contrast, hospital admissions and ED visits for respiratory-related diseases are inconsistently associated with size fractions with upper bounds less than 50 nm (Leitte et al., 2011; Halonen et al., 2008).

A few recent epidemiologic studies focusing on individuals with a combination of respiratory-related diseases that also examined associations with UFP concentrations provide evidence that supports an association with respiratory-related hospital admissions and ED visits. For adults with asthma and COPD in four European cities (Helsinki, Finland; Athens, Greece; Amsterdam, the Netherlands; Birmingham, U.K.), NC_{total} measured outside the home but not at a monitor in the city was associated with lung function decrements (de Hartog et al., 2010). Additionally, within the UFIREG study, within Augsberg, Germany, NC_{total} was found to be highly correlated across four traffic and nontraffic sites (r = 0.77−0.95) (Lanzinger et al., 2016b; Cyrys et al., 2008).

Table 5-44 Epidemiologic studies of UFP and respiratory-related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment	Mean UFP Concentration Particles/cm^{3}[a]	Single Pollutant Effect Estimate 95% CI	Copollutant Examination
Hospital admissions				
†Samoli et al. (2016a) Five European cities 2001−2011 All ages	Barcelona: $NC_{5-1,000}$ nm Copenhagen: NC_{6-700} nm Helsinki: NC_{10-100} nm Rome/Stockholm: $NC_{7-3,000}$ nm One or two monitors per city	Barcelona: 19,554 Copenhagen: 5,105 Helsinki: 7,951 Rome: 34,043 Stockholm: 9,128	(ICD9: 466, 480−487; 490−492, 494, 496; 493) Percent increase per 10,000, lag 5 0.43 (−0.58, 1.45)	Correlation (*r*): 0.38−0.69 NO_2, 0.07−0.67 CO, 0.09−0.57 $PM_{2.5}$ Copollutant models with: NO_2, CO
†Samoli et al. (2016b) London, U.K. 2011−2012 ≥65 yr	Regional nucleation (nuc) factor 20 nm peak, road traffic factor 30 nm mode, urban background (BG) factor 70 nm peak, long-range transport factor 250 nm mode One monitor	Median Regional nuc: 280 Road traffic: 2,355 Urban BG: 1,893 Long-range transport: 105	(ICD10: J00−J99) RR per IQR, lag 2 Regional nuc: 0.99 (0.98, 1.00) Road traffic: 0.99 (0.97, 1.00) Warm season Urban BG: 1.02 (1.00, 1.04) Long-range: 1.01 (1.00, 1.03)	Correlation (*r*): NR Copollutant models with: NR
†Lanzinger et al. (2016b) Five European cities (UFIREG) 2011−2014 across cities All ages	NC_{20-100} nm, NC_{20-800} nm One monitor Prague, number of monitors NR in other cities	NC_{20-100} nm, NC_{20-800} nm Augsburg: 5,880, 7,239 Chernivtsi: 5,511, 7,775 Dresden: 4,286, 5,851 Ljubljana: 4,693, 6,750 Prague: 4,197, 5,799	(ICD10: J00−J99) Percent increase per 2,750, Lag 2−5 NC_{20-100} nm: 2.2 (−0.9, 5.3) Percent increase per 3,675, Lag 2−5 NC_{20-800} nm: 3.1 (−0.1, 6.5)	Correlation (*r*): 0.51 and 0.33 NO_2, 0.37 and 0.30 $PM_{2.5}$ (Augsburg and Dresden) Copollutant models with: NO_2

Table 5-44 (Continued): Epidemiologic studies of ultrafine particle (UFP) and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment	Mean UFP Concentration Particles/cm^{3a}	Single Pollutant Effect Estimate 95% CI	Copollutant Examination
ED visits				
†Leitte et al. (2011) Beijing, China 2004−2006 All ages	NC_{10-30} nm, NC_{30-50} nm, NC_{50-100} nm, NC_{total} SC_{50-100} nm One monitor	NC_{10-30} nm: 6,900 NC_{30-50} nm: 4,900 NC_{50-100} nm: 6,700 UFP (<100 nm): 22,000 NC_{total}: 29,000 SC_{50-100} nm: 110	(J00−J99) RR, lag 0 NC_{10-30} nm, per 4,300 0.98 (0.93, 1.04) NC_{30-50} nm, per 2,300 1.03 (0.99, 1.08) NC_{50-100} nm, per 3,600 1.03 (0.99, 1.07) UFP, per 11,000 1.01 (0.95, 1.07) NC_{total}, per 12,600 1.03 (0.98, 1.09) SC_{50-100} nm, per 60 1.03 (0.99, 1.07)	Correlation (*r*): With NO_2: −0.16 NC_{3-10} nm, −0.09 NC_{10-30} nm, 0.22 NC_{30-50} nm, 0.43 NC_{50-100} nm, 0.27 NC_{total}, 0.45 SC_{50-100} nm Copollutant models with: NO_2

CO = carbon monoxide, COPD = chronic obstructive pulmonary disease, CI = confidence interval, LRI = lower respiratory infection, NC = number concentration, NO_2 = nitrogen dioxide, NR = not reported, RR = relative risk, SC = surface concentration, SD = standard deviation, SO_2 = sulfur dioxide, UFIREG = Ultrafine particles—an evidence-based contribution to the development of regional and European environmental and health policy; UFP = ultrafine particles.

[a]All data are for 24-hour average.

†Studies published since the 2009 PM ISA.

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Recent results from copollutant models provide additional indication that adjustment for NO_2 or CO has varying effect on UFP associations with respiratory-related diseases. Associations for NC with upper bounds of 100 nm are sometimes attenuated with adjustment for NO_2 (Lanzinger et al., 2016b; Leitte et al., 2011). Other results are for larger sized NC with upper bounds ranging from 290−3,000 nm, with many showing that associations persist with adjustment for NO_2 or CO (Samoli et al., 2016a; Halonen et al., 2009b) and some showing attenuation (Andersen et al., 2008b) (Table 5-44). A wide range of correlations was reported for UFP concentrations with NO_2 and CO (r = 0.33−0.69 NO_2, 0.07−0.69 CO), and the magnitude of correlation does not relate to the copollutant model results.

5.5.6 Respiratory Effects in Healthy Populations

Evidence for a relationship between short-term exposure to UFP and respiratory effects in healthy populations was very limited in the 2009 PM ISA (U.S. EPA, 2009). Epidemiologic studies found an association with wheeze in infants. Controlled human exposure studies found inconsistent evidence for decrements in lung function or pulmonary inflammation following short-term UFP exposure. Animal toxicological studies focused on exposure to mixtures such as woodsmoke and motor vehicle emissions and did not distinguish between the effects of particles and gases in the mixture.

5.5.6.1 Lung Function

5.5.6.1.1 Epidemiologic Studies

While the 2009 PM ISA (U.S. EPA, 2009) did not have a delineated discussion of epidemiologic studies that examined respiratory effects in healthy populations, an association between UFPs and wheeze was reported in a study of infants (Andersen et al., 2008a), in whom wheeze is common and transient. Several recent studies have employed scripted exposures to further inform the relationship between UFPs and respiratory effects in healthy populations. Scripted studies measuring personal ambient UFP exposures are designed to minimize uncertainty in the UFP exposure metric by always measuring UFPs at the site of exposure, ensuring exposure to sources of UFPs, such as traffic, and measuring outcomes at well-defined lags after exposure. A limitation of recent scripted exposure studies is that outcome assessment is only performed up to 6 hours after exposure, such that scripted studies do not inform understanding of the persistence of effects. There are recent epidemiologic studies in populations that include a mix of healthy participants and participants with pre-existing respiratory and/or cardiovascular disease, some of which indicate UFP-associated increases in respiratory effects. However, these studies are not evaluated in this section, as it is not known whether the results apply to the healthy portion of the population or are instead driven solely by an association in individuals with pre-existing respiratory conditions.

Respiratory effects were evaluated in recent panel studies of scripted exposures in high or low traffic areas, commute routes, or participants assigned to spend time at varying distance to a steel plant., Exposures ranged from 1 to 8 hours and the nature of exposure varied among the traffic studies, including cycling on roadways (Weichenthal et al., 2011; Zuurbier et al., 2011b), riding in a car or bus on roadways (Zuurbier et al., 2011b), and exercising near high and low traffic areas on stationary bicycles (Matt et al., 2016; Kubesch et al., 2015; Steenhof et al., 2013; Strak et al., 2012). In addition to traffic studies, Dales et al. (2013) randomly assigned participants to spend alternating weeks in a neighborhood within 1 km of a steel plant, and at a neighboring college campus, 4.5 km from the plant. In addition to varying study designs, UFP concentration metrics also varied across studies. Most studies examined NC, with a few specifying sampling in the 10−1,000 nm range (Matt et al., 2016; Kubesch et al., 2015; Dales et al., 2013).

In recent studies, increases in personal ambient UFP exposure were inconsistently associated with decreases in lung function and increases in markers of pulmonary inflammation in healthy adults in recent studies. Some studies provided evidence of transient respiratory effects associated with UFP exposure. Strak et al. (2012) reported decreases in FVC and FEV_1, and increases in eNO immediately after exposure, but not 6 or 18 hours later. Similarly, Matt et al. (2016) observed UFP-related FEV_1 decrements immediately after exposure that were positive 7-hour post exposure. Other studies observed associations with several lung function metrics, including FEV_1, FEV_1/FVC, $FEF_{25–75\%}$, total lung capacity (TLC), and residual volume (RV) (Dales et al., 2013) immediately after exposure, and PEF 2 and 6 hours after exposure (Zuurbier et al., 2011b). Notably, many studies that reported some evidence of associations had inconsistent results across an array of lung function metrics (Matt et al., 2016; Strak et al., 2012; Zuurbier et al., 2011b). Similarly, some studies reported UFP associations with lung function and eNO, but not other subclinical pulmonary effects, including nasal lavage levels of the proinflammatory cytokine IL-6 (Steenhof et al., 2013; Strak et al., 2012) or plasma CC16 levels (Zuurbier et al., 2011a), an indicator of decreased lung epithelial barrier function. Additional studies did not observe any associations between UFP concentrations and lung function or pulmonary inflammation in healthy populations up to 7 hours after exposure (Kubesch et al., 2015; Weichenthal et al., 2011; Strak et al., 2010). While respiratory symptoms are frequently studied in populations with pre-existing respiratory conditions, such as asthma or COPD, the outcome is less often examined in healthy populations. As such, no recent studies of UFP exposure evaluate respiratory symptoms or medication use in healthy populations.

In addition to major uncertainties regarding the spatial variability in UFP and the various size fractions and concentration metrics used as UFP exposure surrogates, the ability to attribute inconsistently observed associations to UFP exposure in the presence of moderately-to-highly correlated traffic-related copollutants (r = 0.50−0.70) remains limited. Only Strak et al. (2012) examined models with these copollutants. The authors reported that UFP associations observed immediately after exposure persisted in copollutant models including EC, Fe, Cu, NO_2, or NO_X, but results may be unreliable for models with moderately-to-highly correlated pollutants.

5.5.6.1.2 Controlled Human Exposure Studies

The 2009 PM ISA (U.S. EPA, 2009) reported evidence of small decrements in lung function following short-term UFP CAPs exposure in healthy humans in one study (Gong et al., 2008) but not another (Samet et al., 2009). In contrast, an increase in BALF IL-8 was found in Samet et al. (2009), but no evidence of pulmonary inflammation was found in Gong et al. (2008).

5.5.6.1.3 Animal Toxicological Studies

The 2009 PM ISA (U.S. EPA, 2009) did not report any animal toxicological studies investigating the effects of short-term exposure to UFP on pulmonary function. Animal toxicological studies investigating the effects of short-term exposure to UFP-containing mixtures on subclinical effects did not distinguish between effects due to particles or gases in the mixture.

Two recent studies examined this endpoint. In one study, Sprague Dawley rats were exposed for 6 hours to filtered and unfiltered GE (count median diameter of 15−20 nm, mass median diameter of approximately 150 nm) (Seagrave et al., 2008). Neither filtered nor unfiltered GE exposure caused any change in breathing frequency, tidal volume, minute volume, or Penh. In the other study, Amatullah et al. (2012) found that a 4-hour exposure of BALB/c mice to Toronto near-UFP CAPs had no effect on pulmonary function. Additional study details for these and other recent animal toxicological studies are found in Table 5-45.

Table 5-45 Study-specific details from animal toxicological studies of short-term exposure to UFP and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
Aztatzi-Aguilar et al. (2015) Species: Rat Sex: Male Strain: Sprague Dawley	UFP CAPs Mexico City Particle size: (UF) Ultrafine $PM_{0.2}$ Control: Filtered air	Route: Inhalation Dose/Concentration: Ultrafine $PM_{0.2}$ 107 µg/m^3 Duration: Acute 5 h/day, 3 days Time to analysis: 24 h	Gene and protein expression in lung tissue • IL-6 • Components of kallikrein-kinin endocrine system and RAS • Heme oxygenase-1
Cheng et al. (2016) Species: Mouse Strain: C57Bl/6J Sex: Male Age: 3 mo	Re-aerosolized collected ambient PM near a Los Angeles freeway Particle sizes: Ultrafine PM < 180 nm, median 60.6 nm Control: Reaerosolized extracts of sham filters	Route: Whole-body inhalation Dose/concentration: 343 µg/m^3 Duration of exposure: 5 h/day, 3 days/week for 5, 20 and 45 h over 3 weeks	Immunohistochemistry of nasal epithelium and brain tissue • Oxidative stress markers • Macrophage activation marker
Seagrave et al. (2008) Species: Rat Strain: Sprague-Darley Sex: Male Age/Weight: 8−10 weeks, 250−300 g	Gasoline engine exhaust (GE) Filtered GE Particle Size: GE MMD 150 nm	Route: Whole-body inhalation Dose/Concentration: GE filtered 2.4 µg/m^3 GE 59 µg/m^3 Duration of exposure: 6 h Coexposure: Combustion vapors	Pulmonary function • Breathing frequency • Tidal volume • Minute volume • Penh
Tyler et al. (2016) Species: Mouse Strain: C57BL/6 and ApoE knockout Age/Weight: 6−8 weeks	Motor vehicle exhaust (DE and GE) passed through a denuder to generate UFP Particle size: 147.1 nm ± 1.3 nm Control: Filtered air	Route: Whole-body inhalation Dose/Concentration: 371.3 ± 15.6 µg/m^3 Duration: 6 h	BALF cells and cytokines Particle uptake in bronchial macrophages

ApoE = apolipoprotein E; DE = diesel exhaust; GE = gasoline exhaust; MMD = mass median diameter; Penh = enhanced pause.

Pulmonary Oxidative Stress

The 2009 PM ISA (U.S. EPA, 2009) did not report any animal toxicological studies investigating the effects of short-term UFP exposure on pulmonary oxidative stress. Two recent studies examined this endpoint. Seagrave et al. (2008) exposed rats to GE (count median diameter 15−20 nm, mass median diameter 150 nm) and found increased lung tissue chemiluminescence that was not present when GE was filtered, indicating that the particulate fraction had a role in the oxidative stress response. Recently,

oxidative stress in olfactory epithelium, as well as olfactory bulb and other brain regions, was examined in mice exposed to resuspended urban UFP (Cheng et al., 2016) (see Section 8.5.2). A single 5-hour exposure to UFP resulted in enhanced markers of oxidative stress in olfactory epithelium, but not olfactory bulb, cerebellum, or cerebral cortex. Multiple exposures over 3 weeks also increased oxidative stress markers in olfactory epithelium, as well as decreased levels of a protein expressed by olfactory sensory nerves, and increased levels of apoptosis-related proteins.

Pulmonary Inflammation

The 2009 PM ISA (U.S. EPA, 2009) did not report any animal toxicological studies investigating the effects of short-term UFP exposure on pulmonary inflammation. Several recent studies examined this endpoint. No effects were observed in terms of BALF inflammatory cells in response to a 4-hour exposure of BALB/c mice to Toronto UFP CAPs (Amatullah et al., 2012) or in response to a 6-hour exposure of C57BL/6 mice to UFP generated from motor vehicle exhaust (Tyler et al., 2016), despite effects observed in the hippocampus of the latter study (see Section 8.5.2). However, inflammation was observed in two other studies measuring effects in lung tissue. Cheng et al. (2016) found inflammatory responses in olfactory epithelium, as well as olfactory bulb and other brain regions, in C57BL/6J mice exposed to resuspended urban UFP (Section 8.5.2). The number of Iba1 positive-macrophages, an indicator of inflammation, increased in olfactory epithelial turbinates and in the olfactory bulb after 5-hours of exposure to UFP ($p < 0.05$). In addition, Aztatzi-Aguilar et al. (2015) found increased levels of IL-6 in lung tissue in Sprague Dawley rats exposed to UFP CAPs in Mexico City for several days ($p < 0.05$). Aztatzi-Aguilar et al. (2015) also found that short-term UFP CAPs exposure had several effects on the two counterbalancing endocrine systems—the RAS and the kallikrein-kinin system in the lung ($p < 0.05$). These effects included upregulation of genes encoding angiotensin 1 receptor and angiotensin converting enzyme and reduced levels of reduced angiotensin 1 receptor protein. Levels of angiotensin converting enzyme protein and angiotensin 2 receptor mRNA were not impacted. The RAS plays an important role in pulmonary and systemic vasculature, with binding of angiotensin to the angiotensin 1 receptor mediating vasoconstriction and oxidative stress. In addition, short-term UFP CAPs exposure resulted in upregulation of the gene encoding kallikrein-1 ($p < 0.05$). Kallikrein-1 is a serine protease enzyme required to produce kinin peptides, which are necessary to activate bradykinin receptors. Bradykinin receptors are involved in the regulation of nitric oxide which mediates vasodilation.

5.5.6.2 Summary of Respiratory Effects in Healthy Populations

Evidence linking short-term UFP exposure and respiratory effects in healthy populations is inconsistent or minimal in epidemiologic studies and controlled human exposure studies. Animal toxicological studies found pulmonary oxidative stress following short-term UFP exposure, but inconsistent evidence of pulmonary inflammation and no evidence of changes in lung function.

5.5.7 Respiratory Effects in Populations with Cardiovascular Disease

As described in the 2009 PM ISA (U.S. EPA, 2009), Kooter et al. (2006) found that a multiday exposure of SH rats to UFP-enriched CAPs in the Netherlands decreased CC16 in BALF. CC16 is a secretory product of nonciliated bronchiolar Club cells and is thought to contribute to control of inflammation. Recently, Tyler et al. (2016) exposed C57BL/7 and ApoE knockout mice for 6-hour to UFP generated from motor vehicle exhaust. No increases in BALF inflammatory cells were observed. However, increases in TNF-α levels in BALF and particle uptake into bronchial macrophages were found in ApoE knockout ($p < 0.001$) but not in C57BL/6 mice. Effects were also seen in the hippocampus (Section 8.5.2). Additional study details are presented in Table 5-45.

5.5.8 Respiratory Mortality

In the 2009 PM ISA (U.S. EPA, 2009), no studies specifically examined associations between short-term UFP exposure and respiratory mortality. Although recent studies examine the relationship between short-term UFP exposure and respiratory mortality, the total body of evidence remains small, as detailed in CHAPTER 11 (Section 11.4.1). Across studies that examined the UFP—respiratory mortality relationship, there is inconsistency in the particle size distribution that was used to represent UFP exposures with some studies measuring NC, while other studies measured NC with the upper end of the size distribution ranging from 100—3,000 nm. This disparity in the measurement of UFPs between studies complicates the overall interpretation of results.

The assessment of the relationship between short-term UFP exposure and respiratory mortality is limited to studies conducted in Europe (Stafoggia et al., 2017; Lanzinger et al., 2016a; Samoli et al., 2016b) and China (Leitte et al., 2012). Across studies of respiratory mortality, NC was used to examine associations with respiratory mortality. Both Lanzinger et al. (2016a), in a study of five central European cities as part of the UFIREG project, and Leitte et al. (2012), in Beijing, China, reported generally positive associations that were imprecise across each of the UFP size distributions examined (Table 11-9, UFP studies in mortality chapter), while Samoli et al. (2016b) did not report any evidence of an association with respiratory mortality. Although there is some evidence of a positive association between short-term UFP exposure and respiratory mortality, within each study only a single monitor was used to estimate exposure to UFPs (Table 11-9, UFP studies in mortality chapter). As detailed in CHAPTER 2 (Section 2.5.1.1.5, Section 2.5.1.2.4, and Section 2.5.2.2.3), the use of a single monitor does not adequately account for the spatial and temporal variability in UFP concentrations as well as the change in the particle size distribution that changes with distance from source.

5.5.9 Summary and Causality Determination

A limited number of studies examining short-term exposure to UFPs and respiratory effects were reported in the 2009 PM ISA (U.S. EPA, 2009), which concluded that the relationship between short-term exposure to UFP and respiratory effects is "suggestive of a causal relationship". This conclusion was based on epidemiologic evidence indicating associations with combined respiratory-related diseases, respiratory infection, and asthma exacerbation. In addition, personal ambient UFP exposure from time spent in high- and low-traffic areas were associated with lung function decrements in adults with asthma. The few available experimental studies provided limited coherence with epidemiologic findings for asthma exacerbation. Recent studies add to this evidence base and support epidemiologic evidence for asthma exacerbation and combined respiratory-related diseases but do not rule out chance, confounding, and other biases. Several animal toxicological studies showing effects related to allergic asthma provide biological plausibility. The evidence characterizing the relationship between short-term exposure to UFP and effects on the respiratory is detailed below (Table 5-46), using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015).

For asthma exacerbation, there is some epidemiologic evidence that is not entirely consistent. Associations persisted in one epidemiologic study with adjustment for NO_2, but not in another. Additional supporting evidence, showing decrements in lung function and enhancement of allergic inflammation and other allergic responses, is provided by a controlled human exposure study in adults with asthma and by animal toxicological studies in an animal model of allergic airway disease. For combined respiratory-related diseases, recent findings add consistency for hospital admissions and ED visits and indicate lung function changes among adults with asthma or COPD. Uncertainty remains regarding the representativeness of UFP concentrations as a surrogate for exposure and for copollutant confounding, which limits inference about an independent effect of UFP. Additionally, there remains limited information on the spatial and temporal variability of UFP concentrations (Section 2.4.3.1). **Overall, the evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term UFP exposure and respiratory effects.**

Table 5-46 Summary of evidence for that is suggestive of, but not sufficient to infer, a causal relationship between short-term UFP exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	UFP Concentrations Associated with Effects[c]
Asthma exacerbation and combined respiratory-related diseases			
Evidence from multiple, high quality epidemiology studies at relevant UFP concentrations is generally consistent, but limited	Increases in asthma-related hospital admissions, ED visits, and physician visits in children and all ages combined.	Samoli et al. (2016a) Iskandar et al. (2012) Evans et al. (2014)	
	Increases in combined respiratory-related diseases observed in single-city and multicity studies.	Section 5.5.5	
Uncertainty regarding confounding by copollutants	Potential copollutant confounding for asthma-related hospital admissions and lung function is examined in a few studies, with some evidence that associations remain robust in models with gaseous pollutants.	Andersen et al. (2008b) McCreanor et al. (2007) Samoli et al. (2016a) Halonen et al. (2009b)	
Limited coherence in epidemiologic studies across the continuum of effects	Increases in respiratory symptoms, pulmonary inflammation and lung function decrements observed in a limited number of panel studies in adults with asthma provide limited support for asthma exacerbation in children.	Mar et al. (2004) von Klot et al. (2002) McCreanor et al. (2007) Mirabelli et al. (2015)	
Uncertainty regarding exposure measurement error	Most studies relied on one monitor to measure UFPs, which is inadequate based on limited data demonstrating both that there is greater spatial variability in UFPs (i.e., NC) and that the particle size distribution changes with distance from source. Additionally, there is limited information on the temporal variability in UFP concentrations.	Section 2.4.3.1	
Uncertainty regarding exposure metric and UFP size fraction	Inconsistency in the UFP metric used (i.e., NC, SC, and MC) and UFP size fraction examined complicating interpretation of results across studies.	Table 5-40 Table 5-42 Table 5-43 Table 5-44 Section 5.5.8	

Table 5-46 (Continued): Summary of evidence for that is suggestive of, but not sufficient to infer, a causal relationship between short term ultrafine particle (UFP) exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	UFP Concentrations Associated with Effects[c]
Limited evidence from controlled human exposure studies	In adults with asthma, decreases in pulmonary function are observed.	Gong et al. (2008)	100 μg/m^3
Limited evidence from toxicological studies at relevant concentrations	Enhancement of allergic inflammation and other allergic responses is observed in animal model of allergic airway disease.	Section 5.5.2.3 Li et al. (2009)	101 μg/m^3
Biological plausibility for allergic asthma	Evidence from animal toxicological studies provides biological plausibility for epidemiologic findings of allergic asthma, the most common phenotype in children.	Section 5.5.1 Section 5.5.2.3	
Respiratory effects in healthy populations			
Some evidence from toxicological studies at relevant concentrations	Pulmonary function was not affected. Inconsistent results were found for pulmonary inflammation, while some evidence was found for oxidative stress and changes in the RAS.	Section 5.5.6.1.3	59−793 μg/m^3

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the UFP concentrations and metric (i.e., number concentration [NC], surface area concentration [SC], mass concentration [MC]) with which the evidence is substantiated.

5.6 Long-Term UFP Exposure and Respiratory Effects

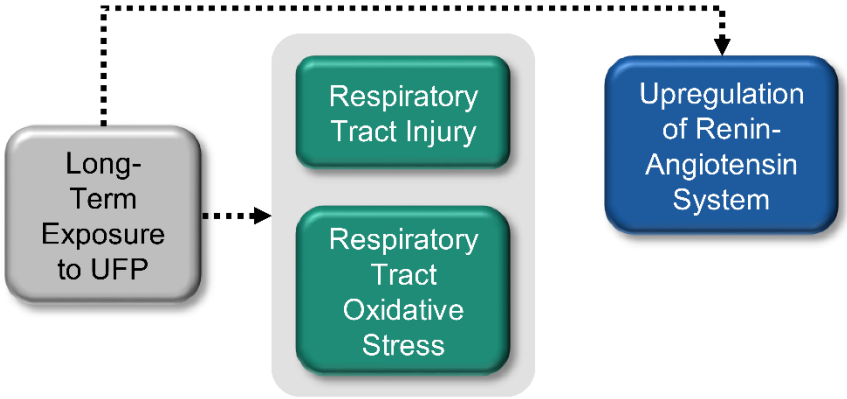
The 2009 PM ISA concluded that the evidence was inadequate to assess the relationship between long-term exposure to UFP and respiratory effects (U.S. EPA, 2009). At that time, there were no epidemiologic studies available to address this relationship. Animal toxicological studies found that long-term exposure to UFP CAPs had no effect, while long-term exposure to GE and DE altered respiratory-related endpoints. Studies with DE did not determine whether the effects were due to the particulate or gaseous part of the mixture. However, the effects of the GE were attributable to particulate matter. Recent studies consist of one epidemiologic study that examines the association between long-term exposure to UFP and respiratory outcomes and a small number of recent animal toxicological studies that provide evidence for respiratory effects.

5.6.1 Biological Plausibility

Due to a paucity of data, it is not possible to describe biological pathways that potentially underlie respiratory effects resulting from long-term exposure to UFP. Figure 5-50 graphically depicts the upstream events that may lead to downstream events observed in the single epidemiologic study. This discussion of "how" long-term exposure to UFP may lead to respiratory effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 5.6.

Once UFP deposits in the respiratory tract, it may be retained, cleared, or solubilized (see CHAPTER 4). UFP and its soluble components may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate ROS and this capacity is termed "oxidative potential." Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see CHAPTER 4). Immune system responses due to the presence of particles in the interstitial space may contribute to respiratory health effects.

Although all size fractions of PM may contribute to oxidative stress, UFPs may contribute disproportionately more as a function of their mass due to their large surface/volume ratio. The relative enrichment of redox active surface components, such as metals and organics, per unit mass may translate to a relatively greater oxidative potential of UFPs compared with larger particles with similar surface components. In addition, the greater surface per unit volume may deliver relatively more adsorbed soluble components to cells. These components may undergo intra-cellular redox cycling following cellular uptake. Furthermore, per unit mass, UFPs may have more opportunity to interact with cell surfaces due to their greater surface area and their greater particle number compared with larger PM. These interactions with cell surfaces may lead to ROS generation, as described in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). Recent studies have also demonstrated that UFPs have the capacity to cross cellular membranes by nonendocytotic mechanisms involving adhesive interactions and diffusion, as described in CHAPTER 4. This may allow UFPs to interact with or penetrate intra-cellular organelles.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 5-50 Potential biological pathways for respiratory effects following long-term UFP exposure.

Evidence that long-term exposure to UFP may affect the respiratory tract is provided by a limited number of experimental studies. While markers of injury and oxidative stress were increased (Zhang et al., 2012; Reed et al., 2008), no inflammatory changes were observed (Tyler et al., 2016; Aztatzi-Aguilar et al., 2015; Araujo et al., 2008; Reed et al., 2008). In Tanaka et al. (2013a), the enhancement of allergic responses seen following long-term exposure to UFP-enriched DE was not attributable to particulate components, suggesting a role for combustion gases in mediating the response. Similarly, the presence of 8-OH deoxy-guanosine observed in lung tissue was likely due to combustion gases. Upregulation of the RAS, as indicated by an increase in mRNA and protein levels of angiotensin receptor Type 1, was observed in the lung (Aztatzi-Aguilar et al., 2015). Angiotensin receptor Type 1 mediates the effects of angiotensin II, which is a potent vasoconstrictor and mediator in the vasculature. The SNS and the RAS are known to interact in a positive feedback fashion (Section 8.1.2) with important ramifications in the cardiovascular system. However, it is not known whether SNS activation or some other mechanism mediated the changes in the RAS observed in the respiratory tract in this study. The upstream events presented here may provide biological plausibility for epidemiologic evidence of respiratory health effects and will be used to inform a causality determination, which is discussed later in the chapter (Section 5.4.9).

5.6.2 Development of Asthma

The 2009 PM ISA (U.S. EPA, 2009) did not report any studies evaluating allergic responses resulting from long-term exposure to UFP. Recently, Tanaka et al. (2013a) evaluated the enhancement of allergic responses by exposure to UFP-enriched DE. ICR mice were exposed to two concentrations of diluted DE and to particle-depleted diesel exhaust (0DE) for 8 weeks. Concentrations of gaseous components of DE were similar in the high DE and 0DE atmospheres (3.3 ppm CO, 1.4 ppm NO_X, and 0.51 ppm NO_2), but the low DE had approximately 1/3 of these concentrations (1.2, 0.41, and 0.15, respectively). Mice were sensitized and challenged with OVA administered by intra-tracheal instillation during the 8-week inhalation exposure. Mice exposed to filtered air and OVA had a modest increase in airway eosinophils that was enhanced by exposure to low and high DE in a dose-dependent fashion ($p < 0.05$ compared with OVA controls). This response was not dependent on the particulate part of the aerosol, since numbers of eosinophils in allergic animals exposed to 0DE, which was depleted of particles, were similar in the high DE group. Furthermore, increases in IL-5, IL-13, eotaxin, and myeloperoxidase protein in lung tissue reached similar levels in allergic mice exposed to either high DE or 0DE ($p < 0.05$ compared with OVA controls). Interestingly, only the allergic mice exposed to the particle-depleted 0DE had increases in lung tissue IL-4, IL-17α, IL-1β, lipid peroxidase, and serum IgE ($p < 0.05$ compared with OVA controls). Results from this study indicate a critical role for the combustion gases in DE-associated enhancement of allergic responses. Companion studies also detected the presence of 8-OH deoxy-guanosine in lung tissue in high DE and particle-depleted 0DE allergic mice (Tanaka et al., 2013b). Additional study details are found in Table 5-47.

Table 5-47 Study-specific details from animal toxicological studies of long-term UFP exposure and allergic responses.

Study/Study Population	Pollutant	Exposure	Endpoints
Tanaka et al. (2013a) Species: Mouse Sex: Female Strain: ICR Age/Weight: 6 weeks	Diesel engine exhaust Low DE = 36 μg/m^3 High DE = 169 μg/m^3 Particle size: 26−27 nm in low and high DE	Route: Whole-body inhalation Dose/Concentration: 5 h/day, 5 days/week for 8 weeks OVA intra-tracheal every other week (5 total) Time to analysis: 24 h after last instillation	BALF cells BALF cytokines Serum IgE
Tanaka et al. (2013b) Species: Mouse Sex: Female Strain: ICR Age/Weight: 6 weeks	Diesel engine exhaust Low DE = 36 μg/m^3 High DE = 169 μg/m^3 Particle size: 26−27 nm in low and high DE	Route: Whole-body inhalation Dose/Concentration: 5 h/day, 5 days/week for 8 weeks OVA intra-tracheal every other week (5 total) Time to analysis: 24 h after last instillation	Oxidative stress • -Lung 8-OH deoxy guanosine levels

BALF = bronchoalveolar lavage fluid; DE = diesel exhaust; IgE = Immunoglobulin E; OVA = ovalbumin.

5.6.3 Subclinical Effects in Healthy Populations and Populations with Cardiovascular Disease

Animal toxicological studies provide evidence for subclinical effects potentially underlying the development of respiratory disease in healthy populations and in populations with cardiovascular disease. The 2009 PM ISA (U.S. EPA, 2009) reported several studies that evaluated the effects of long-term exposure to UFP on subclinical effects. Reed et al. (2008) exposed F344 rats for 6 months to GE containing UFP (count median diameter 15−20 nm, MMD 150 nm). LDH was increased in BALF of rats, but no inflammatory or histopathologic changes were found except for the accumulation of PM-containing macrophages. However, hypermethylation of lung DNA was observed. The significance of DNA methylation in terms of respiratory health is unclear, although it is known that altered patterns of DNA methylation can affect gene expression and are sometimes associated with altered immune responses and/or the development of cancer. The LDH and hypermethylation responses were prevented by addition of a particle filter, indicating that the particulate portion of the GE mixture played a role in the response. In a study in ApoE knockout mice exposed to UFP CAPs for 40 days, Araujo et al. (2008) found no increase in BALF inflammatory cells exposed to UFP CAPs for 40 days.

Several recent studies have become available since the 2009 PM ISA that examine the effects of long-term UFP exposure on pulmonary oxidative stress and inflammation. Zhang et al. (2012) collected ambient UFP near a Los Angeles freeway. Exposure of C57BL/6J mice to the reaerosolized UFP for

10 weeks resulted in increases in mRNA and protein levels of heme oxygenase-1, NADPH quinone oxidoreductase 1, γ-glutamyl cysteine ligase catalytic subunit, and γ-glutamyl cysteine synthetase modifier subunit in the lung ($p < 0.05$). These are Phase II regulated detoxifying enzymes and are important in defense against oxidative stress. Young mice (3 months) had a more robust increase in gene expression and protein levels than older mice (18 months). Zhang et al. (2012) also found evidence of upregulation of Phase II enzymes in specific brain regions (Section 8.6.3) and the liver. In contrast, Aztatzi-Aguilar et al. (2015) found decreased lung tissue heme oxygenase-1 activity in Sprague-Dawley rats following 8-weeks exposure to Mexico City UFP CAPs ($p < 0.05$) and no change in γ-glutamyl cysteine ligase catalytic subunit was observed. Aztatzi-Aguilar et al. (2015) also found decreased protein levels of IL-6 in lung tissue ($p < 0.05$). Further, Tyler et al. (2016) exposed C57BL/7 and ApoE-knockout mice to UFP generated from motor vehicle exhaust. A 30-day exposure resulted in no increase in inflammatory cells or cytokines in the BALF. Particle uptake into bronchial macrophages was increased in both C57BL/6 and ApoE knockout mice ($p < 0.05$). Effects were also seen in the hippocampus (Section 8.6.3). Aztatzi-Aguilar et al. (2015) found that long-term UFP CAPs exposure had several effects on the RAS, including induced lung expression of the angiotensin 1 receptor gene, and increased angiotensin 1 receptor protein levels ($p < 0.05$). Protein levels and mRNA of angiotensin converting enzyme were not impacted. Components of the RAS play an important role in the pulmonary circulation. Overall, older and recent studies provide some limited evidence for pulmonary injury, DNA hypermethylation, and changes in the RAS, inconsistent evidence for pulmonary oxidative stress and no evidence for pulmonary inflammation. Additional study details for these recent animal toxicological studies are found in Table 5-48.

Table 5-48 Study-specific details from animal toxicological studies of long-term UFP exposure and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
Aztatzi-Aguilar et al. (2015) Species: Rat Sex: Male Strain: Sprague Dawley	UFP CAPs Mexico City Particle size: Ultrafine $PM_{0.2}$ Control: Filtered air	Route: Inhalation Dose/Concentration: Ultrafine $PM_{0.2}$ 107 µg/m^3 Duration: Subchronic 5 h/day, 4 days/week, 8 weeks Time to analysis: 24 h	Gene and protein expression in lung tissue • IL-6 • Components of kallikrein-kinin endocrine system and RAS • Heme oxygenase-1
Reed et al. (2008) Species: Rat Sex: Male and Female Strain: F344 Age/Weight:	DE and filtered DE Particle size: MMAD 150 nm	Route: Whole-body Inhalation Dose/Concentration: 3 concentrations, H 59 µg/m^3, M 30 µg/m^3, L 6.6 µg/m^3, high filtered 2 µg/m^3 Duration: 6 h/day for 7 days/week, 3 days (1 week), 6 mo Coexposure: Combustion products	Lung Injury • -BALF LDH Lung DNA Alteration—Hypermethylation
Tyler et al. (2016) Species: Mouse Strain: C57BL/6 and ApoE knockout Age/Weight: 6−8 weeks	Motor vehicle exhaust (DE and GE) passed through a denuder to generate UFP Particle size: 147.1 nm ± 1.3 nm Control: Filtered air	Route: Whole-body inhalation Dose/Concentration: 371.3 ± 15.6 µg/m^3 Duration: 6 h/day for 30 days	BALF cells and cytokines Particle uptake in bronchial macrophages
Zhang et al. (2012) Species: Mouse Strain: C57BL/6J Sex: Male Age: 3 mo, 18 mo	Reaerosolized collected ambient PM near a freeway Particle size: Ultrafine PM < 200 nm	Route: Whole-body inhalation Dose/concentration: 200−400 ug/m^3 Duration of exposure: 5 h/day, 3 days/week for 10 weeks	Oxidative Stress Markers—Lung GCLC and GCLM mRNA and protein

ApoE = apolipoprotein E; BALF = bronchoalveolar lavage fluid; DNA = deoxyribonucleic acid; DE = diesel exhaust; GCLC = glutamate cysteine ligase catalytic subunit; GCLM = glutamate cysteine ligase modifier subunit; H = high; IL-6 = interleukin 6; L = low; M = medium; MMAD = mass median aerodynamic diameter; LDH = lactate dehydrogenase; Mrna = messenger ribonucleic acid; RAS = renin-angiotensin system.

1

5.6.4 Respiratory Mortality

2 Overall, the literature base for long-term UFP exposure and respiratory mortality remains very
3 small, with one study (Ostro et al., 2015) reporting results for UFP mass concentration. The authors
4 examined the association between UFP (<0.1 µm) mass concentrations and respiratory mortality among

women in the California Teachers Cohort using a CTM to predict UFP concentrations with a 4-km spatial resolution and observed an association near the null value.

5.6.5 Summary and Causality Determination

Based on limited evidence from animal toxicological studies and a lack of epidemiologic studies, the 2009 PM ISA (U.S. EPA, 2009) concluded that evidence was inadequate to assess the relationship between long-term exposure to UFP and respiratory effects. Since then, only a few new studies have become available. The evidence characterizing the relationship between long-term exposure to $PM_{10-2.5}$ and respiratory effects is detailed below (Table 5-49), using the framework for causality determination described in the Preamble to the ISAs (U.S. EPA, 2015). Currently, there is limited epidemiologic evidence for respiratory mortality. But uncertainty regarding copollutant confounding and exposure measurement error results in an inability to rule out chance and confounding. A few animal toxicological studies provide evidence of effects resulting from long-term exposure to UFP. **Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between long-term UFP exposure and respiratory effects.**

Table 5-49 Summary of evidence that is inadequate to infer the presence or absence of a causal relationship between long-term UFP exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	UFP Concentrations Associated with Effects[c]
Limited epidemiologic evidence does not support a relationship	No association was observed with UFP mass concentrations in a single study of respiratory mortality from the California Teachers Study cohort.	Ostro et al. (2015)	UF mass concentration: 1.29
Uncertainty regarding confounding by copollutants and exposure measurement error	Uncertainties are not addressed.	Ostro et al. (2015)	
Some evidence for respiratory effects from toxicological studies at relevant concentrations	Results show injury, oxidative stress, DNA hypermethylation, and changes in the RAS, but no pulmonary inflammation.	Section 0	59−400 μg/m^3

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

bDescribes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the UFP concentrations and metric (i.e., number concentration [NC], surface area concentration [SC], mass concentration [MC]) with which the evidence is substantiated.

5.7 References

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CHAPTER 6 CARDIOVASCULAR EFFECTS

Summary of Causality Determinations for Short- and Long-Term Particulate Matter (PM) Exposure and Cardiovascular Effects

This chapter characterizes the scientific evidence that supports causality determinations for short- and long-term PM exposure and cardiovascular effects. The types of studies evaluated within this chapter are consistent with the overall scope of the ISA as detailed in the Preface (see Section P.3.1). In assessing the overall evidence, strengths and limitations of individual studies were evaluated based on scientific considerations detailed in the Appendix. More details on the causal framework used to reach these conclusions are included in the Preamble to the ISA (U.S. EPA, 2015). The evidence presented throughout this chapter support the following causality conclusions:

Size Fraction	Causality Determination
Short-Term Exposure	
$PM_{2.5}$	Causal
$PM_{10-2.5}$	Suggestive of, but not sufficient to infer
UFP	Suggestive of, but not sufficient to infer
Long-Term Exposure	
$PM_{2.5}$	Causal
$PM_{10-2.5}$	Suggestive of, but not sufficient to infer
UFP	Inadequate

6.1 Short-Term $PM_{2.5}$ Exposure and Cardiovascular Effects

The 2009 PM ISA concluded that "a causal relationship exists between short-term exposure to $PM_{2.5}$ and cardiovascular effects." This conclusion was based on multiple lines of evidence including consistently positive associations between short-term exposure to $PM_{2.5}$ and emergency department (ED) visits and hospital admissions for cardiovascular disease (U.S. EPA, 2009). Results from HA and ED visit studies were supported by associations between $PM_{2.5}$ and cardiovascular mortality. In addition, controlled human exposure (CHE) and animal toxicological studies provided evidence of changes in various measures of cardiovascular function to establish biological plausibility for the epidemiologic findings. The most consistent $PM_{2.5}$ effect was for reduced vascular function. Toxicological studies finding reduced myocardial blood flow during ischemia and altered vascular reactivity provided coherence and biological plausibility for the myocardial ischemia that was observed in both controlled

human exposure and epidemiologic studies. Further, $PM_{2.5}$ effects on ST segment depression—an electrocardiogram change that potentially indicates ischemia—were also observed.

Key uncertainties from the last review included inconsistent results across disciplines with respect to the relationship between short-term exposure to $PM_{2.5}$ and changes in blood pressure, blood coagulation markers, and markers of systemic inflammation. In addition, uncertainties remained with respect to biological plausibility; that is, how inhalation exposure to $PM_{2.5}$ could trigger molecular, cellular, and tissue responses that result in serious cardiovascular outcomes. For example, in the 2009 PM ISA (U.S. EPA, 2009), there was a growing body of evidence from CHE, animal toxicological, and epidemiologic studies demonstrating changes in markers of systemic oxidative stress following $PM_{2.5}$ exposure. However, uncertainties remained as to the relationship between changes in markers of oxidative stress and more serious cardiovascular health outcomes.

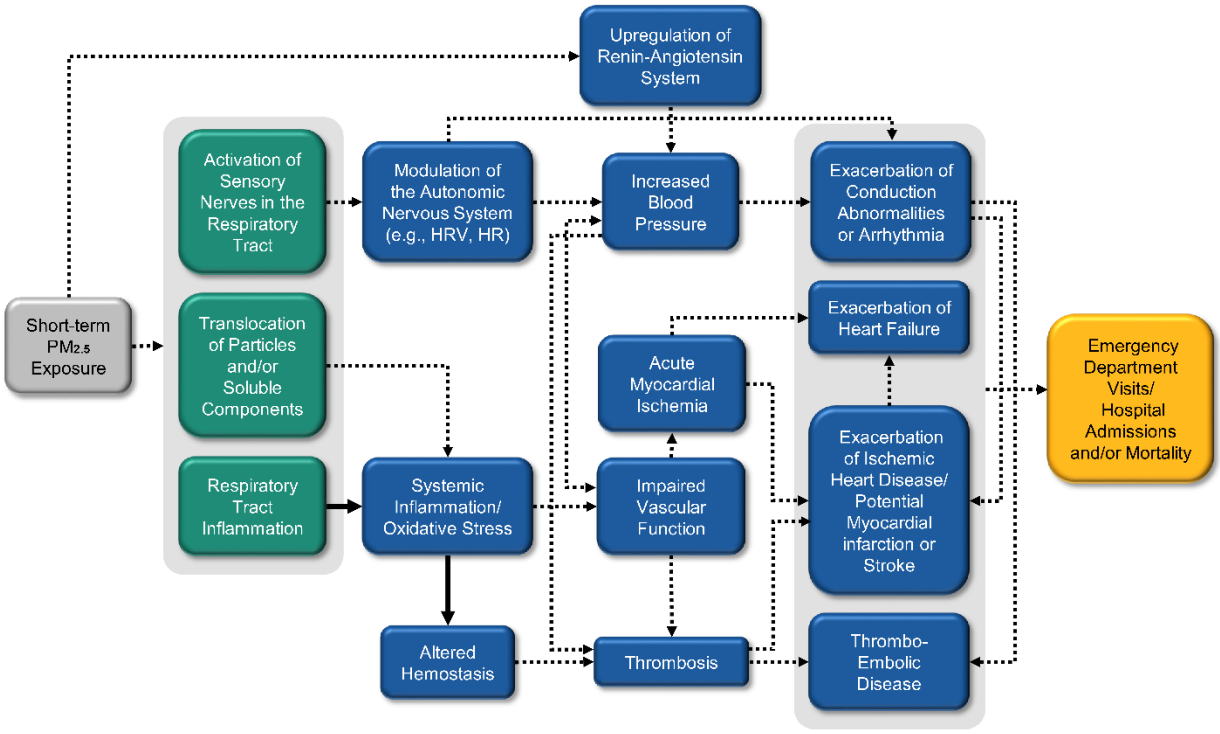
Since the last review, the evidence relating short-term $PM_{2.5}$ CAP exposure and cardiovascular health effects has expanded greatly, further strengthening the conclusions reached in the 2009 PM ISA. Recent health evidence continues to show a clear relationship between short-term $PM_{2.5}$ exposure and cardiovascular outcomes such as ED visits and hospital admissions for ischemic heart disease (IHD) and heart failure (HF). Additionally, recent epidemiologic studies confirm the relationship between short-term exposure to $PM_{2.5}$ and cardiovascular mortality. Results from epidemiologic studies are supported by CHE and animal toxicological evidence demonstrating that exposure to $PM_{2.5}$ can result in a variety of cardiovascular effects including endothelial dysfunction, increases in blood pressure, and conduction abnormalities. Thus, the epidemiologic, CHE and animal toxicological evidence presented in this section continues to support a causal relationship between short-term $PM_{2.5}$ exposures and cardiovascular effects, with the strongest evidence supporting this determination still coming from the epidemiologic literature. As discussed in detail below, recent evidence also reduces uncertainties from the previous review with respect to the potential for copollutant confounding and provides additional evidence for biological plausibility.

The subsections below provide an evaluation of the most policy relevant scientific evidence relating-short-term $PM_{2.5}$ exposure to cardiovascular health effects. To clearly characterize and put this evidence into context, there is first a discussion of the biological plausibility of cardiovascular effects following short-term $PM_{2.5}$ exposure (Section 6.1.1). Following this discussion, the health evidence relating short-term $PM_{2.5}$ exposure and specific cardiovascular health outcomes is discussed in detail: ischemic heart disease and myocardial infarction (Section 6.1.2), heart failure and impaired heart function (Section 6.1.3) cardiac electrophysiology and arrhythmia (Section 6.1.4), cerebrovascular disease and stroke (Section 6.1.5), increased blood pressure and hypertension (Section 6.1.6), peripheral vascular disease (PVD), venous thromboembolism and pulmonary embolisms (Section 6.1.7), aggregated cardiovascular outcomes (Section 6.1.8), and cardiovascular-related mortality (Section 6.1.9). The evidence for an effect of $PM_{2.5}$ exposures on endpoints such as changes in heart rate variability (HRV) and endothelial function are discussed (Section 6.1.10, Section 6.1.11, Section 6.1.12, and

Section 6.1.13), as are policy relevant considerations (Section 6.1.14), and the relationship between health effects and exposure to specific $PM_{2.5}$ components (Section 6.1.15). Finally, considering the all of the information presented above, summary and causal determinations are presented (Section 6.1.16). Of note, when discussing the health evidence and causal determinations, effect estimates from epidemiologic studies adjusted for potential confounders are presented when available and new epidemiologic, CHE, and animal toxicological studies that address uncertainties and limitations noted in the previous review are emphasized.

6.1.1 Biological Plausibility

This subsection describes the biological pathways that potentially underlie cardiovascular health effects resulting from short-term inhalation exposure to $PM_{2.5}$. Figure 6-1 graphically depicts these proposed pathways as a continuum of pathophysiological responses—connected by arrows—that may ultimately lead to the apical cardiovascular events observed in epidemiologic studies (e.g., ED visits and hospital admissions). This discussion of "how" short-term exposure to $PM_{2.5}$ may lead to these cardiovascular events also provides biological plausibility for the epidemiologic results reported later in Section 6.1. In addition, most studies cited in this subsection are discussed in greater detail throughout Section 6.1.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Solid arrows denote direct evidence of the relationship as provided, for example, by an inhibitor of the pathway or a genetic knock-out model used in an experimental study. Progression of effects is depicted from left to right and color-coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes.

Figure 6-1 Potential biological pathways for cardiovascular effects following short-term exposure to $PM_{2.5}$.

When considering the available health evidence, plausible pathways connecting short-term exposure to $PM_{2.5}$ to the apical events reported in epidemiologic studies are proposed in Figure 6-1. The first pathway begins as respiratory tract inflammation leading to systemic inflammation[61]. The second pathway involves activation of sensory nerve pathways in the respiratory tract that lead to modulation of the autonomic nervous system. Once these pathways are initiated, there is evidence from experimental and observational studies that short-term exposure to $PM_{2.5}$ may result in a series of pathophysiological responses that could lead to cardiovascular events such as emergency department (ED) visits and hospital admissions for ischemic heart disease (IHD) and heart failure (HF), and ultimately mortality.

[61] It is also possible that particles ~200 nm or less, or soluble particle components can translocate directly into the circulatory system (Chapter 4) and lead to systemic inflammation, although the extent to which particle translocation occurs remains unclear.

Short-term inhalation exposure to $PM_{2.5}$ may result in respiratory tract inflammation and oxidative stress (Chapter 5). Inflammatory mediators such as cytokines produced in the respiratory tract have the potential to enter into the circulatory system where they may amplify the initial inflammatory response and/or cause distal pathophysiological events that can contribute to overt cardiovascular disease. For example, following short-term $PM_{2.5}$ exposure in mice, Budinger et al. (2011) demonstrated that inflammation that began in the lung resulted in an increase in circulating markers of coagulation. Thus, it is important to note that there is evidence from CHE (Behbod et al., 2013; Urch et al., 2010; Brook et al., 2009; Gong et al., 2004); epidemiologic panel (Steenhof et al., 2014; Strak et al., 2013a; Huttunen et al., 2012; Delfino et al., 2009b), and animal toxicological (Xu et al., 2013) studies that short-term exposure to $PM_{2.5}$ can result in an increase in circulating inflammatory cells and cytokines. Elevated levels of cytokines such as interlukin-6 (IL-6) have been correlated with elevated markers of thrombosis (Chiarella et al., 2014; Budinger et al., 2011). It is therefore also important to note that in CHE (Lucking et al., 2011; Ghio et al., 2003; Jr et al.; Ghio et al., 2000), epidemiologic panel (Croft et al., 2017; Strak et al., 2013a), and animal toxicological (Budinger et al., 2011; Kodavanti et al.) studies that there is evidence of increased protein levels associated with coagulation and/or decreased protein levels associated with fibrinolysis following short-term $PM_{2.5}$ exposure. This alteration in hemostasis increases the potential for thrombosis (Lucking et al., 2011), which can potentially exacerbate existing IHD and HF.

In addition to affecting hemostasis, systemic inflammation may result in impaired vascular function that could potentially lead to rupture of existing plaques (Halvorsen et al., 2008). Dislodged plaques may then obstruct blood flow to the heart or stimulate intravascular clotting (Karoly et al., 2007), both of which could result in acute myocardial ischemia, and set the stage for HF. If the dislodged plaque obstructs blood flow to the brain, the potential for a stoke exists. Impaired vascular function has been reported following short-term $PM_{2.5}$ exposure in CHE (Hemmingsen et al., 2015b; Tong et al., 2015; Lucking et al., 2011; Brook et al., 2009), epidemiologic panel (Ljungman et al., 2014; Madrigano et al., 2010; Liu et al., 2009) and animal toxicological studies (Davel et al., 2012; Haberzettl et al., 2012; O'Toole et al., 2010). In addition, clinical indicators of potential ischemia (e.g., ST segment depression on an electrocardiogram) have been shown in epidemiologic panel studies (Delfino et al., 2011; Zhang et al., 2009) following short-term exposure to $PM_{2.5}$. Impaired vascular function can also lead to increases in blood pressure (BP) through vasoconstriction. Given that increases in BP may exacerbate IHD or HF through shear stress induced arterial thrombosis and/or impaired vascular function, it is notable that following short-term $PM_{2.5}$ exposure, there is direct evidence for increases in BP from CHE (Tong et al., 2015; Bellavia et al., 2013; Brook et al., 2009), epidemiologic panel (Hicken et al., 2014; Brook et al., 2011; Dvonch et al., 2009), and animal toxicological studies (Bartoli et al., 2009; Ito et al., 2008; Chang et al., 2007; Chang et al., 2004). These studies are consistent with additional evidence from animal toxicological studies (Aztatzi-Aguilar et al., 2015; Ghelfi et al., 2010) reporting increases in renin-angiotensin system gene expression consistent with vasoconstriction and increases in BP. Taken together, there are plausible pathways by which respiratory tract inflammation could exacerbate existing IHD and HF, contribute to the development of a myocardial infarction or stroke, and lead to ED visits and hospital admissions.

There is also evidence that exposure to $PM_{2.5}$ could lead to these outcomes through activation of sensory nerves in the respiratory tract (CHAPTER 5). Once activated, autonomic nervous system modulation may cause a shift toward increased sympathetic tone. Shifts toward increased sympathetic nervous system tone may result in increases in BP and decreased in vascular function, which as mentioned above, could exacerbate IHD and/or HF. It is therefore important to note that there is evidence from CHE (Tong et al., 2012); epidemiologic panel (Liu et al., 2015b; Hampel et al., 2014; Weichenthal et al., 2014a; Zanobetti et al., 2010) and animal toxicological studies (Wagner et al., 2014a; Wagner et al., 2014b; Rohr et al., 2011) of autonomic nervous system modulation—including a shift toward increased sympathetic tone (as evidenced by changes in HRV and/or HR)—following short-term $PM_{2.5}$ exposure. Modulation of the autonomic nervous system may also contribute to conduction abnormalities (Ghelfi et al., 2010) or worsening of arrhythmia (Cascio, 2016). Thus, also of note is evidence from CHE (Tong et al., 2012; Sivagangabalan et al., 2011), epidemiologic panel (Zanobetti et al., 2014a; Link et al., 2013; Dockery et al., 2005a; Dockery et al., 2005b; Rich et al., 2005; Peters et al., 2000)and animal toxicological studies (Farraj et al., 2015; Ghelfi et al., 2010; Nadziejko et al., 2004) that short-term exposure to $PM_{2.5}$ can result in conduction abnormalities or arrhythmia. Conduction abnormalities or arrhythmia could then potentially exacerbate IHD and subsequently, HF. Taken together, there are multiple potential pathways by which activation of sensory nerves in the respiratory tract may lead to worsening of IHD or HF.

When considering the available evidence, there are plausible pathways connecting short-term exposure to $PM_{2.5}$ to cardiovascular health effects (Figure 6-1). The first potential pathway begins with respiratory tract inflammation that may lead to systemic inflammation, altered hemostasis, impaired vascular function and potential worsening of IHD and HF. The second potential pathway involves the activation of sensory nerves in the respiratory tract that may modulate autonomic nervous system responses potentially leading to exacerbation of IHD and HF through changes in BP and worsening of conduction abnormalities or arrhythmia. Collectively, these proposed pathways provide biological plausibility for epidemiologic results of ED visits and hospital admissions for cardiovascular-related causes and will be used to inform a causal determination, which is discussed later in the chapter (Section 0).

6.1.2 Ischemic Heart Disease and Myocardial Infarction

IHD is a chronic condition characterized by atherosclerosis and reduced blood flow to the heart (Section 6.2.2 and Section 6.2.4). Myocardial infarction (MI), more commonly known as a heart attack, occurs when heart tissue death occurs secondary to prolonged ischemia. The effect of short-term $PM_{2.5}$ exposure on acute MI, complications from recent MI, and other acute or chronic IHD are generally evaluated using ICD codes recorded when a patient is admitted or discharged from the hospital or emergency department (ICD9: 410−414 or ICD10: I20−I25). In experimental or epidemiologic panel studies, indicators of MI include ST segment depression as measured by an electrocardiograph (ECG).

The ST segment of an electrocardiogram recorded by surface electrodes corresponds to the electrical activity of the heart registered between ventricular depolarization and repolarization, and is normally isoelectric.

In the 2009 PM ISA, most of the evidence for IHD and MI was from epidemiologic studies of emergency department (ED) visits and hospital admissions. This evidence included the U.S. Medicare Air Pollution Study (MCAPS) (Dominici et al., 2006), a four-city study in Australia (Barnett et al., 2006), and a study among older adults in several French cities (Host et al., 2008). The positive associations reported in these studies were important considerations in the determination of a causal relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects.

Evidence from the current review strengthens the epidemiologic results reported in the 2009 PM ISA. Several new epidemiologic studies conducted in the U.S. and Europe provide additional evidence of positive associations between short-term $PM_{2.5}$ exposure and IHD ED visits and hospital admissions (Section 6.2.2.1). Uncertainties noted in the last review with respect to exposure measurement error for those not living near a $PM_{2.5}$ monitor were reduced in the current review by consideration of recent studies that applied hybrid exposure assessment techniques that combine land use regression data with satellite aerosol optical depth (AOD) measurements and $PM_{2.5}$ concentrations measured at fixed-site monitors to estimate $PM_{2.5}$ concentrations. In addition to these ED visit and hospital admissions studies, there is also evidence for ST segment depression from epidemiologic panel studies (Section 6.1.2.2).

6.1.2.1 Emergency Department Visits and Hospital Admissions

In the last review, epidemiologic studies that examined the effect of $PM_{2.5}$ on IHD ED visits and hospital admissions provided some of the strongest evidence supporting the causal relationship between short-term $PM_{2.5}$ exposure and cardiovascular disease, including several multicity studies [U.S. Medicare Air Pollution Study (MCAPS) (Dominici et al., 2006), a study among older adults (65+ years) in four cities in Australia (Barnett et al., 2006), and a study among older adults in several French cities (Host et al., 2008)]. In the current review, several recent multicity studies in the U.S. and Europe provide additional evidence for positive associations between short-term $PM_{2.5}$ exposure and IHD ED visits and HA, including some studies conducted in areas of lower $PM_{2.5}$ concentrations than those included in the 2009 PM ISA. This section first reviews recent studies that have considered IHD as a composite endpoint, and subsequently considers those studies focusing specifically on MI and angina. Additional study details and results are presented in Table 6-1.

Table 6-1 Epidemiologic studies of short-term $PM_{2.5}$ exposure and ischemic heart disease and myocardial infarction hospital admission and emergency department visits.

Study/Location/Population	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m^3	Copollutant Examination
Dominici et al. (2006) 204 U.S. Urban Counties (1999−2002) Age ≥65 yr	Monitors in county averaged Number NR. Study population reside an average of 5.9 miles from monitor. Median pairwise correlation between same-county monitors 0.91.	IHD	13.4 (IQR 3.9) 75th: 15.2	Correlation (*r*): NA Copollutant models with: NA
Barnett et al. (2006) Four Australian Cities (1998−2001) Age ≥65 yr	Monitors in city averaged 3 monitors Sydney, 2 monitors Melbourne and Perth, 1 monitor Brisbane.	IHD	8.1 to 9.7 (NR) (across four cities) Max: 29.3 to 122.8 (across four cities)	Correlation (*r*): NA Copollutant models with: NA
Host et al. (2007) Six French Cities (2000−2003) Age ≥65 yr	Monitors in city averaged 4 monitors Paris, 1 monitor Toulouse, 2 monitors other cities. Residents within 20 km. Between-monitor $r > 0.60$.	IHD	13.8 to 18.6 (NR) (across six cities) 95th: 25.0 to 33.0 (across six cities)	Correlation (*r*): $PM_{10-2.5}$: 0.28−0.73 across cities Copollutant models with: NA
Zanobetti and Schwartz (2006) Boston, Massachusetts (1995−1999) Age ≥65 yr	1 monitor Data missing for 1998.	MI	Median: 11.1 (IQR 8.9) 75th: 16.1	Correlation (*r*): BC: 0.66, NO_2: 0.55, CO: 0.52, O_3: 0.20 Copollutant models with: NA

Table 6-1 (Continued): Epidemiologic studies of short-term $PM_{2.5}$ exposure and ischemic heart disease and myocardial infarction hospital admission and emergency department visits.

Study/Location/Population	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m³	Copollutant Examination
†Bell et al. (2015) 213 U.S. Counties (1999−2010) Age ≥65 yr	Monitors in county averaged	IHD, MI	12.3 (NR) Max: 20.2	Correlation (*r*): NA Copollutant models with: NA
†Kloog et al. (2014) Seven Mid-Atlantic States and Washington, D.C. (2000−2006) Age ≥65 yr	Spatiotemporal modelling at incorporating 10 km × 10 km satellite-derived AOD observations, $PM_{2.5}$ monitoring data, and land use variables. Cross-validation R^2 = 0.81.	IHD	2-day avg: 11.92 (5.68) 75th: 14.65 Max: 95.85	Correlation (*r*): NA Copollutant models with: NA
†Haley et al. (2009) Eight New York Cities (2001−2005)	Weighted averages across monitors in each city 39 monitors in total.	IHD	5.8 (IQR 5.9) 75th: 8.0 Max: 42.2	Correlation (*r*): NA Copollutant models with: NA
†Hsu et al. (2017) Four New York Regions (1991−2006)	Adjusted CMAQ-simulated model (see Hogrefe et al. (2009)) 12 × 12 km grid resolution with patient residential address	IHD	Graphically reported only	Correlation (*r*): NA Copollutant models with: NA
†Talbott et al. (2014) Seven U.S. States (2001−2009)	Fuse-CMAQ CMAQ model combined with monitoring data, downscaled to Census Tract resolution.	IHD, MI	6.46 to 12.83 (2.55 to 7.66) (across seven states) 75th: 7.64 to 16.55 (across seven states)	Correlation (*r*): NA Copollutant models with: NA
†Milojevic et al. (2014) 15 Conurbations in England and Wales (2003−2009)	Nearest monitor to patient's residence (50 km). Number NR.	IHD, MI	Median: 10.0 (IQR 8.0) 75th: 15.0	Correlation (*r*): CO: 0.48, NO_2: 0.53, O_3: −0.10, PM_{10}: 0.86, SO_2: 0.41
†Zanobetti et al. (2009) 26 U.S. Cities (2000−2003) Age ≥65 yr	Monitors in county averaged 1 to 4 monitors per county. Monitor data discarded if between-monitor correlation <0.8	MI	2-day avg: 15.3 (8.2) (across 26 cities)	Correlation (*r*): NA Copollutant models with: NA

Table 6-1 (Continued): Epidemiologic studies of short-term $PM_{2.5}$ exposure and ischemic heart disease and myocardial infarction hospital admission and emergency department visits.

Study/Location/Population	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m^3	Copollutant Examination
†Weichenthal et al. (2016b) 16 Cities in Ontario, Canada (2004−2011)	Nearest monitor to patient's population-weighted postal code centroid	MI	6.91 (5.97) Max: 56.8	Correlation (*r*): NO_2: 0.51, O_3: −0.49 Copollutant models with: NO_2, O_3

CMAQ = Community Multiscale Air Quality Modeling System, CO = carbon monoxide, HR = hazard ratio, IHD = Ischemic Heart Disease, max = maximum, MI = Myocardial Infarction, NO_2 = nitrogen dioxide, NR = not reported, OR = odds ratio, $PM_{2.5}$ = particulate matter with mean aerodynamic diameter 2.5 µm, PM_{10} = particulate matter with mean aerodynamic diameter 10 µm, $PM_{10-2.5}$ = particulate matter with mean aerodynamic diameter between 2.5 µm and 10 µm, RR = relative risk, SO_2 = sulfur dioxide.

For the included epidemiologic studies, the focus is on those studies conducted in areas where mean $PM_{2.5}$ concentrations are <20 µg/m^3 or in the case of a multi-city study where more than half of the cities have concentrations <20 µg/m^3. Other studies maybe be included if they contribute to evaluating important uncertainties (see Preface).

†Studies published since the 2009 PM ISA.

Since the 2009 PM ISA, studies making use of the large Medicare database have evaluated IHD hospital admission records and observed an 0.18% (95% CI: −0.09, 0.45%) increase in admissions associated with $PM_{2.5}$ concentrations on the same day (Bell et al., 2015), and 0.99% (95% CI: 0.62, 1.37%) increase over the previous two days (lag 0−1) (Kloog et al., 2014). Notably, unlike most previous studies that rely on monitored $PM_{2.5}$ concentrations, Kloog et al. (2014) applied land use regression (LUR) in conjunction with satellite AOD observations and monitoring data to estimate $PM_{2.5}$ exposures across the study area. This hybrid prediction model attempts to reduce exposure measurement error through more spatially resolved exposure estimates and increase coverage by estimating exposure for populations that do not live near a $PM_{2.5}$ monitor. Similarly, two multicity studies conducted in New York observed positive associations between short-term $PM_{2.5}$ concentrations and ED visits and hospital admissions for IHD (Hsu et al., 2017; Haley et al., 2009). Hsu et al. (2017) utilized a hybrid estimation of $PM_{2.5}$ from monitoring data and CMAQ output, and reported a positive association with IHD in the greater New York City (NYC) region (including NYC, counties to the north of NYC, and Long Island), but null associations in the remaining regions of the state. Talbott et al. (2014) examined hospital admissions for IHD in seven U.S. states (Florida, Massachusetts, New Hampshire, New Jersey, New Mexico, New York, and Washington) and reported positive associations in New Jersey and New York, but not in the other five states. Neither Hsu et al. (2017) nor Talbott et al. (2014) presented pooled results across all study areas; however, inconsistent results between regions provide evidence of potential regional heterogeneity. In contrast to other large, multicity studies, an administrative database study across England and Wales observed a decrease in risk of hospitalizations for IHD corresponding to increasing $PM_{2.5}$ concentrations averaged over the previous 5 days (RR: 0.986, 95% CI: 0.975, 0.996), and in sensitivity analyses at lag 0−1 (quantitative results not presented) (Milojevic et al., 2014). Recent single-city studies were inconsistent in observing associations between $PM_{2.5}$ concentrations and IHD, with one study observing positive associations in Denver, CO (Kim et al., 2012) and another observing a null association in St. Louis, MO (Sarnat et al., 2015).

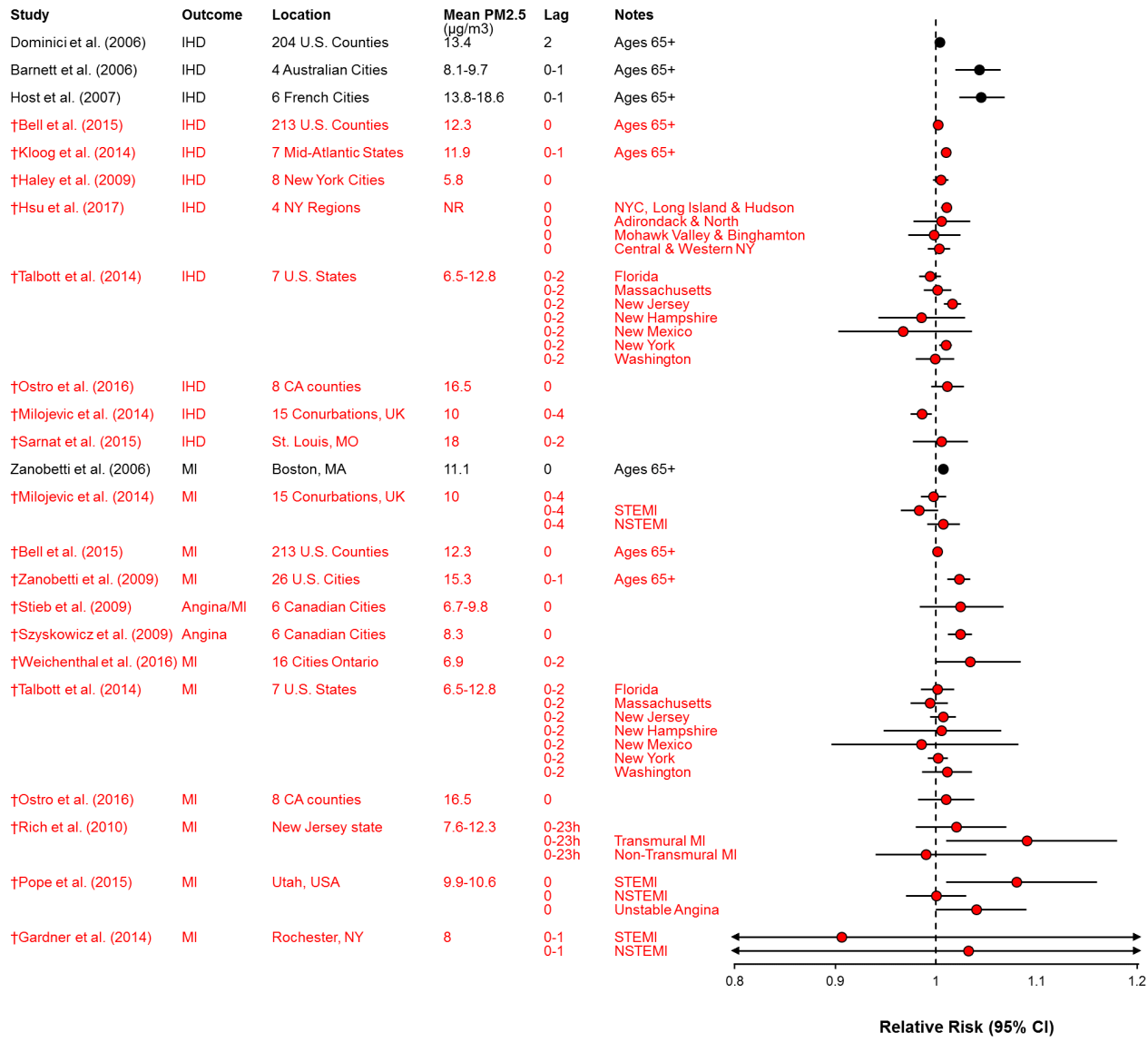
Overall, recent epidemiologic studies continue to provide evidence for positive associations between short-term $PM_{2.5}$ exposure and IHD ED visits and HA. Several recent studies used hybrid exposure assessment techniques incorporating both remote sensing and monitor data, allowing them to include study subjects that do not live near PM monitors, and addressing a previous source of uncertainty in these studies.

6.1.2.1.1 Emergency Department (ED) Visits and Hospital Admissions for Acute Myocardial Infarction (MI) and Angina Pectoris

A prevailing hypothesis in the literature is that $PM_{2.5}$ could be more strongly associated with the more specific outcome of MI as compared to studies considering the composite endpoint of IHD. In the 2009 PM ISA, a limited number of epidemiologic studies generally observed positive associations between $PM_{2.5}$ and MI, although not without some inconsistency in results across registry-based studies

(Sullivan et al., 2005; Peters et al., 2004; Peters et al., 2001). Recent studies evaluating the potential association between $PM_{2.5}$ and MI continue to provide evidence of a positive association based on additional administrative database and registry-based studies; however, some inconsistency in results still remains, and the evidence overall is less consistent when compared to associations between $PM_{2.5}$ and IHD.

Among recent investigations of MI, larger administrative database studies generally reported positive associations (Figure 6-2), using either $PM_{2.5}$ concentration estimates from local monitors or spatiotemporal models incorporating land use variables, AOD observations, and monitor measurements (Section 3.3, Table 6-1). Several U.S. studies reported positive associations at short lag periods (Ostro et al., 2016; Talbott et al., 2014; Zanobetti et al., 2009), with the notable exception of a large, nationwide Medicare study that observed null associations at lag 0 (Bell et al., 2015). Similarly, a study in England and Wales observed a negative association for MI (Milojevic et al., 2014) for a longer multi-day lag period (lag 0−4), and a null association for analyses at lag 0−1. It should also be noted that Talbott et al. (2014) observed some evidence of regional heterogeneity, with positive associations in three of the seven U.S. states. Meanwhile, recent multicity Canadian studies reported positive associations between short-term $PM_{2.5}$ exposure and ED visits and hospital admissions for MI (Weichenthal et al., 2016b; Stieb et al., 2009; Szyszkowicz, 2009) (Figure 6-2). Weichenthal et al. (2016b) also examined effect modification by city-level PM2.5 oxidative potential and observed an increasing association between $PM_{2.5}$ and MI as oxidative potential increased. Recent administrative studies of MI add to the limited number of studies from the 2009 PM ISA. Although not all studies observed positive associations, overall, recent administrative studies continue to provide evidence of a positive association between $PM_{2.5}$ and MI, particularly for immediate lag periods (see Section 6.2).



Note: †Studies published since the 2009 PM ISA. IHD = ischemic heart disease, MI = myocardial infarction, STEMI = ST segment elevation MI, NSTEMI = non-ST segment elevation MI, NR = not reported. Corresponding quantitative results are reported in Supplemental Table S6-1 (U.S. EPA, 2018).

Figure 6-2 Results of studies of short-term ambient $PM_{2.5}$ exposure and hospital admissions and emergency department visits for ischemic heart disease.

While these administrative-based studies generally observe positive associations between $PM_{2.5}$ and MI, smaller recent studies based on MI registries, which are thought to have less outcome misclassification compared to administrative data sets, have not consistently observed associations between $PM_{2.5}$ exposure and MI incidence (Pope et al., 2015; Gardner et al., 2014; Rich et al., 2010).

$PM_{2.5}$ exposure estimates from studies were based on either data from the nearest available monitoring station, or averages of measured concentrations from multiple monitors. This is consistent with the 2009 PM ISA, where registry-based MI studies reported inconsistent results for an association between $PM_{2.5}$ and MI; however, some inconsistency may be due to the type of event, as studies of ST segment elevation MI (STEMI) (Pope et al., 2015; Gardner et al., 2014) and transmural MI (Rich et al., 2010) reported positive associations, while null or negative associations were observed in studies of non-ST segment elevation MI (Pope et al., 2015; Gardner et al., 2014). In contrast, results from European studies, which had generally higher mean $PM_{2.5}$ concentrations, do not provide consistent evidence for an association between $PM_{2.5}$ and STEMI (Caussin et al., 2015; Claeys et al., 2015).

While the above studies reported inconsistent associations, recent meta-analyses by Mustafic et al. (2012) and Luo et al. (2015) reported overall associations between $PM_{2.5}$ and ED visits or hospital admissions for MI that were both positive and statistically significant. The magnitude of the association based on the meta-analytic summary estimates is on the order of 2% to 2.5% excess risk of ED visits and hospital admissions for MI.

In summary, several large studies published since the release of the 2009 PM ISA (U.S. EPA, 2009) provide continued support for an association between $PM_{2.5}$ exposure and ED visits or hospital admissions for IHD among study populations that generally had lower $PM_{2.5}$ exposures (Table 6-1) than those reported in the 2009 PM ISA. There were generally consistent results across recent studies looking specifically at MI, and registry studies, which are likely to reduce outcome misclassification, report evidence of positive associations with MI subtypes. The positive associations reported across these studies is supported by formal meta-analyses that document the presence of an association between $PM_{2.5}$ and MI. Additionally, few studies utilized modeled $PM_{2.5}$ concentrations to study a wider population, including rural populations. The rest of the studies conducted exposure assessment using a single monitor or an average of fixed-site monitors, which restricts the study population to people living near monitors. Consistent, positive associations across multicity and single-city studies continue to provide strong evidence for the relationship between short-term $PM_{2.5}$ and IHD that is unlikely to be driven by chance or systematic bias.

6.1.2.2 Panel Epidemiologic Studies of ST Segment Depression

The 2009 PM ISA reviewed a handful of panel studies investigating ST-segment changes in relation to short-term exposure to $PM_{2.5}$. These studies reported associations between 1 hour−2 days $PM_{2.5}$ concentrations and ST-segment depression. Since the 2009 PM ISA, two studies have examined potential changes in ST segment depression relative to $PM_{2.5}$ concentrations. In a study of 38 older adults with IHD in nursing homes in Los Angeles, CA, Delfino et al. (2011) observed that $PM_{2.5}$ concentrations averaged over 1 hour up to 4 days were associated with ST-segment depression ≥1.0 mm [OR 1.68 (95% CI: 1.20, 2.35) Notably, this association was attenuated in models including BC or primary OC, but remained

positive. In another study, Zhang et al. (2009) observed associations between $PM_{2.5}$ concentrations and ST-abnormality in the Women's Health Initiative at lag 0–2-days [4% (95% CI–3%, to 10%)]. Evidence from these recent studies further support results from the 2009 PM ISA. More information on these studies can be found in Table 6-2 below.

Table 6-2 Details from panel studies of ST segment depression.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI	Copollutant Examination
†Delfino et al. (2011) Los Angeles, CA 2005–2007	n = 38 nonsmoking older adults (≥65 yr) with history of coronary artery disease. Consecutive ECG monitoring for two 5-day periods in the warm and cool season (7,273 hours of measurements). Hourly diary during study periods. Recruited from 4 retirement communities.	Residential monitoring 24 h avg Mean (SD): 21.1 (11.4) Max: 77.4	ST-segment depression 1-day avg: 1.68 (1.20, 2.43) 2-day avg: 1.62 (1.08, 2.43)	Correlation (*r*) = 0.44 OC, 0.58 BC, 0.43 primary OC, 0.2 $PM_{0.25}$, 0.14 NO_X, 0.31 CO, 0.04 O_3 Copollutant models with: BC, OC.
†Zhang et al. (2009) 49 U.S. cities 1999–2003	Women's Health Initiative n = 55,529 postmenopausal women, 52–90 yr 52% with hypertension 20% with hypercholesterolemia	Kriging of fixed-site monitors for participants' geocoded address 24 hr avg Mean (SD): 13.9 (7)	Minnesota Code 4 (ST abnormalities) Lag 0–2: 1.04 (0.97, 1.10)	Correlation (*r*): NR

BC = black carbon, CO = carbon monoxide, O_3 = ozone, NO_2 = nitrogen dioxide, NO_X = oxides of nitrogen, OC = organic carbon, hr = hour, avg = average, SD = standard deviation, km = kilometer, ECG = electrocardiograph.

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

6.1.3 Heart Failure and Impaired Heart Function

HF refers to a set of conditions in which the heart's pumping action is weakened. In congestive heart failure (CHF), the flow of blood from the heart slows, failing to meet the oxygen demands of the body, and returning blood can back up, causing swelling or edema in the lungs or other tissues (typically in the legs and ankles). The effect of short-term $PM_{2.5}$ exposure on people with CHF—which is a chronic

condition—is generally evaluated using ICD codes recorded when a patient is admitted or discharged from the hospital or ED. The relevant diagnostic codes for heart failure are ICD9 428 and ICD10 I50. These codes encompass left, systolic, diastolic and combined heart failure (Section 6.2.5). In experimental studies, indicators of HF include decreased contractility and/or relaxation in response to pharmacological challenge, reduced ejection fraction (i.e., the percent of blood pumped from the ventricle during each contraction), and decreases in left ventricular developed pressure (LVDP). Effects on endpoints such as these are plausible given that there is evidence that short-term $PM_{2.5}$ exposure can result in a number of cardiovascular effects, including arrhythmia and increases in BP.

In the 2009 PM ISA, the majority of the evidence for HF was from epidemiologic studies of ED visits and HA. The strongest evidence for an association came from multicity studies in the U.S. (Dominici et al., 2006) and Australia (Barnett et al., 2006). Results from single-city studies reviewed in the 2009 PM ISA also provided supporting evidence of a positive association between short-term exposure to $PM_{2.5}$ and CHF-related ED visits and hospital admissions (Section 6.1.3.1). In the 2009 PM ISA, there was also limited evidence of decreased contractility in mice following exposure to carbon black, but not in studies using $PM_{2.5}$ CAPS.

Evidence from the current review strengthens the epidemiologic results reported in the 2009 PM ISA. Since the last review, multicity epidemiologic studies conducted in the U.S., Canada, and Europe generally report positive associations between short-term $PM_{2.5}$ exposure and ED visits and hospital admissions for HF. Additional evidence of these associations was also found in single-city studies, although these results tended to be more inconsistent. Supporting the ED visit and hospital admissions studies was a single toxicological study showing impaired contractility and LVDP following short-term $PM_{2.5}$ exposure.

6.1.3.1 Emergency Department Visits and Hospital Admissions

Numerous studies reviewed in the 2009 PM ISA provided evidence of positive associations between short-term $PM_{2.5}$ exposure and ED visits or hospital admissions for heart failure. The strongest evidence came from multicity studies in the U.S. (Dominici et al., 2006) and Australia (Barnett et al., 2006). Results from single-city studies reviewed in the 2009 PM ISA provided additional evidence of positive associations between $PM_{2.5}$ and CHF.

Since the 2009 PM ISA, a number of recent studies add to the available evidence and further support the presence of a positive association between short-term $PM_{2.5}$ exposure and ED visits and hospital admissions for heart failure (Table 6-3), including among study populations that had lower $PM_{2.5}$ exposures than populations in the 2009 PM ISA.

Table 6-3 Epidemiologic studies of short-term $PM_{2.5}$ exposure and congestive heart failure hospital admission and emergency department visits.

Study	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m^3	Copollutant Examination
Dominici et al. (2006) 204 U.S. Urban Counties (1999−2002) Age ≥65 yr	Monitors in county averaged Number NR. Study population reside an average of 5.9 miles from monitor. Median pairwise correlation between same-county monitors 0.91.	Heart Failure	13.4 (IQR 3.9) 75th: 15.2	Correlation (*r*): NA Copollutant models with: NA
Barnett et al. (2006) Four Australian Cities (1998−2001)	Monitors in city averaged 3 monitors Sydney, 2 monitors Melbourne and Perth, 1 monitor Brisbane.	Heart Failure	8.1 to 9.7 (NR) (across four cities) Max: 29.3 to 122.8 (across four cities)	Correlation (*r*): NA Copollutant models with: NA
†Bell et al. (2015) 213 U.S. Counties (1999−2010) Age ≥65 yr	Monitors in county averaged	Heart Failure	12.3 (NR) Max: 20.2	Correlation (*r*): NA Copollutant models with: NA
†Zanobetti et al. (2009) 26 U.S. Cities (2000−2003) Age ≥65 yr	Monitors in county averaged 1 to 4 monitors per county. Monitor data discarded if between-monitor correlation <0.8	Heart Failure	2-day avg: 15.3 (8.2) (across 26 cities)	Correlation (*r*): NA Copollutant models with: NA
†Talbott et al. (2014) Seven U.S. States (2001−2009)	Fused-CMAQ CMAQ model combined with monitoring data, downscaled to Census Tract resolution.	Heart Failure	6.46 to 12.83 (2.55 to 7.66) (across seven states) 75th: 7.64 to 16.55 (across seven states)	Correlation (*r*): NA Copollutant models with: O_3
†Hsu et al. (2017) Four New York Regions (1991−2006)	Adjusted CMAQ-simulated model (see Hogrefe et al. (2009)) 12 × 12 km grid resolution with patient residential address	Heart Failure	Graphically reported only	Correlation (*r*): NA Copollutant models with: NA

Table 6-3 (Continued): Epidemiologic studies of short-term $PM_{2.5}$ exposure and congestive heart failure hospital admission and emergency department visits.

Study	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m³	Copollutant Examination
†Haley et al. (2009) Eight New York Cities (2001−2005)	Weighted averages across monitors in each city; 39 monitors in total.	Heart Failure	5.8 (IQR 5.9) 75th: 8.0 Max: 42.2	Correlation (*r*): NA Copollutant models with: NA
†Ostro et al. (2016) Eight California Counties (2005−2009)	Nearest monitor Within 20 km of population-weighted centroid of zip code	Heart Failure	Overall mean: 16.5 (IQR: 11.4) (across 8 counties)	Correlation (*r*): NA Copollutant models with: NA
†Stieb et al. (2009) Six Canadian Cities (1992−2003)	Monitors in city averaged. 1 monitor Halifax, Ottawa, Vancouver, 3 Edmonton, 7 Montreal, and Toronto	Heart Failure	6.7 to 9.8 75th: 8.5 to 11.3	Correlation (*r*): O_3: −0.05−0.62; NO_2: 0.27−0.51; SO_2: 0.01−0.55; CO: 0.01−0.42 Copollutant models with: NA
†Milojevic et al. (2014) 15 Conurbations in England and Wales (2003−2009)	Nearest monitor to patient's residence (50 km). Number NR.	Heart Failure	Median: 10.0 (IQR 8.0) 75th: 15.0	Correlation (*r*): CO: 0.48; NO_2: 0.53, O_3: −0.10; PM10: 0.86, SO_2: 0.41 Copollutant models with: NA
Rodopoulou et al. (2015) Central Arkansas, U.S. (2002−2012)	Single monitor - NCore site (AQS # 05-119-0007)	Heart Failure and Hypertensive Heart Disease	12.4 75^{th}: 15.6	Correlation (*r*): NA Copollutant models with: O_3
Sarnat et al. (2015) St. Louis, MO – Illinois Metropolitan Area (2001−2003)	Monitors in metropolitan area averaged; 13 monitors in total	Heart Failure	18.0	Correlation (*r*): CO: 0.25; NO_2: 0.35, O_3: 0.23; SO_2: 0.08 Copollutant models with: CO, NO_2, O_3, SO_2

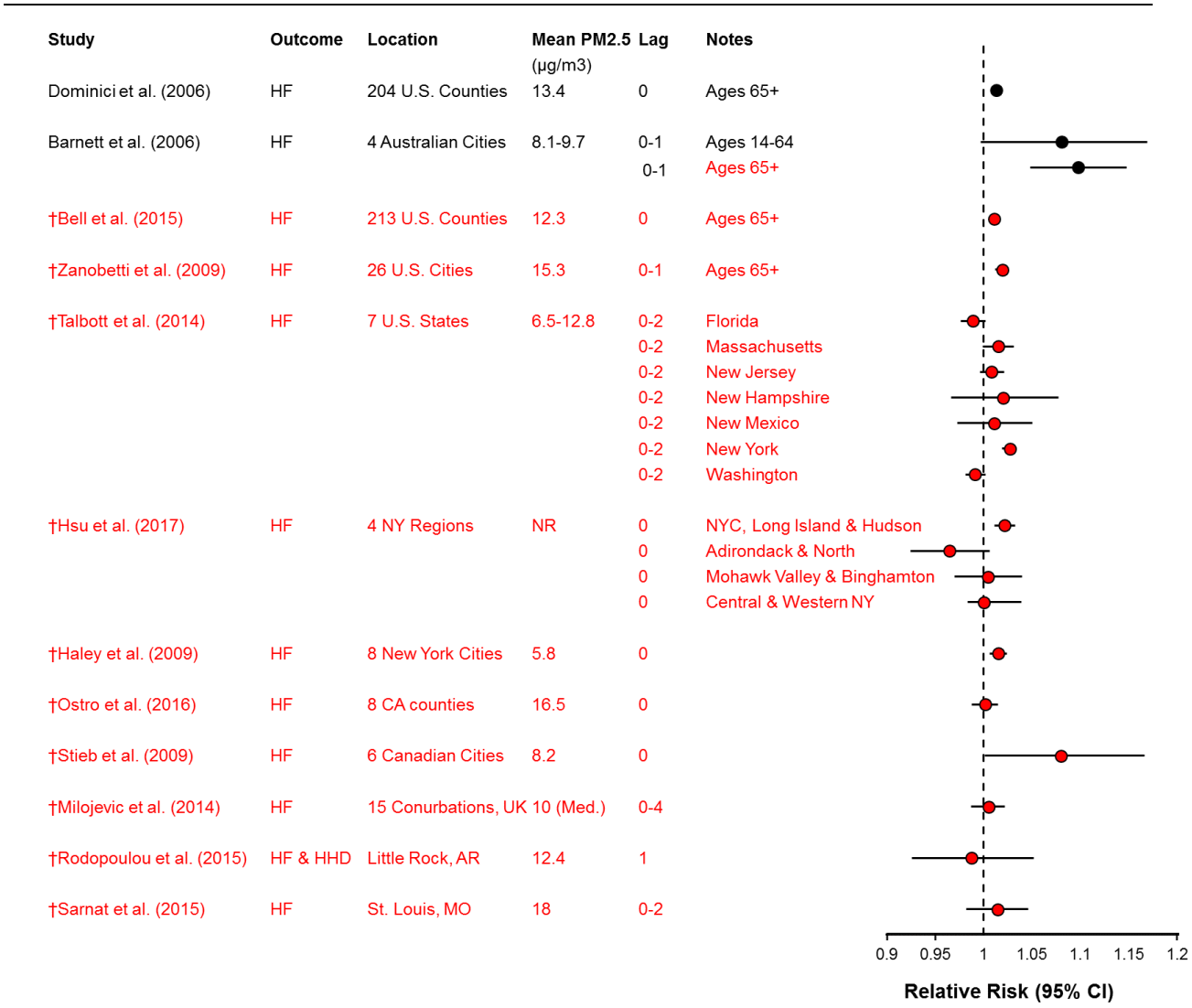
CMAQ = Community Multiscale Air Quality Modeling System, CO = carbon monoxide, HR = hazard ratio, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, OR = odds ratio, $PM_{2.5}$ = particulate matter with mean aerodynamic diameter 2.5 µm, PM_{10} = particulate matter with mean aerodynamic diameter 10 µm, $PM_{10-2.5}$ = particulate matter with mean aerodynamic diameter between 2.5 µm and 10 µm, RR = relative risk, SO_2 = sulfur dioxide.

†Studies published since the 2009 PM ISA.

For the included epidemiologic studies, the focus is on those studies conducted in areas where mean $PM_{2.5}$ concentrations are <20 µg/m³ or in the case of a multi-city study where more than half of the cities have concentrations <20 µg/m³. Other studies maybe be included if they contribute to evaluating important uncertainties (see Preface).

Several recent multicity studies in the U.S., Canada, and Europe examined the relationship between $PM_{2.5}$ and ED visits and hospital admissions for heart failure and generally observed positive associations (Figure 6-3). Two large Medicare studies (Bell et al., 2015; Zanobetti et al., 2009) observed similar estimates to those published by Dominici et al. (2006), reporting a 1.1% (95% CI: 0.8, 1.5%) and 1.9% (95% CI: 1.2, 2.5%) increase in HA, respectively. Talbott et al. (2014) examined hospital

admissions in seven U.S. states and, though they did not pool their results, they observed positive associations between hospital admissions for heart failure and $PM_{2.5}$ concentrations on the same day in Massachusetts, New Jersey, and New York, but not in New Hampshire, Washington, New Mexico, or Florida. Similarly, another large administrative data study in New York, which estimated $PM_{2.5}$ exposures using a hybrid of both monitored $PM_{2.5}$ data and modeled $PM_{2.5}$ estimates, reported a positive association with heart failure in the greater NYC region, but null associations throughout the remainder of the state (Hsu et al., 2017). The observed differences in effect estimates within or between states in Talbott et al. (2014) and Hsu et al. (2017) indicates the potential for regionally heterogeneous associations. Smaller multicity studies in New York (Haley et al., 2009), California (Ostro et al., 2016), and Canada (Stieb et al., 2009) reported positive associations between $PM_{2.5}$ exposure and ED visits and hospital admissions for heart failure, ranging from 1.1% to 8.0% increases in ED visits and HA. In contrast, a study of hospital admissions for heart failure in England and Wales reported a null association between short-term $PM_{2.5}$ exposure and heart failure (Milojevic et al., 2014).



Note: †Studies published since the 2009 PM ISA. HF = heart failure, HHD = hypertensive heart disease, NR = not reported. Corresponding quantitative results are reported in Supplemental Table S6-4 (U.S. EPA, 2018).

Figure 6-3 Results of studies of short-term ambient $PM_{2.5}$ concentrations and hospital admissions and emergency department visits for heart failure.

In summary, recent multicity studies, along with studies published in the 2009 PM ISA, provide continued evidence for an association between short-term $PM_{2.5}$ exposure and ED visits and hospital admissions for heart failure, including among study populations with generally lower $PM_{2.5}$ concentrations than those in the previous ISA (Table 6-3). Several studies conducted exposure assessment using a single monitor or an average of fixed-site monitors, which restricts the study population to people living near monitors, and may result in exposure misclassification due to spatial variation of $PM_{2.5}$;

however, consistent positive associations across multicity and single-city studies continues to provide strong evidence for an association between short-term $PM_{2.5}$ and CHF that is unlikely to be driven by chance or systemic bias.

6.1.3.2 Controlled Human Exposure Studies of Impaired Heart Function

In the 2009 PM ISA, there were no CHE studies examining the effect of short-term exposure to $PM_{2.5}$ on impaired heart function. Since the publication of that document, Vieira et al. (2016b) have reported that in both exercising heart failure and control patients, short-term exposure to DE results statistically significant ($p < 0.05$) decreases in estimates of left ventricular stroke volume (i.e., the amount of blood the left ventricle pumps per beat). The authors also reported that particle filtration of DE attenuated this effect in both groups. More information on studies published since the 2009 ISA can be found in Table 6-4 below.

Table 6-4 Study-specific details from controlled human exposure (CHE) studies of short-term $PM_{2.5}$ exposure and impaired heart function.

Study	Population	Exposure Details	Endpoints Examined
(Vieira et al., 2016b)	Healthy adults n = 8 M, 7 F; 45 ± 10 yr; 7 with a history of smoking HF patients n = 16 M, 10 F; 51 ± 9 yr; 19 white; 17 with a history of smoking	325 ± 31 µg/m^3 $PM_{2.5}$ DE generated from a diesel engine and conditioned through a refrigerated metal retainer 25 ± 6 µg/m3 $PM_{2.5}$ filtered DE 21 min total exposure, 15 at rest and 6 while walking	O_2 pulse as a surrogate for stroke volume during 6 min walking exposure

DE = diesel Exhaust, F = female, HF = heart failure, M = male, n = number, O_2 = Oxygen SD = standard deviation.

6.1.3.3 Toxicology Studies of Impaired Heart Function

In the 2009 PM ISA (U.S. EPA, 2009), a study found decreased contractility after exposure to carbon black in mice (Yan et al., 2008). Since the 2009 PM ISA, Kurhanewicz et al. (2014) demonstrated that in mice, short-term $PM_{2.5}$ exposure statistically significantly decreased ($p < 0.05$) LVDP and contractility compared to filtered air controls. However, a separate study did not report cardiac gene expression consistent with cardiac damage (Aztatzi-Aguilar et al., 2015) following short-term $PM_{2.5}$ exposure in rats. Taken together, there is some additional evidence from more recent toxicological studies

that short-term exposure to $PM_{2.5}$ may result in impaired heart function in mice. More information on studies published since the 2009 ISA can be found in Table 6-5 below.

Table 6-5 Study-specific details from toxicological studies of short-term $PM_{2.5}$ exposure and impaired heart function.

Study	Population	Exposure Details	Endpoints Examined
(Kurhanewicz et al., 2014)	C57BL/6 mice; F, n = 5−8 per treatment group	Inhalation of 190 μg/m^3 $PM_{2.5}$ for 4 h from Research Triangle Park, NC	LVDP and contractility 24 h post
(Aztatzi-Aguilar et al., 2015)	Adult Sprague-Dawley rats, M, n = 4 per treatment group	Inhalation of 178 μg/m^3 $PM_{2.5}$ for 5 h/day for 3 days from a high traffic and industrial area north of Mexico City in early summer	Gene expression consistent with cardiac damage (Acta1 and Col3a1) in heart tissue collected 24 h post

Acta1 = skeletal alpha-actin, Col3a1 = collagen Type 3 alpha, d = day, f = female, h = hour, M = male, n = number, LVDP = left ventricular developed pressure.

6.1.4 Cardiac Electrophysiology, Arrhythmia, and Cardiac Arrest

In epidemiologic studies, the effect of short-term $PM_{2.5}$ exposure on arrhythmia is generally evaluated using ICD codes for ED visits, HA, and out-of-hospital cardiac arrests (OHCA) that typically result from ventricular arrhythmia. In addition, there is a body of epidemiologic studies that examine arrhythmias recorded on implantable cardiodefibrillators.

Experimental and epidemiologic panel studies typically use surface ECGs to measure electrical activity in the heart resulting from depolarization and repolarization of the atria and ventricles. The *P* wave of the ECG represents atrial depolarization, while the QRS represents ventricular depolarization and the T wave, ventricular repolarization. Because the ventricles account for the largest proportion of heart mass overall and thus are the primary determinants of the electrical activity recorded in the ECG, ECG changes indicating abnormal electrical activity in the ventricles are of greatest concern. Such endpoints denoting ventricular electrical activity include QTc interval, transmural dispersion (Tp-Te) duration, and T-wave shape. Changes in QTc, RT, and/or Tp-Te duration as wells as changes in T-wave shape and amplitude may be indicative of abnormal impulse propagation in the ventricles. Effects on these endpoints are plausible given that exposure to PM is associated with changes in cardiac autonomic tone and systemic inflammatory responses that may in turn influence cardiac ion channels, adrenergic and cholinergic receptors and gap junction proteins, all of which contribute to normal impulse conduction in heart muscle (Brook et al., 2004). Cardiac arrhythmias can vary in severity from the benign to the potentially lethal as in cardiac arrest, which causes loss of heart function and results from an electrical disturbance that disrupts the heart's pumping action.

In the 2009 PM ISA, results from studies of arrhythmia-related hospitalizations was limited. Since the publication of the 2009 PM ISA, evidence of arrhythmia-related hospitalizations remains limited. However, there is some evidence from epidemiologic panel studies of an association between short-term $PM_{2.5}$ exposure and potential indicators of arrhythmia. Moreover, both CHE and animal toxicological studies provide some evidence that $PM_{2.5}$ exposure influences the electrical activity of the heart.

With respect to OHCA, the 2009 PM ISA reviewed a handful of small studies examining the association between $PM_{2.5}$ exposure and OHCA. Each of these studies reported no evidence of an association between short-term $PM_{2.5}$ exposure and OHCA. Since the publication of the 2009 PM ISA, additional ED visit and hospital admissions studies with substantially larger populations have evaluated the relationship between short-term $PM_{2.5}$ exposure and OHCA. In contrast to the studies from the previous review, recent studies have reported generally positive associations between short-term $PM_{2.5}$ exposure and OHCA. That being said, potential copollutant confounding remains an uncertainty in these studies.

6.1.4.1 Emergency Department Visits and Hospital Admissions for Arrhythmia and Out-of-Hospital Cardiac Arrest

A number of studies based on administrative databases have sought to evaluate the association between short-term $PM_{2.5}$ exposure and HAs for cardiac arrhythmias (also known as dysrhythmias). In these studies, a primary discharge diagnosis of ICD-9 427 has typically been used to identify hospitalized patients. ICD-9 427 includes a heterogeneous group of arrhythmias including paroxysmal ventricular or supraventricular tachycardia, atrial fibrillation and flutter, ventricular fibrillation and flutter, cardiac arrest, premature beats, and sinoatrial node dysfunction.

6.1.4.1.1 Arrhythmias

In the 2009 PM ISA, studies of arrhythmia-related hospital admissions reported inconsistent results and most studies provided little evidence of an association. The multicity U.S. MCAPS study observed a modest increase (0.6% [95% CI: 0.0−1.2%]) in hospital admissions for the combined outcome of cardiac arrhythmias and conduction disorders (Dominici et al., 2006). However, a multicity study in Australia and New Zealand (Barnett et al., 2006) and a study in Atlanta, GA (Metzger et al., 2004) observed null associations between arrhythmia ED visits and hospital admissions and $PM_{2.5}$ exposure. Since the publication of the 2009 PM ISA, recent studies continue to provide inconsistent evidence of an association between $PM_{2.5}$ and arrhythmia-related hospital admissions (Table 6-6).

Table 6-6 Epidemiologic studies of short-term $PM_{2.5}$ exposure and cardiac arrhythmia hospital admission and emergency department visits.

Study	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m³	Copollutant Examination
Dominici et al. (2006) 204 U.S. Urban Counties (1999−2002) Age ≥65 yr	Monitors in county averaged Number NR. Study population reside an average of 5.9 miles from monitor. Median pairwise correlation between same-county monitors 0.91.	Arrhythmia	13.4 (IQR 3.9) 75th: 15.2	Correlation (*r*): NA Copollutant models with: NA
†Bell et al. (2015) 213 U.S. Counties (1999−2010) Age ≥65 yr	Monitors in county averaged	Heart Rhythm Disturbance	12.3 Max: 20.2	Correlation (*r*): NA Copollutant models with: NA
†Talbott et al. (2014) Seven U.S. States (2001−2009)	Fused-CMAQ CMAQ model combined with monitoring data, downscaled to Census Tract resolution.	Arrhythmia	6.46 to 12.83 (across seven states) 75th: 7.64 to 16.55 (across seven states)	Correlation (*r*): NA Copollutant models with: O_3
†Hsu et al. (2017) Four New York Regions (1991−2006)	Adjusted CMAQ-simulated model (see Hogrefe et al. (2009)) 12 × 12 km grid resolution with patient residential address	Arrhythmia	Graphically reported only	Correlation (*r*): NA Copollutant models with: NA
†Milojevic et al. (2014) 15 Conurbations in England and Wales (2003−2009)	Nearest monitor to patient's residence (50 km). Number NR.	Arrhythmia Atrial Fibrillation	Median: 10.0 (IQR 8.0) 75th: 15.0	Correlation (*r*): CO: 0.48, NO_2: 0.53, O_3: −0.10, PM_{10}: 0.86, SO_2: 0.41 Copollutant models with: NA
†Stieb et al. (2009) Six Canadian Cities (1992−2003)	Monitors in city averaged. 1 monitor Halifax, Ottawa, Vancouver, 3 Edmonton, 7 Montreal, and Toronto	Arrhythmia	6.7 to 9.8 75th: 8.5 to 11.3	Correlation (*r*): O_3: −0.05−0.62; NO_2: 0.27−0.51; SO_2: 0.01−0.55; CO: 0.01−0.42 Copollutant models with: NA
†Haley et al. (2009) Eight New York Cities (2001−2005)	Weighted averages across monitors in each city 39 monitors in total.	Rhythm/Conduction	5.8 (IQR 5.9) 75th: 8.0 Max: 42.2	Correlation (*r*): NA Copollutant models with: NA

Table 6-6 (Continued): Epidemiologic studies of short-term $PM_{2.5}$ exposure and cardiac arrhythmia hospital admission and emergency department visits.

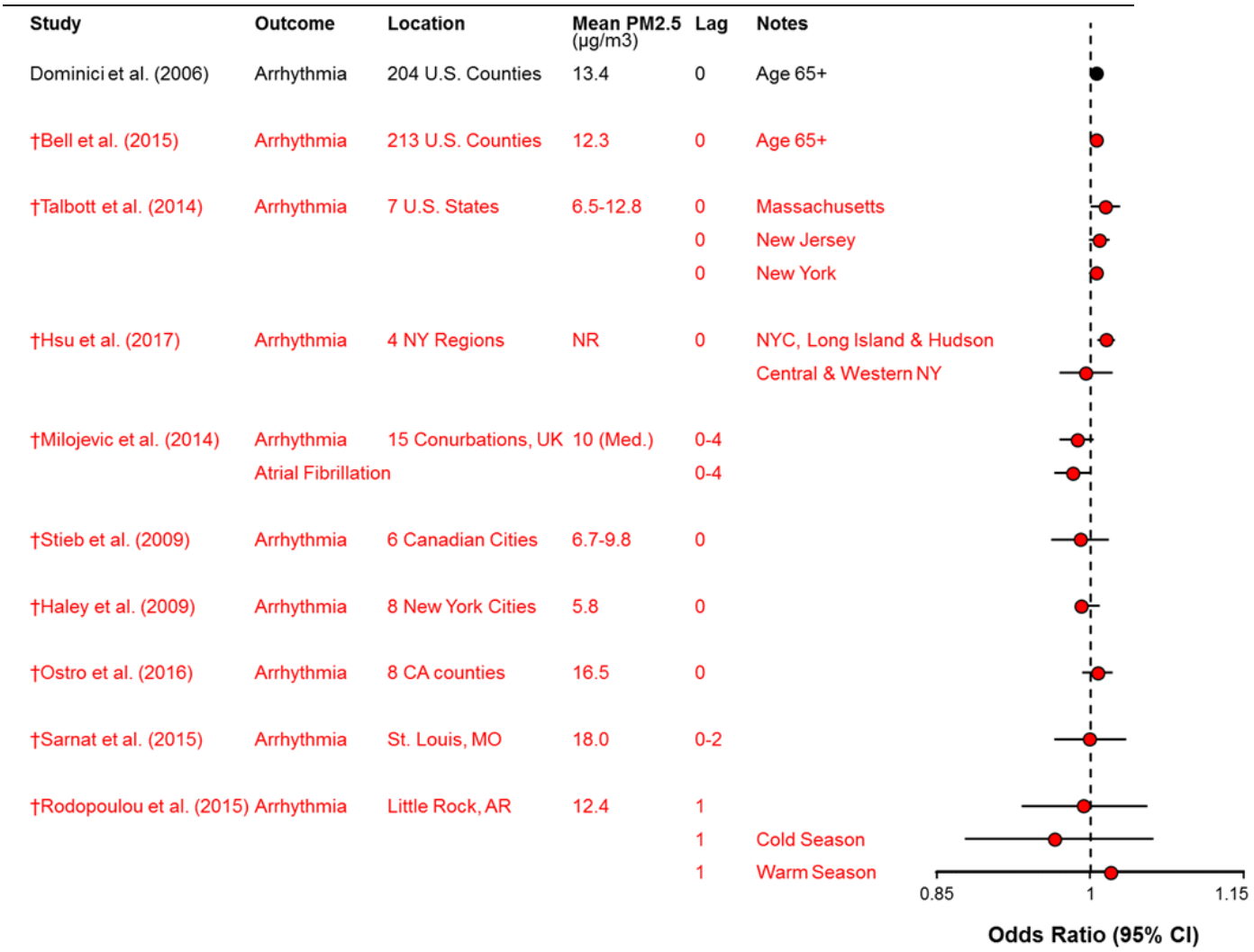
Study	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m³	Copollutant Examination
†Ostro et al. (2016) Eight California Counties (2005−2009)	Nearest monitor Within 20 km of population-weighted centroid of zip code	Arrhythmia	Overall mean: 16.5 (IQR: 11.4) (across 8 counties)	Correlation (*r*): NA Copollutant models with: NA

CMAQ = Community Multiscale Air Quality Modeling System, CO = carbon monoxide, HR = hazard ratio, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, OR = odds ratio, $PM_{2.5}$ = particulate matter with mean aerodynamic diameter 2.5 µm, PM_{10} = particulate matter with mean aerodynamic diameter 10 µm, $PM_{10-2.5}$ = particulate matter with mean aerodynamic diameter between 2.5 µm and 10 µm, RR = relative risk, SO_2 = sulfur dioxide.

†Studies published since the 2009 PM ISA. For the included epidemiologic studies, the focus is on those studies conducted in areas where mean $PM_{2.5}$ concentrations are <20 µg/m³ or in the case of a multi-city study where more than half of the cities have concentrations <20 µg/m³. Other studies maybe be included if they contribute to evaluating important uncertainties (see Preface).

Several multicity studies in the U.S., Canada, and Europe examined the relationship between $PM_{2.5}$ exposure and arrhythmia-related ED visits and hospital admissions and observed inconsistent associations (Figure 6-4). Similar to the U.S. MCAPS study by Dominici et al. (2006), Bell et al. (2015) reported a positive increase (0.6% [95% CI: 0.3−1.0%]) in risk of hospitalization for heart rhythm disturbance (ICD 426, 427) among Medicare beneficiaries. Talbott et al. (2014) also examined hospital admissions for arrhythmias in seven U.S. states and, though they did not pool their results, they observed evidence of positive associations on the same day in Massachusetts, New Jersey, and New York. Another large administrative data study in New York, using a hybrid estimation of $PM_{2.5}$ exposure combining monitor data and model predictions, reported a positive association with arrhythmia hospital admissions in the NYC region, but null and imprecise associations (i.e., wide 95% CI; Figure 6-4) in the other three NY regions (Hsu et al., 2017). Conversely, Milojevic et al. (2014) considered arrhythmia HAs in England and Wales and observed negative associations with $PM_{2.5}$ concentrations. However, it's possible that the examined lag period (lag 0−4) was long, and could have diluted any immediate effect, as the authors conducted a sensitivity analysis and reported that arrhythmia hospital admissions were positively associated with $PM_{2.5}$ exposure at lag 0−1 (quantitative results not presented). Additional multicity studies in Canada Stieb et al. (2009), New York (Haley et al., 2009), and California (Ostro et al., 2016) also reported null or negative associations.

Results from single-city studies in the U.S. were also inconsistent, with some studies reporting generally null associations (Rodopoulou et al., 2015; Sarnat et al., 2015), while another study observed a positive association (quantitative results not presented (Bunch et al., 2011)). In whole, recent evidence continues to provide inconsistent evidence of an association between short-term in $PM_{2.5}$ exposure and ED visits and hospital admissions for arrhythmias.



Note: †Studies published since the 2009 PM ISA. NR = not reported. Corresponding quantitative results are reported in Supplemental Table S6-6 (U.S. EPA, 2018).

Figure 6-4 Results of studies of short-term $PM_{2.5}$ exposure and hospital admissions and emergency department visits for arrhythmia.

6.1.4.1.2 Out-of-Hospital Cardiac Arrest

The majority of out-of-hospital cardiac arrests (OHCA) are due to cardiac arrhythmias. The 2009 PM ISA reviewed several studies examining the association between $PM_{2.5}$ and OHCA (Rosenthal et al., 2008; Sullivan et al., 2003; Levy et al., 2001). Two of these studies were conducted in Seattle and reported no evidence of an association between $PM_{2.5}$ and OHCA (Sullivan et al., 2003; Levy et al., 2001). The third, a study in Indianapolis, Indiana did not observe an association with $PM_{2.5}$ (Rosenthal et al., 2008). However, Rosenthal et al. (2008) did find a positive association between hourly $PM_{2.5}$ and the subset of events that were witnessed by bystanders, which potentially reduces misclassification of

outcome in regard to cause and timing. Since the publication of the 2009 PM ISA, a number of additional studies have been published on $PM_{2.5}$ and OHCA. The recent literature reports consistent, positive associations between short-term exposure to $PM_{2.5}$ and risk of OHCA (Table 6-7).

Table 6-7 Epidemiologic studies of short-term $PM_{2.5}$ exposure and out-of-hospital cardiac arrest.

Study	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m³	Effect Estimates[a] 95% CI	Copollutant Examination
Sullivan et al. (2003) Seattle, Washington (1985−1994)	Monitors in city averaged 3 monitors; R^2 = 0.85.	OHCA	(0.71 × 10−1 km −1 bsp) IQR: 13.8 µg/m³	OR Lag 0: 0.96 (0.91, 1.01) Lag 1: 0.96 (0.91, 1.01) Lag 2: 1.00 (0.95, 1.06)	Correlation (*r*): NA Copollutant models with: NA
Levy et al. (2001) Seattle, Washington (1988−1994) Age 25−75 yr Married and in-person interview	Monitors in city averaged 3 monitors R^2 to $PM_{2.5}$ = 0.85.	OHCA	18.4 (NR) 75th: 23.0 Max: 96.0	RR Lag 1: 0.91 (0.93, 1.02)	Correlation (*r*): NA Copollutant models with: NA
Rosenthal et al. (2008) Indianapolis, Indiana (2002−2006)	1 monitor 2002 data from separate monitor. R^2 = 0.87.	OHCA	Median: 13.9 75th: 19.5 90th: 25.8	HR All OHCA Lag 0: 1.02 (0.94, 1.11) Witnessed OHCA (n = 511) Lag 0: 1.12 (1.01, 1.25)	Correlation (*r*): NA Copollutant models with: NA

Table 6-7 (Continued): Epidemiologic studies of short-term $PM_{2.5}$ exposure and out-of-hospital cardiac arrest.

Study	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m³	Effect Estimates[a] 95% CI	Copollutant Examination
†Ensor et al. (2013) Houston, Texas (2004−2011) Age ≥18 yr	Monitors in city averaged 12 monitors	OHCA	1 h avg: 11.42 (5.98) 75th: 14.37 95th: 22.8 11.42 (4.73) 75th: 13.71 95th: 20.96	RR Hourly Lag Lag 0: 1.015 (0.977, 1.057) Lag 1: 1.018 (0.978, 1.059) Daily Lag Lag 0−1: 1.066 (1.008, 1.126) Lag 1−2: 1.078 (1.020, 1.140)	Correlation (*r*): NO_2: 0.24, SO_2: 0.05, CO: 0.34, O_3: 0.01 Copollutant models with: NA
†Silverman et al. (2010) New York, New York (2002−2006)	Monitors in city averaged 33 monitors located within 32 km radius of NYC center	OHCA	Median: 12 IQR: 10 75th: 18 95th: 30	RR Case-Crossover; Lag 0−1 All Year: 1.04 (0.99, 1.08) Warm: 1.08 (1.02, 1.15) Cold: 0.99 (0.93, 1.06) Time-Series; Lag 0−1 All Year: 1.06 (1.02, 1.10) Warm: 1.09 (1.03, 1.15) Cold: 1.01 (0.95, 1.07)	Correlation (*r*): Warm season: NO_2: 0.77, SO_2: 0.66, CO: 0.67, O_3: −0.43; Cold season: NO_2: 0.54, SO_2: 0.51, CO: 0.40, O_3: 0.63 Copollutant models with: NA
†Dennekamp et al. (2010) Melbourne, Australia (2003−2006) Age ≥35 yr	1 monitor	OHCA	6.35 IQR: 4.26 75th: 7.45	RR Lag 0: 1.058 (1.013, 1.106) Lag 1: 1.059 (1.008, 1.113) Lag 0−1: 1.087 (1.031, 1.146)	Correlation (*r*): NO_2: 0.49, O_3: 0.13, CO: 0.55 Copollutant models with: NO_2, O_3, CO
†Raza et al. (2014) Stockholm, Sweden (2000−2010)	Monitors in city averaged Number NR.	OHCA	8.1 IQR: 4.81 Max: 161.7	No quantitative results presented; results presented graphically. No association between $PM_{2.5}$ and OHCA (OR ~1.00).	Correlation (*r*): NO_2: 0.24, O_3 (urban): 0.17, O_3 (rural): 0.25, $PM_{10-2.5}$: 0.19 Copollutant models with: NA

Table 6-7 (Continued): Epidemiologic studies of short-term $PM_{2.5}$ exposure and out-of-hospital cardiac arrest.

Study	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m³	Effect Estimates[a] 95% CI	Copollutant Examination
†Rosenthal et al. (2013) Helsinki, Finland (1998−2006)	2 monitors Data for 1999−2006 from Kallio site (urban background, nearest road >80 m), while for 1998 Vallila site used (near major urban road). Correlation between Kallio and Vallila 0.83.	OHCA	1-h avg: 8.7 IQR: 7.7	OR All Cardiac Causes Lag 0 h: 1.09 (1.01, 1.17) Lag 1 h: 1.08 (1.01, 1.16) Lag 0 days: 1.09 (1.00, 1.20) Lag 0−3 days: 1.07 (0.95, 1.21) MI Caused OHCA Lag 0 h: 1.19 (1.04, 1.36) Lag 1 h: 1.19 (1.04, 1.35) Lag 0 days: 1.23 (1.04, 1.45) Lag 0−3 days: 1.15 (0.91, 1.43)	Correlation (*r*): <0.6 for $PM_{10-2.5}$, UFP, SO_2, O_3, CO, NO, and NO_2. Copollutant models with: $PM_{10-2.5}$, UFP, SO_2, O_3, CO, NO, and NO_2.
†Straney et al. (2014) Perth, Australia (2000−2010) Age ≥35 yr	Nearest monitor to arrest location. 4 available $PM_{2.5}$ monitors.	OHCA	1-h avg Median: 6.8 75th: 9.8 95th: 17.7	OR Lag 0−8 h: 1.06 (1.00, 1.12) Lag 0−12 h: 1.07 (1.01, 1.14) Lag 0−24 h: 1.09 (1.02, 1.17) Lag 0−48 h: 1.11 (1.01, 1.20)	Correlation (*r*): NA Copollutant models with: NA
†Wichmann et al. (2013) Copenhagen, Denmark (2000−2010)	1 monitor Restricted to cases ~5 km of monitor.	OHCA	10.16 75th: 11.57	RR Lag 2: 1.049 (0.964, 1.141) Lag 3: 1.090 (1.004, 1.184) Lag 4: 1.107 (1.020, 1.199)	Correlation (*r*): NO_X: 0.37, NO_2: 0.40, O_3: 0.11, CO: 0.37, UFP: 0.34, $PM_{10-2.5}$: 0.10 Copollutant models with: O_3

CMAQ = Community Multiscale Air Quality Modeling System, CO = carbon monoxide, HR = hazard ratio, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, OHCA = out-of-hospital cardiac arrest, OR = odds ratio, $PM_{2.5}$ = particulate matter with mean aerodynamic diameter 2.5 µm, PM_{10} = particulate matter with mean aerodynamic diameter 10 µm, $PM_{10-2.5}$ = particulate matter with mean aerodynamic diameter between 2.5 µm and 10 µm, RR = relative risk, SO_2 = sulfur dioxide.

†Studies published since the 2009 PM ISA. For the included epidemiologic studies, the focus is on those studies conducted in areas where mean $PM_{2.5}$ concentrations are <20 µg/m³ or in the case of a multi-city study where more than half of the cities have concentrations <20 µg/m³. Other studies maybe be included if they contribute to evaluating important uncertainties (see Preface).

A number of recently published studies report positive associations between $PM_{2.5}$ exposure and OHCA in the United States, Europe, and Australia. In the U.S., Ensor et al. (2013) and Silverman et al. (2010) observed positive associations in Houston, Texas (lag 0−1, lag 1−2) and New York City (lag 0−1), respectively (see Table 6-7). In Australia, Dennekamp et al. (2010) reported an 8.7% (95% CI: 3.1, 14.6%) increase in OHCA in Melbourne, while Straney et al. (2014) also observed a positive association in Perth (OR: 1.11, 95% CI: 1.01, 1.20; lag 0−48 hours). European studies also observed positive associations in Copenhagen, Denmark (e.g., RR: 1.090, 95% CI: 1.004, 1.184; lag 3) (Wichmann et al., 2013) and Helsinki, Finland (e.g., OR: 1.09, 95% CI: 1.00, 1.20; lag 0) (Rosenthal et al., 2013) (see Table 6-7). However, a study in Stockholm, Sweden found no evidence of an association (quantitative results not presented) (Raza et al., 2014). The study by Rosenthal et al. (2013) in Helsinki additionally considered whether associations differ depending on the type of OHCA, specifically comparing those due to myocardial infarction to those due to other cardiac causes. They found that $PM_{2.5}$ was more strongly associated with OHCA presumed to be due to myocardial infarction.

In summary, the current state of the literature provides evidence for an association between short-term $PM_{2.5}$ exposure and OHCA. This association is typically observed with $PM_{2.5}$ concentrations averaged over the past 0 to 2 days, although associations with $PM_{2.5}$ concentrations as far back as 4 days prior to the event have been reported. Additionally, all of the studies in this section relied on a single monitor or an average of fixed-site monitors to estimate $PM_{2.5}$ exposure, which restricts the study population to people living near monitors, a limitation identified in the 2009 PM ISA, that persists when the recent body of evidence is included.

6.1.4.2 Panel Epidemiologic Studies for Arrhythmia and Conduction Abnormalities

The body of evidence examining the relationship between ventricular arrhythmias and short-term exposures to $PM_{2.5}$ is small and limited to studies that were evaluated in the 2009 PM ISA (U.S. EPA, 2009). These studies included patients with implantable cardioverter defibrillators (ICDs) and examined associations between ICD-detected arrhythmic events and $PM_{2.5}$ exposures. Generally, there were inconsistent results across study cohorts, with some evidence for positive associations in studies conducted in Boston using 1 or 2-day averages of $PM_{2.5}$. However, results from other studies did not demonstrate a consistent relationship between short-term $PM_{2.5}$ exposures and ventricular arrhythmias.

No recently published panel studies are available to inform the relationship between ventricular arrhythmia and $PM_{2.5}$ exposures; however, there is new evidence for other types of arrhythmic measures including ectopy and atrial fibrillation. Several panel studies used ECG measurements to examine for the presence of ectopic beats or tachycardia, which are often benign but can indicate greater risk for more serious arrhythmias, particularly when heart disease is present.

As in the 2009 PM ISA (U.S. EPA, 2009), recent studies have generally found positive associations between ectopic measures and short-term PM2.5 exposures (Table 6-8). Among a large cohort of older men in the Boston, MA area included in the Normative Ageing Study, positive associations were observed between 2- and 4-day averages of $PM_{2.5}$ predictions, obtained from a geospatial model incorporating AOD observations and surface monitoring $PM_{2.5}$ data, and arrhythmia measured as ventricular ectopy (bigeminy, trigeminy or couplet episodes) (OR of 1.45 (95% CI: 1.08, 1.96) and 1.79 [95% CI: 1.22, 2.59]) (Zanobetti et al., 2014a). Similarly, in a study of nursing home residents with coronary artery disease in Los Angeles, CA, ventricular tachycardia was associated with exposure to $PM_{2.5}$ in the prior 24-hour period [29% higher daily rate (95% CI: 1, 63)] (Bartell et al., 2013). Another measure of ectopy, premature ventricular contractions, was positively associated with 30-minute personal exposures to $PM_{2.5}$ in a large panel of healthy, nonsmoking adults in central Pennsylvania (He et al., 2011). Characteristics of cardiac rate and rhythm including measures of supraventricular or ventricular ectopic runs were also associated with $PM_{2.5}$ exposures in a study conducted in Ottawa, Canada in patients having ECGs for clinical purposes; however, confidence intervals around these associations were large (Cakmak et al., 2014). In addition, Cakmak et al. (2014) reported strong, positive associations with heart block, or the failure of the SA signal to move through the AV node.

Atrial fibrillation has also been examined with $PM_{2.5}$ exposures in a few recent studies. This arrhythmic disorder in the atria can cause symptoms such as fatigue, palpitations, shortness of breath and anxiety. Atrial fibrillation also greatly increase risk for stroke, dementia, congestive heart failure and premature mortality (Kwok et al., 2011; Paquette et al., 2000; Benjamin et al., 1998). As described in the 2009 PM ISA, Rich et al. (2006b) found positive, but imprecise associations between atrial fibrillation and 24-hour $PM_{2.5}$ exposures in a cohort of patients with ICDs. A recent study, also conducted in Boston, MA observed associations between $PM_{2.5}$ over the subsequent 0−24 hours and higher risk of atrial fibrillation in a cohort of patients with ICDs (26% (95% CI: 8, 47), but associations in this study were strongest for subdaily averaging times (e.g., 2 or 6 hours) (Link et al., 2013). This study also found that associations were stronger when analyses were limited to study participants residing within 25 km of the monitoring station compared to those residing within a 50 km radius (Link et al., 2013). Similar results were observed by Liao et al. (2011) in a panel study in Pennsylvania as associations with atrial fibrillation were observed for $PM_{2.5}$ exposures 30 minutes to 2 hours prior. In contrast, other studies examining atrial fibrillation or premature atrial contractions found weak or null associations with 24-hour $PM_{2.5}$ exposures (Cakmak et al., 2014; He et al., 2011).

In summary, there is recent evidence of an association with measures of ectopy and atrial fibrillation with short-term exposure to $PM_{2.5}$.

Table 6-8 Epidemiologic panel studies of short-term $PM_{2.5}$ exposure and arrhythmia.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI	Copollutant Examination
†Bartell et al. (2013) Los Angeles, CA 2005−2007	n = 55 nonsmoking older adults (≥65 yr) with history of coronary artery disease. Consecutive ECG monitoring for two 5-day periods in the warm and cool season (8,952 h of measurements) Recruited from 4 retirement communities	Monitoring outside residences 24-h avg Mean (SD): 21.1 (11.4) Max: 77.4	Ventricular tachycardia: 1.29 (1.01, 1.63)	Correlation (r) = 0.44 OC, 0.58 BC, 0.14 NO_X, 0.31 CO, 0.04 O_3
†Cakmak et al. (2014) Ottawa and Gatineau, Canada (2004−2009)	n = 8,595 observations Mean age: 59 yr (12−99) ECG monitoring for 24 h, participants included all residents referred for a 24 h period of cardiac monitoring	One fixed-site monitor in Gatineau Average of 3 area monitors in Ottawa Annual mean (SD): 13.11 (9.93) Warm season (SD): 11.69 (9.96) Cool season (SD): 14.55 (9.67)	Atrial fibrillation/flutter (Highest daily 3-h avg, IQR 10.72 μg/m^3): 2.11 (−1.25, 5.58) Supraventricular ectopic runs: 1.05 (−2.34, 4.56) Ventricular ectopic runs: 1.05 (−0.26, 2.38) Heart block: 1.13 (1.045, 1.21)	NR
Dockery et al. (2005a) Boston, MA (1995−2002)	N = 203 patients with ICDs living within 40 km of monitoring site 84 patients with detected ventricular episode	Fixed-site monitor 48-h avg Mean: 10.3 95th: 23.3 IQR 6.9	Ventricular arrhythmic episode 1.12 (0.94, 1.33) Ventricular arrhythmia following arrhythmic episode in prior 3 days 1.98 (1.46, 2.65)	NR

Table 6-8 (Continued): Epidemiologic panel studies of short-term $PM_{2.5}$ exposure and arrhythmia.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI	Copollutant Examination
Dockery et al. (2005b) Boston, MA (1995−2002)	n = 72 patients with ICDs Mean age: 66.6 yr (19−90) Follow-up visits approximately every 3 mo over study period.	Two fixed-site monitors 24-h avg Mean: 11.6 Max: 53.2 IQR 7 (48 h)	Ventricular arrhythmias 2-day avg: 1.10 (0.92, 1.34) Ventricular arrhythmia following arrhythmia episode in prior 3 days 1.96 (1.38, 2.77) Supraventricular arrhythmias 1.34 (0.81, 2.28) Supraventricular arrhythmias following arrhythmia episode in prior 3 days 1.27 (0.32, 4.99)	Correlation (r) = 0.54 NO_2, 0.41 CO, 0.33 SO_2, 0.18 O_3, 0.77 SO_4^{2-}, 0.67 BC Copollutant models with: NO_2, CO, and SO_2.
†He et al. (2011) Harrisburg, PA Nov 2007−June 2009	Air Pollution and Cardiac Risk and its Time Course (APACR) study n = 105 healthy, nonsmoking individuals >45 yr Holter monitoring performed continuously for 24 h	Total personal exposure monitoring 1-min measurements averaged every 30-min. 24-h avg Mean (SD): 13.49 (22)	Premature ventricular contractions count, Lag 0: 1.08 (1.05, 1.10) Premature atrial contractions count, Lag 0: 0.94 (0.85, 1.04) Total ectopy count, Lag 0: 1.05 (1.02, 1.07)	Correlations NR.
†Liao et al. (2009) 49 U.S. cities (1999−2004)	The Environmental Epidemiology of Arrhythmogenesis in Women's Health Initiative (EEAWHI) N = 57,422 postmenopausal women (50−79 yr)	Kriging interpolation of fixed-site monitors for participants' geocoded address 24-h avg Mean: 13.8 (7.9) 95th: 29.1	Ventricular ectopy Lag 2: 1.09 (0.98, 1.21) Supraventricular ectopy Lag 2: 1.01 (0.93, 1.10)	Correlations (r): NR.

Table 6-8 (Continued): Epidemiologic panel studies of short-term $PM_{2.5}$ exposure and arrhythmia.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI	Copollutant Examination
†Liao et al. (2011) Harrisburg, PA	Air Pollution and Cardiac Risk and its Time Course (APACR) study N = 106 nonsmoking adults (≥45 yr) Holter monitoring performed continuously for 24 h	Total personal 1-min measurements averaged every 30-min 24 h avg Mean (SD): 13.61 (21.59)		Correlations (*r*): NR.
†Link et al. (2013) Boston, MA (2006−2010)	N = 49 patients with ICDs living within 50 km of clinic Follow up every 3 mo over study period	Fixed-site monitor 24 h avg: 8.4 75th: 10.2	Risk of ICD-detected atrial fibrillation 24-h avg: 1.30 (0.88, 1.80) 2-h avg: 1.26 (1.08, 1.47); IQR: 6	Correlation (*r*): 0.22 SO_2, 0.37 NO_2, 0.18 O_3, 0.64 BC, 0.82 SO_4^{2-}, −0.17 PNC
Metzger et al. (2007) Atlanta, GA (1998−2002)	N = 518 patients with ICDs Mean age 61 yr	Fixed-site monitor 24-h avg Mean (SD): 17.8 (8.6)	All ventricular tachyarrhythmic events Lag 0: 0.995 (0.953, 1.039) Events resulting in defibrillation Lag 0: 0.969 (0.848, 1.110)	Correlation (*r*): 0.47 PM coarse, 0.64 O_3, 0.49 NO_2, 0.46 CO, 0.2 SO_2
Peters et al. (2000) Eastern MA (1995−1997)	N = 100 patients with ICDs with clinic follow-up every 3−6 mo Mean age 62.2 yr 33 patients with a measured defibrillator discharge, 6 patients with ≥10 discharges	Fixed-site monitor 24-h avg Mean: 12.7 Max: 53.2	Defibrillator discharge (patients with at least one event) Lag 2: 1.05 (0.88, 1.26) Defibrillator discharge (patients with ≥10 events) Lag 2: 1.25 (1.01, 1.55)	Correlation (*r*): 0.74 BC, 0.56 CO, 0.06 O_3, 0.57 NO_2, 0.37 SO_2
Rich et al. (2006a) St. Louis, MO (2001−2002)	N = 55 patients with ICDs living within 40 km of monitoring station Mean age 63 yr 139 arrhythmic events	Fixed-site monitor 24-h avg Mean: 16.2 75th: 21.8	Ventricular arrhythmia Lag 0−23 h: 0.95 (0.71, 1.28)	Correlation (*r*): NR.

Table 6-8 (Continued): Epidemiologic panel studies of short-term $PM_{2.5}$ exposure and arrhythmia.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI	Copollutant Examination
Rich et al. (2005) Boston, MA (1995−2002)	N = 203 patients with ICDs living within 40 km of monitoring site 84 patients with detected ventricular episode Case-cross over analysis	Fixed-site monitor 24-h avg Mean: 9.8 Max: 53.2 IQR lag 0−2: 9.2 IQR lag 0−23: 7.8	Ventricular arrhythmia Lag 0−2 h: 1.09 (0.95, 1.231) Lag 0−23 h: 1.25 (1.03, 1.51) Ventricular arrhythmia following arrhythmic event in prior 3 days Lag 0−23 h: 1.43 (1.05, 1.96)	Correlation (*r*): NR. Copollutant models with: O_3, NO_2, and SO_2.
Rich et al. (2006b) Boston, MA (1995−2002)	N = 203 patients with ICDs residing within 40 km radius of monitor; 29 patients with a measured atrial fibrillation	Fixed-site monitor, hourly measurements 24 h avg Mean: 9.8 Max: 53.2	Paroxysomal atrial fibrillation Lag 0: 1.44 (0.81, 2.56) Lag 0−23: 1.17 (0.55, 2.48)	Correlation (*r*): NR.
Sarnat et al. (2006) Steubenville, OH (June−December 2015)	N = 32 nonsmoking older adults living within a community. 30-min Holter monitoring at weekly clinic visits 98% female	Fixed-site monitor 24 h avg Mean (SD): 19.6 (10.4) Max: 48.4	5-day avg: Supraventricular ectopy 1.42 (0.99, 2.04) Ventricular ectopy 1.02 (0.62, 1.65)	Correlation (*r*): 0.89 $SO_4$2−, 0.51 EC, 0.20 O_3, 0.34 NO_2, 0.41 SO_2, 0.45 CO
†Zanobetti et al. (2014a) Boston, MA (2000−2010)	Normative Aging Study N = 1,448 measurements 5−10 min ECG recordings were taken at clinic visits	Estimated from model integrating data from satellite-derived AOD observations (10×10 km^2 resolution), 78 ground monitoring sites, and land use variables.	Ventricular ectopy 2-day avg: 1.45% (1.08, 1.96) 4-day avg: 1.79% (1.22, 2.59)	Correlation (*r*): NR.

avg = average, BC = black carbon, CO = carbon monoxide, EC = elemental carbon, ECG = electrocardiograph, hr = hour, ICD = implantable cardiac device, IQR=interquartile range, km = kilometer, NO_2 = nitrogen dioxide, NO_X = oxides of nitrogen, NR=not reported, O_3 = ozone, OC = organic carbon, PNC = particle number count, SO_4^{2-} = sulfate, SO_2=sulfur dioxide, SD = standard deviation, yr=year(s).

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

6.1.4.2.1 Conduction Abnormalities

Electrocardiograms register the electrical activity of the whole heart across time using skin surface electrodes. Depolarization and repolarization of the ventricles occurs during the QT interval. Electrical impulse (i.e., action potential) propagation involves a complex interplay of sodium, potassium and calcium channels. Disturbances in depolarization and repolarization can be measured by QRS width, QT prolongation (or QTc corrected for heart rate) T-wave width and T-wave complexity and are associated with increased risks of ventricular arrhythmias (Castro-Torres et al., 2015).

A limited number of studies was available in the 2009 PM ISA (U.S. EPA, 2009) that considered the association between PM and ECG markers of repolarization. These publications all used the same panel of study participants with ischemic heart disease from Erfurt, Germany and demonstrated associations between higher 5-hour levels of $PM_{2.5}$ and lower T-wave amplitude, higher T-wave complexity and longer QT duration.

A number of additional studies have been published since the 2009 PM ISA that examine associations between short-term $PM_{2.5}$ concentrations and ventricular depolarization and repolarization changes, but there is considerable variability in the ECG endpoints studied and findings across these studies are inconsistent. These results are summarized below and in Table 6-9.

Short-term $PM_{2.5}$ exposure and repolarization disturbances related to QTc prolongation, T-wave amplitude or T-wave width were examined in several studies (Rich et al., 2012; Baja et al., 2010; Hampel et al., 2010; Liao et al., 2010; Zhang et al., 2009). In a large cross-sectional analysis from the national Women's Health Initiative, authors reported associations between $PM_{2.5}$ concentrations (lag 0−2) and a 5% increase in the relative odds of a T-wave abnormality in post-menopausal women in addition to associations with reduced T-wave amplitude (Zhang et al., 2009). However, strong positive associations between $PM_{2.5}$ concentrations averaged over the previous 0−23 hours and T-wave amplitude were reported in a panel study of ischemic heart disease participants from Augsburg, Germany [3.3% increased T-amplitude (95%CI 0.2, 6.3)] (Hampel et al., 2010). Similarly, QTc prolongation, a more well-studied risk marker for ventricular arrhythmias, was associated with 0 to up to 5-day averages of $PM_{2.5}$ concentrations in this panel of MI survivors [e.g., 0.5% (95% CI 0.0, 1.0), 24−47 hour average of $PM_{2.5}$] (Hampel et al., 2010). Positive associations between short-term $PM_{2.5}$ exposure and QTc prolongation were also observed in a panel of healthy adults in Pennsylvania (Liao et al., 2010), but not among adults in Boston, MA (Baja et al., 2010). No associations were observed between $PM_{2.5}$ levels and QTc prolongation or time between T-wave peak and T-wave end in cardiac rehabilitation patients in New York (Rich et al., 2012). Although evidence from recent studies is inconclusive, taken together these studies indicate a potential for cardiac depolarization and repolarization disturbances by $PM_{2.5}$. These disturbances may increase the risk for malignant ventricular arrhythmias that could result in cardiac arrest.

Table 6-9 Epidemiologic panel studies of short-term PM2.5 exposure and conduction abnormalities.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI[a]	Copollutants Examination
†Baja et al. (2010) Boston, MA (2000−2008)	Normative Aging Study n = 580 men ECG measurements recorded for 5−10 min during study visits (every 3−5 yr), 926 valid readings	Fixed-site monitor 10-h avg Mean (SD): 10.72 (7.88)	Change in mean QTc (ms) Lag 4-h: 0.64 (−1.60, 2.89)	*r* = 0.69 for BC, others NR
†Hampel et al. (2010) Augsburg, Germany May 2003−February 2004	N = 67 nonsmoking MI survivors Participants submitted 16-sec ECG readings either when experiencing symptoms or at the same time daily	Fixed-site monitor 24-h avg Mean (SD): 17.7 (6.2)	% change in QTc 24−47-h avg: 0.5 (0.0, 1.0) 48−71-h avg: 0.4 (0.0, 0.9) % change in T-wave amplitude 0−23-h avg: 3.3 (0.2, 6.3) 24−47-h avg: 2.8 (−0.3, 5.9)	*r* = 0.80 $PM_{10-2.5}$, 0.32 PNC, 0.55 NO_2, 0.56 CO
†Liao et al. (2010) (Nov 2007−June 2009)	Air Pollution and Cardiac Risk and its Time Course (APACR) study N = 106 nonsmoking adults (≥45 yr) Holter monitoring performed continuously for 24 h	Total personal 1-min measurements averaged every 30-min 24 h avg Mean (SD): 13.61 (21.59)	QTcB (msec) Lag 4-h: 1.24 (1.04, 1.49)	Correlations NR.
†Rich et al. (2012) Rochester, NY (June 2006−November 2009)	N = 76 participants with recent MI or unstable angina, residing within 21 km of monitor Up to 10 weekly ECG measurements (1−3-h) conducted for each participant.	Fixed-site monitor 24-h avg Mean (SD): 8.67 (6.06) Max: 42.85 IQR: 6.5 for 24 h	QTc (msec) Lag 96−119-h: 0.56 (−0.97, 2.09)	*r* = 0.11 UFP

Table 6-9 (Continued): Epidemiologic panel studies of short-term PM2.5 exposure and conduction abnormalities.

Study	Study Population	Exposure Assessment	Effect Estimates 95% CI[a]	Copollutants Examination
†Zhang et al. (2009) 49 U.S. cities (1999−2003)	Women's Health Initiative n = 55,529 postmenopausal women, 52−90 yr 52% with hypertension 20% with hypercholesterolemia	Kriging interpolation of fixed-site monitors for participants' geocoded address 24-h avg Mean (SD): 13.9 (7)	Minnesota Code 5 (T-wave abnormality) (per 10-ug/m^3) Lag 0−2: 1.05 (1.00, 1.09) Changes in T-wave amplitude (μV) (per 10-ug/m^3) Lag 0−2: −2.20 (−5.38, 1.06)	Correlations NR

avg = average, BC = black carbon, CO = carbon monoxide, EC = elemental carbon, ECG = electrocardiograph, hr = hour, ICD = implantable cardiac device, IQR=interquartile range, km = kilometer, ms=millisecond, NO_2 = nitrogen dioxide, NO_X = oxides of nitrogen, NR=not reported, O_3 = ozone, OC = organic carbon, PNC = particle number count, SO_4^{2-} = sulfate, SO_2=sulfur dioxide, SD = standard deviation, yr=year(s).

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

6.1.4.3 Controlled Human Exposure Studies for Arrhythmia and Conduction Abnormalities

In prior reviews, there were a limited number of controlled human exposure studies examining the relationship between short-term $PM_{2.5}$ exposure and ventricular arrhythmia. The 2004 ACQD included one study reporting that healthy adults exposed to $PM_{2.5}$ CAPs displayed no significant changes in ECG (Gong et al., 2000). These results remained consistent when this experiment was repeated with additional subjects exposed to a similar concentration of $PM_{2.5}$ (Gong et al., 2003). However, Gong et al. (2004) did report that ectopic heartbeats (i.e., a type of arrhythmia) increased in healthy subjects, but decreased in COPD subjects.

Recent CHE studies expand our knowledge of the relationship between $PM_{2.5}$ and indicators of possible ventricular arrhythmia. In healthy adults, there was little change and no statistically significant differences in T-wave amplitude (Kusha et al., 2012) or Tp-Te (Sivagangabalan et al., 2011) when exposure to $PM_{2.5}$ CAP was compared to control exposures. In contrast, in the same study, Sivagangabalan et al. (2011) reported QTd dispersion (Max QT interval-Min QT interval) increased ($p = 0.008$) following $PM_{2.5}$ CAP exposure when compared to FA. Moreover, in a double-blind dietary intervention study of healthy middle-aged adults, participants were supplemented with either fish oil or olive oil for 28-days prior to FA (Day 1) and then, CAP exposure (Day 2). Results indicated that the duration of the QTc interval was statistically significantly ($p < 0.05$) increased 20 h after exposure in the olive oil group only. In contrast, relative to FA exposure, Tp-Te was increased significantly ($p < 0.05$) in

the fish oil group only. The authors concluded that fish oil blocked CAP-induced QTc prolongation, but not Tp-Te prolongation (Tong et al., 2012).

Taken together, and similar to the previous review, these more recent CHE studies show some evidence that short-term exposure to $PM_{2.5}$ can result in abnormal electrical activity in the heart. For more information on these recently published studies, see Table 6-10 below.

Table 6-10 Study-specific details from controlled human exposure (CHE) studies of short-term $PM_{2.5}$ exposure and arrhythmia and conduction abnormalities.

Study	Population	Exposure Details	Endpoints Examined
(Tong et al., 2012)	Healthy adults n = 8 M 21 F; 50−72 yr 57.4 ± 1.4	278 ± 19 µg/m^3 CAP for 2 h at rest CAPS from Chapel Hill, NC Effect of 28-day supplementation pre-exposure with fish oil or olive oil	QTc and Tp-Te pre, and 20 h post
(Kusha et al., 2012)	Healthy adults n = 8 M 9 F; 18−38 yr M 28.1 ± 7.0; F 23.7 ± 4.3	154 ± 54 µg/m^3 $PM_{2.5}$; CAP from Toronto	T-wave alternans magnitude measured continuously during exposure
(Sivagangabalan et al., 2011)	Healthy adults n = 11 M, 14 F; 18−50 yr	150 µg/m^3 CAP from Toronto	QT and Tp-Te: throughout the exposure

c = corrected for heart rate, CAP = concentrated ambient particle, ECG = electrocardiogram, F = female, M = male, n = number, QT = time interval between from beginning of the Q-wave, to end of the T-wave, SD = standard deviation, Tp-Te = time interval from peak to end of the T-wave.

6.1.4.4 Toxicology Studies for Arrhythmia and Conduction Abnormalities

In the 2009 PM ISA, Wellenius et al. (2006) reported that inhalation of $PM_{2.5}$ decreased incidence of supraventricular arrhythmia in a rat model of acute myocardial infarction. In contrast, Nadziejko et al. (2004) found that in male rats that develop spontaneous arrhythmias, inhalation exposure to $PM_{2.5}$ increased ($p < 0.05$) the frequency of irregular and delayed heart beats.

Since the publication of the 2009 PM ISA, there is additional evidence that short-term exposure to $PM_{2.5}$ can result in conduction abnormalities that may be indicative of arrhythmias. In rats, Ghelfi et al. (2010) reported that short-term exposure to $PM_{2.5}$ significantly increased ($p < 0.05$) *P* wave duration and the RTp interval, while decreasing Tp-Te ($p = 0.02$). Of note, these authors also reported that blocking

synthesis of the hormone angiotensin (see Section 6.1.6.4.1) reversed these effects. Similarly, in SH rats Farraj et al. (2015) reported a statistically significant decrease ($p < 0.05$) in the duration of the PR interval during short-term exposure to $PM_{2.5}$ in summer, but not winter. These authors also demonstrated that short-term exposure to summer but not winter $PM_{2.5}$ increased sensitivity to triggered cardiac arrhythmia.

In contrast to the results presented above, Ghelfi et al. (2010) did not find a statistically significant effect of short-term $PM_{2.5}$ exposure on the QRS complex and Ghelfi et al. (2010) and Farraj et al. (2015) both reported no change in the QT interval in response to short-term exposure to $PM_{2.5}$. In addition, in female mice Kurhanewicz et al. (2014) did not find statistically significant indicators of conduction abnormalities in response to short-term $PM_{2.5}$ exposure.

Taken, the current ISA provides evidence that short-term $PM_{2.5}$ exposure may increase the potential for developing an arrhythmia. Most studies found at least some indication of conduction abnormalities as measured by ECG. There is also some evidence that these conduction abnormalities may be dependent upon the season in which $PM_{2.5}$ was collected. More information on studies published since the 2009 ISA can be found in Table 6-11 below.

Table 6-11 Study-specific details from toxicological studies of short-term $PM_{2.5}$ exposure and arrhythmia and conduction abnormalities.

Study	Study Population	Exposure Details	Endpoints Examined
(Farraj et al., 2015)	Adult SH rats (12 weeks) M, n = 6/group	Inhalation of 168.7 µg/m^3 summer or 78.5 µg/m^3 winter $PM_{2.5}$ CAPs collected from Durham NC. Exposed for 4 h	QTc and PR in the time period immediately post to 6 h post arrhythmia development using aconitine infusion one-day post.
(Ghelfi et al., 2010)	Adult Sprague Dawley rats, n = 80 total	Inhalation of 510 µg/m^3 $PM_{2.5}$ some groups pretreated with valsartan or benazepril Exposed for 5 h	PR, QT, QRS, RTp, Tp-Te, and Pdur measured continuously during exposure
(Kurhanewicz et al., 2014)	Adult, C57BL/6 mice, f, n = 5−8/group	Inhalation of 190 µg/m^3 $PM_{2.5}$ from Research Triangle Park, NC Exposed for 4 days, 4 h/day.	QRS, QTc, *P*-wave, Tp-Te ST, and RT measured continuously pre- to post exposure

c = corrected for heart rate, CAPs = concentrated ambient particles, d = day, ECG = electrocardiogram, F = female, h = hour, M = male, n = number, post = after-exposure, pre = before exposure, Pdur = time interval of a complete *P*-wave, PR = time interval between the beginning of the *P*-wave to the peak of the *R*-wave, QRS = time interval between the beginning of the Q-wave and the peak of the S-wave, QT = time interval between from beginning of the Q-wave, to end of the T-wave, RTp = time interval between the beginning of *R*-wave and peak of the T-wave, SH = spontaneously hypertensive, ST = beginning of S-wave to end of T-wave, Tp-Te = time interval from peak to end of the T-wave.

6.1.5 Cerebrovascular Disease and Stroke

Cerebrovascular disease (CBVD) typically includes conditions classified under ICD10 codes I60−I69 (ICD 9: 430−438) such as hemorrhagic stroke, cerebral infarction (i.e., ischemic stroke) and occlusion of the precerebral and cerebral arteries. Ischemic stroke results from an obstruction within a blood vessel that supplies oxygen to the brain, potentially leading to infarction, and accounts for 87% of all strokes (Goldberger et al., 2008). Hemorrhagic stroke is less common, but results in a disproportionate number of fatalities. The hemorrhagic stroke subtype results from a brain aneurysm or leaking vessel in the brain and can be further categorized by brain region (e.g., intracerebral or subarachnoid). Older age, female sex, smoking, obesity and prior stroke are known risk factors for stroke and should be considered in epidemiologic analysis. Comorbidities that increase stroke risk but may also be associated with $PM_{2.5}$ exposure include hypertension, diabetes and CHD and atrial fibrillation.

In the 2009 PM ISA, inconsistent results were found in several epidemiologic studies that considered the relationship between short-term $PM_{2.5}$ exposure and ED visits and hospital admissions for CBVD. Similarly, results from studies published since the last review for CBVD or all stroke outcomes have been largely inconsistent, with most studies reporting a lack of an association.

6.1.5.1 Emergency Department Visits and Hospital Admissions

The 2009 PM ISA reviewed several epidemiologic studies of short-term $PM_{2.5}$ exposure and ED visits and hospital admissions for CBVD and reported inconsistent results across studies. For example, the U.S. MCAPS study observed a modest increase (0.8% [95% CI: 0.3−1.4%]) in hospital admissions for CBVD (Dominici et al., 2006); however, a multicity study in Australia and New Zealand observed a null association (Barnett et al., 2006). This section first reviews recent studies that have considered all strokes or CBVD as a composite endpoint, and subsequently considers those studies focusing specifically on ischemic or hemorrhagic strokes. Results from recent studies examining CBVD or all stroke outcomes, as well as those examining more specific stroke outcomes, have been largely inconsistent. Study details and results are presented in Table 6-12.

Table 6-12 Epidemiologic studies of short-term $PM_{2.5}$ exposure and cerebrovascular and stroke-related hospital admission and emergency department (ED) visits.

Study	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m³	Copollutant Examination
Dominici et al. (2006) 204 U.S. Urban Counties (1999−2002) Age ≥65 yr	Monitors in county averaged Number NR. Study population reside an average of 5.9 miles from monitor. Median pairwise correlation between same-county monitors 0.91.	CBVD	24-h avg: 13.4 (IQR 3.9) 75th: 15.2	Correlation (*r*): NA Copollutant models with: NA
†Bell et al. (2015) 213 U.S. Counties (1999−2010) Age ≥65 yr	Monitors in county averaged	CBVD	24-h avg: 12.3 Max: 20.2	Correlation (*r*): NA Copollutant models with: NA
†Kloog et al. (2012) Six New England States (2000−2008) Age ≥65 yr	LUR modelling at 10 × 10 km spatial resolution using satellite-derived AOD observations. Cross-validation R^2 = 0.85.	Stroke	24-h avg: 9.6 75th: 11.7 Max: 72.6	Correlation (*r*): NA Copollutant models with: NA
†Kloog et al. (2014) Seven Mid-Atlantic States and Washington, D.C. (2000−2006) Age ≥65 yr	LUR modelling at 10 × 10 km spatial resolution using satellite-derived AOD observations. Cross-validation R^2 = 0.81.	Stroke	2-day avg: 11.92 75th: 14.65 Max: 95.85	Correlation (*r*): NA Copollutant models with: NA
†Haley et al. (2009) Eight New York Cities (2001−2005)	Weighted averages across monitors in each city. 39 monitors in total	CBVD	24-h avg: 5.8 (IQR 5.9) 75th: 8.0 Max: 42.2	Correlation (*r*): NA Copollutant models with: NA
†Hsu et al. (2017) Four New York Regions (1991−2006)	Adjusted CMAQ-simulated model (see Hogrefe et al. (2009)) 12 × 12 km grid resolution with patient residential address	CBVD	Graphically reported only	Correlation (*r*): NA Copollutant models with: O_3

Table 6-12 (Continued): Epidemiologic studies of short-term $PM_{2.5}$ exposure and cerebrovascular and stroke-related hospital admission and emergency department (ED) visits.

Study	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m³	Copollutant Examination
†Milojevic et al. (2014) 15 Conurbations in England and Wales (2003−2009)	Nearest monitor to patient's residence (50 km). Number NR.	Stroke	24-h avg Median: 10.0 (IQR 8.0) 75th: 15.0	Correlation (*r*): CO: 0.48, NO_2: 0.53, O_3: −0.10, PM_{10}: 0.86, SO_2: 0.41 Copollutant models with: NA
†Talbott et al. (2014) Seven U.S. States (2001−2009)	Fuse-CMAQ CMAQ model combined with monitoring data, downscaled to Census Tract resolution.	CBVD	24-h avg: 6.46 to 12.83 (across seven states) 75th: 7.64 to 16.55 (across seven states)	Correlation (*r*): NA Copollutant models with: O_3
†Kim et al. (2012) Denver, Colorado (2003−2007)	1 monitor 90% of 5 county population within 25 km of monitor	CBVD	24-h avg: 7.98 Max: 59.41	Correlation (*r*): O_3: 0.30, NO_2: 0.26, CO: 0.23, SO_2: 0.23 Copollutant models with: NA
†Villeneuve et al. (2012) Edmonton, Canada (2003−2009) Ages ≥20 yr	Monitors in city averaged 3 monitors	Stroke Hemorrhagic Stroke Ischemic Stroke Transient Ischemic Attacks	24-h avg: 8.1 75th: 10.2	Correlation (*r*): NA Copollutant models with: SO_2, NO_2, CO, O_3
†Yitshak Sade et al. (2015) Southern Israel (2005−2012)	Hybrid model at 1 × 1 km spatial resolution using LUR and satellite-derived AOD observations. Out-of-sample cross-validation R^2 = 0.72	Ischemic Stroke Hemorrhagic Stroke	24-h avg Winter: 21.9 Spring: 21.6 Summer: 20.4 Fall: 20.2	Correlation (*r*): NA Copollutant models with: NA
†Wellenius et al. (2012a) Boston, MA (1999−2008)	1 monitor Patients excluded if >40 km, sensitivity analysis at >20 km	Acute Ischemic Stroke	24-h avg: 10.2 75th: 12.5	Correlation (*r*): NO_2: 0.46, CO: 0.35, O_3: 0.24 Copollutant models with: NA
†Lisabeth et al. (2008) Nueces County, TX (2001−2005) Age ≥45 yr	1 monitor	Ischemic Stroke Transient Ischemic Attacks	24-h avg Median: 7.0 IQR: 4.8−10.0	Correlation (*r*): NA Copollutant models with: O_3
†Wing et al. (2015) Nueces County, TX (2000−2012) Age ≥45 yr	1 monitor 85% cases within 20 km, median distance 6.9 km	Ischemic Stroke	24-h avg: 7.7 IQR: 5.7−10.6	Correlation (*r*): NA Copollutant models with: O_3

Table 6-12 (Continued): Epidemiologic studies of short-term $PM_{2.5}$ exposure and cerebrovascular and stroke-related hospital admission and emergency department (ED) visits.

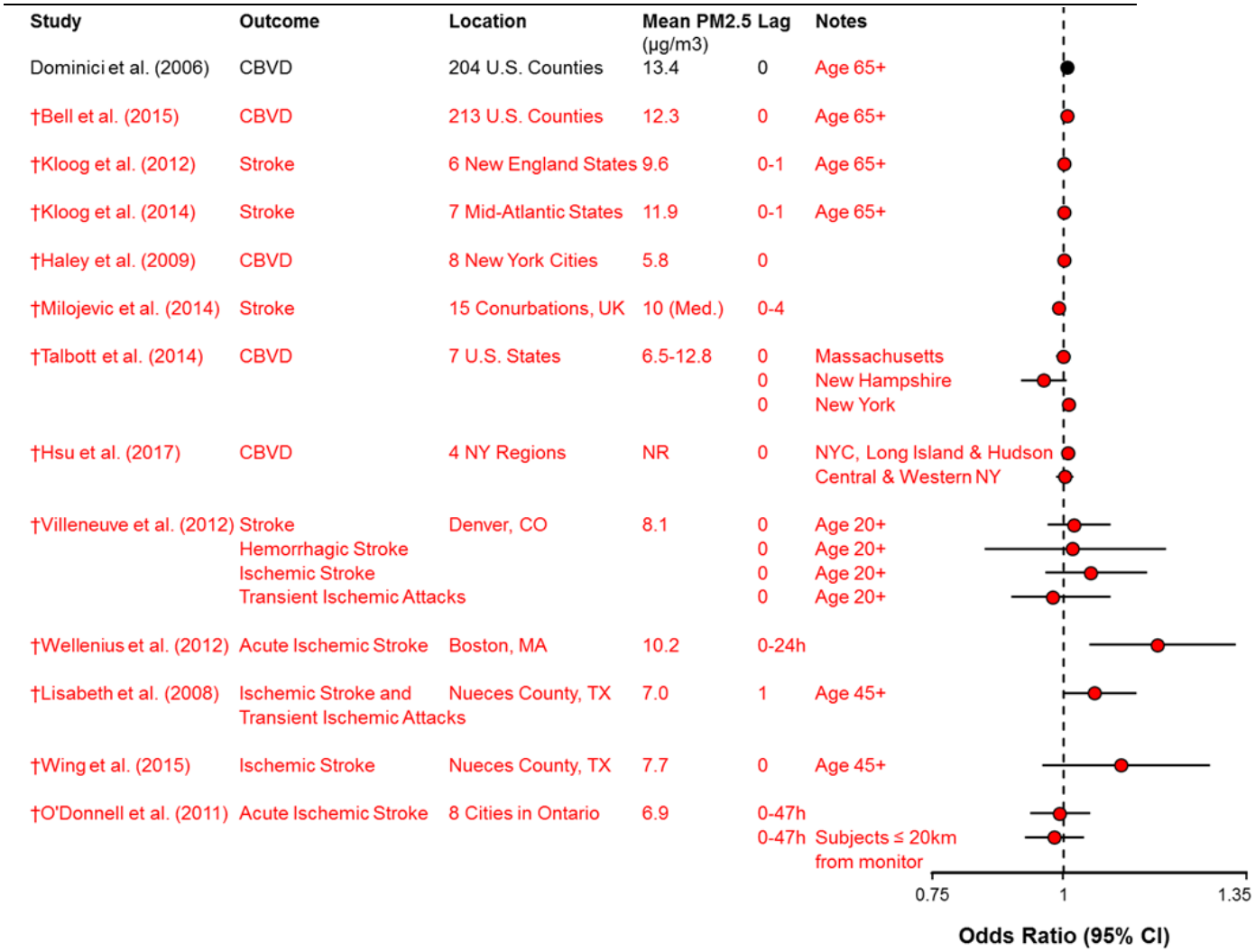
Study	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m³	Copollutant Examination
†O'Donnell et al. (2011) Eight Cities in Ontario, Canada (2003−2008)	Monitors in city averaged 7 monitors Toronto, 6 monitors Hamilton, 1 monitor London, Ottawa, Kingston, North Bay, Thunder Bay, Sudbury. Excluded if >50, 40, or 20 km from monitor in analyses.	Acute Ischemic Stroke	24-h avg: 6.9 (across eight cities)	Correlation (*r*): NA Copollutant models with: NA
†Chen et al. (2014b) Edmonton, Canada (1998−2002) Age ≥25 yr	Monitors in city averaged 3 monitors	Acute Ischemic Stroke	1-h avg: 8.53 95th: 22.00	Correlation (*r*): NO_2: 0.43, SO_2: 0.15, CO: 0.48, O_3: −0.15, PM_{10}: 0.79 Copollutant models with: NA

CMAQ = Community Multiscale Air Quality Modeling System, CO = carbon monoxide, HR = hazard ratio, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, OR = odds ratio, $PM_{2.5}$ = particulate matter with mean aerodynamic diameter 2.5 µm, $PM_{10-2.5}$ = particulate matter with mean aerodynamic diameter between 2.5 µm and 10 µm, PM_{10} = particulate matter with mean aerodynamic diameter 10 µm, RR = relative risk, SO_2 = sulfur dioxide.

†Studies published since the 2009 PM ISA. For the included epidemiologic studies, the focus is on those studies conducted in areas where mean $PM_{2.5}$ concentrations are <20 µg/m³ or in the case of a multi-city study where more than half of the cities have concentrations <20 µg/m³. Other studies maybe be included if they contribute to evaluating important uncertainties (see Preface).

Recent multicity studies examining the composite endpoint of all strokes or CBVD in relation to short-term $PM_{2.5}$ exposure have generally reported the lack of a positive association, although a few studies have found small but precise associations. The results of Bell et al. (2015) provide modest evidence for a positive association between $PM_{2.5}$ and CBVD in the Medicare study (0.7% [95% CI: 0.3, 1.0%] at lag 0), and are consistent with the results of Dominici et al. (2006), included in the 2009 PM ISA. In contrast, several additional multicity studies primarily observed null or negative associations across study regions using novel $PM_{2.5}$ exposure metrics that combine measured and modeled $PM_{2.5}$ concentrations (Hsu et al., 2017; Kloog et al., 2014; Talbott et al., 2014; Kloog et al., 2012) or measured $PM_{2.5}$ concentrations from monitors (Milojevic et al., 2014; Haley et al., 2009). Positive associations were reported in certain regions of some studies, such as New York state (Talbott et al., 2014) and the New York City metro area (Hsu et al., 2017). Single-city studies in the U.S. and Canada tended to report null associations (Rodopoulou et al., 2015; Kim et al., 2012; Villeneuve et al., 2012). Overall, recent epidemiologic evidence for an association between short-term $PM_{2.5}$ exposure and composite CBVD

endpoints continues to be inconsistent, though studies have generally reported null or low-magnitude associations (Figure 6-5).



Note: †Studies published since the 2009 PM ISA. CBVD = cerebrovascular disease, NR = not reported. Corresponding quantitative results are reported in Supplemental Table S6-7 (U.S. EPA, 2018).

Figure 6-5 Results of studies of short-term $PM_{2.5}$ exposure and hospital admissions and emergency department visits for cerebrovascular disease.

Emergency Department Visits and Hospital Admissions Visits for Stroke Subtypes

Cerebrovascular disease and stroke ED visits and hospital admissions can be further classified as ischemic strokes, hemorrhagic strokes, transient ischemic attacks (TIAs), and a number of other, less

well-defined clinical syndromes resulting from derangements in the cerebral circulation. Studies focused specifically on ischemic stroke have yielded inconsistent results (Figure 6-5). The observed variability in results among these studies may be due to the majority of the studies being conducted in single cities and having smaller sample sizes due to the focus on a more specific outcome. Several U.S. based single-city studies reported positive associations for ischemic stroke in Boston, MA (Wellenius et al., 2012a) and Nueces County, Texas (Wing et al., 2015; Lisabeth et al., 2008). Conversely, other single-city studies have reported null or negative associations in Edmonton, Canada (Chen et al., 2014b; Villeneuve et al., 2012) and southern Israel (Yitshak Sade et al., 2015). Additionally, a null association (OR: 0.99, 95% CI: 0.94, 1.05) was observed in Ontario, Canada (O'Donnell et al., 2011) using data from a stroke registry, which is thought to have reduced outcome misclassification compared to administrative data sets.

Fewer studies have focused specifically on the association between $PM_{2.5}$ and the risk of hemorrhagic stroke, in part because hemorrhagic strokes are much less common than ischemic strokes. Several recent studies provide contrasting results, including null associations observed in small studies in Edmonton, Canada (Villeneuve et al., 2012) and southern Israel (Yitshak Sade et al., 2015). Overall, the recent epidemiologic evidence for an association between short-term $PM_{2.5}$ and various stroke subtypes continues to remain inconsistent and limited.

6.1.6 Blood Pressure and Hypertension

The pressure on blood vessel walls from circulating blood is referred to as BP. Persistently elevated BP is referred to as hypertension. Increases in BP can lead to a number of cardiovascular endpoints including IHD, HF, and arrhythmia (Section 6.1.1). BP is tightly regulated through numerous homeostatic mechanisms including through the renal system (Section 6.1.6.4.1). Thus, in addition to discussing the effect of $PM_{2.5}$ exposure on changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and pulse pressure, this section also presents evidence for potential $PM_{2.5}$-induced changes in BP through the renal system.

In the 2009 PM ISA, there were no epidemiologic studies examining the relationship between short-term $PM_{2.5}$ exposure and ED visits and hospital admissions for hypertension. However, there was some evidence from CHE and animal toxicological studies for a relationship between short-term $PM_{2.5}$ exposure and increases in BP.

The evidence relating short-term $PM_{2.5}$ exposure and increases in BP or to hypertension has increased since the last review. Although more recent ED visit and hospital admissions studies for hypertension are largely inconsistent (i.e., some studies show positive associations while others do not), evidence from CHE and animal toxicological studies generally show changes in some measure of BP following short-term $PM_{2.5}$ exposure. Notably, results from animal toxicological studies also suggest that diet and genetics may be influential factors in BP changes following short-term $PM_{2.5}$ exposure (Section 6.1.6.4).

6.1.6.1 Emergency Department Visits and Hospital Admissions

Patients with a primary discharge diagnosis related to hypertension are likely have a documented history of hypertension and present to EDs because they are experiencing asymptomatic blood pressure elevations, severe hypertension accompanied by concerning symptoms, or a hypertension-related emergency (Bender et al., 2006). In interpreting the results of these studies it is important to note that patients experiencing an acute cardiovascular event (e.g., acute coronary event or stroke) would be expected to have a primary discharge diagnosis related to the acute cardiovascular event, even if hypertension was believed to be a proximal cause (Szyszkowicz et al., 2012).

The 2009 PM ISA did not review any epidemiologic studies of ambient $PM_{2.5}$ and ED visits and hospital admissions for hypertension. This section focuses on the few available recent studies providing limited and inconsistent evidence of an association between hypertension and short-term $PM_{2.5}$ exposure (Table 6-13).

Table 6-13 Epidemiologic studies of short-term ambient $PM_{2.5}$ concentrations using hypertension-related hospital admission and emergency department visits.

Study	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m^3	Effect Estimates 95% CI	Copollutant Examination
†Hsu et al. (2017) Four New York Regions (1991−2006)	Adjusted CMAQ-simulated model (see Hogrefe et al. (2009)) 12 × 12 km grid resolution with patient residential address	Hypertension	NR	RR (Lag 0) NYC, Long Island and Hudson: 1.093 (1.007, 1.032) Adirondack and North: 1.065 (0.979, 1.154) Mohaweek Valley and Binghamton: 1.020 (0.939, 1.108) Central and Western NY: 1.007 (0.976, 1.039)	Correlation (*r*): NA Copollutant models with: O_3
†Rodopoulou et al. (2015)	1 monitor	Hypertension	24-h avg: 12.4 75th: 15.6	RR	Correlation (*r*): NA

Table 6-13 (Continued): Epidemiologic studies of short-term ambient $PM_{2.5}$ concentrations using hypertension-related hospital admission and emergency department visits.

Study	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m³	Effect Estimates 95% CI	Copollutant Examination
Little Rock, Arkansas (2002−2012) Age ≥15 yr	60% residents within 10 km			Year-Round (Lag 1): 0.990 (0.973, 1.007) Cold Season (Lag 1): 1.020 (0.946, 1.047) Warm Season (Lag 1): 0.968 (0.979, 0.991)	Copollutant models with: O_3
†Szyszkowicz et al. (2012) Edmonton, Canada (1992−2002) All ages	Average of 3 monitors Max distance apart 10 km (Zemek et al., 2010)	Hypertension	24-h avg: 8.5 75th: 10.9	Odds Ratio Lag 0: 1.01 (0.98, 1.05) Lag 1: 1.03 (0.99, 1.06) Lag 5: 1.02 (0.99, 1.05) Lag 6: 1.05 (1.01, 1.07) Lag 4−6: 1.04 (1.00, 1.08)	Correlation (*r*): PM10: 0.76, NO_2: 0.39, CO: 0.32, SO_2: 0.21, O3: 0.05 Copollutant models with: NA
†Franck et al. (2011) Leipzig, Germany (Feb. 2002−Jan. 2003)	Monitors in city averaged Number monitors NR. City approx. 200 km^2	Hypertension	24-h avg: 20.61 Max: 84.06	No quantitative results presented; results presented graphically. Negative associations at lags 0 and 1. Positive associations at lags 8 and 9.	Correlation (*r*): UFP: −0.06 Copollutant models with: NA

Table 6-13 (Continued): Epidemiologic studies of short-term ambient $PM_{2.5}$ concentrations using hypertension-related hospital admission and emergency department visits.

Study	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m³	Effect Estimates 95% CI	Copollutant Examination
†Brook and Kousha (2015) Calgary and Edmonton, Canada (Jan. 2010−Dec. 2011)	Average of monitors in 35 km of patient zip code centroid	Hypertension	24-h avg Calgary: Median: 10.1 Max: 138.4 Edmonton: Median: 8.1 Max: 156.3	Odds Ratio Males; Cold Season; Lag 6: 1.158 (1.006, 1.323) Females; Cold Season; Lag 5: 1.141 (1.012, 1.275)	Correlation (*r*): NA Copollutant models with: NA

CMAQ = Community Multiscale Air Quality Modeling System, CO = carbon monoxide, HR = hazard ratio, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, OR = odds ratio, PM_{10} = particulate matter with mean aerodynamic diameter 10 µm, $PM_{10-2.5}$ = particulate matter with mean aerodynamic diameter between 2.5 µm and 10 µm, $PM_{2.5}$ = particulate matter with mean aerodynamic diameter 2.5 µm, RR = relative risk, SO_2 = sulfur dioxide.

†Studies published since the 2009 PM ISA. For the included epidemiologic studies, the focus is on those studies conducted in areas where mean $PM_{2.5}$ concentrations are <20 µg/m³ or in the case of a multi-city study where more than half of the cities have concentrations <20 µg/m³. Other studies maybe be included if they contribute to evaluating important uncertainties (see Preface).

A study of hypertension ED visits and hospital admissions in New York State using a hybrid method to estimate $PM_{2.5}$ exposure from monitor and modeled data over the years 1991−2006 (Hsu et al., 2017) reported a 1.93% (95% CI: 0.69, 3.18%) increased risk of ED visits on the concurrent day (lag 0) near New York City; however, Hsu et al. (2017) observed no associations in the remaining regions of the state. Hsu et al. (2017) did not present pooled results across the state, but the differing results across the state provide evidence of potential regional heterogeneity in risk estimates. In contrast, a single-city study in Little Rock, Arkansas, reported a negative association for the risk of ED visits (−1.03%, 95% CI: −2.69%, 0.67%; lag 1) (Rodopoulou et al., 2015). The observed association was attenuated but remained negative in a copollutant model adjusting for O_3 (−0.58%, 95% CI: −2.34%, 1.21%; lag 1). Rodopoulou et al. (2015) reported a positive association in the cold season, indicating that a negative association in the warm season is driving the overall results. Similarly, a two-city Canadian study in Edmonton and Calgary observed positive associations in the cold season (Brook and Kousha, 2015). The authors did not report quantitative results for the warm season, but they stated that there were "no statistically significant positive results". In a study in Edmonton, Canada, Szyszkowicz et al. (2012) observed a positive year-round association between short-term $PM_{2.5}$ concentrations and hypertension. Additionally, a single-city study examined emergency calls for hypertensive crisis in Leipzig, Germany across multiple lag periods. Franck et al. (2011) reported generally negative or null associations across lag periods (lag 1 to 7).

In summary, there is limited and inconsistent evidence for a year-round association between short-term $PM_{2.5}$ exposure and ED visits and hospital admissions for hypertension. Studies reported evidence of seasonal differences, with positive associations in the cold season and negative or null associations in the warm season (Brook and Kousha, 2015; Rodopoulou et al., 2015); however, among these studies only Rodopoulou et al. (2015) examined the potential for copollutant confounding, which remains an important limitation for both year-round and seasonal analyses.

6.1.6.2 Panel Epidemiologic Studies of Changes in Blood Pressure (BP)

Studies of short-term $PM_{2.5}$ exposure and blood pressure included in the 2009 PM ISA (U.S. EPA, 2009) were limited in size and number and results were not consistent across studies. While the majority of studies supported associations between $PM_{2.5}$ and higher systolic blood pressure (SBP) and diastolic blood pressure (DBP), other studies reported lower BP or no association. Several studies have since been published investigating associations between short-term $PM_{2.5}$ concentrations and blood pressure, but overall, the recent evidence is similar to that in that last review in providing mixed evidence for associations (Table 6-14).

Since the publication of the 2009 PM ISA, there are a number of quasi-experimental studies available. As noted previously, these studies are advantageous in that they include well-characterized exposures across a range of $PM_{2.5}$ concentrations. Across these studies, results generally did not show associations between short-term $PM_{2.5}$ exposures and changes in SBP or DBP. Kubesch et al. (2014) and Weichenthal et al. (2014a) conducted similar randomized crossover studies with participants exposed for 2 hours to ambient $PM_{2.5}$ in a high or low exposure site. While Kubesch et al. (2014) reported positive associations for BP and $PM_{2.5}$ during the exposure period and up to five hours after, Weichenthal et al. (2014a) reported null associations with $PM_{2.5}$ during the exposure period and SBP or DBP. Chung et al. (2015) similarly observed no associations with BP in a study examining $PM_{2.5}$ from traffic exposures and BP measurements from individuals residing in communities near highways and other residing in urban background locations.

Liu et al. (2014b) and Morishita et al. (2015a) also conducted studies utilizing ambient gradients of $PM_{2.5}$ concentrations by transporting study participants to specific locations to reflect differences in $PM_{2.5}$ concentrations. Liu et al. (2014b) monitored BP during 5-day exposures near a steel mill (daily average $PM_{2.5}$ 11.0 $\mu g/m^3$) and on a college campus (daily average $PM_{2.5}$ 9.4 $\mu g/m^3$), and Morishita et al. (2015a) transported study participants from a rural Michigan community to an urban area over 5 days; neither study reported an association between $PM_{2.5}$ and changes in BP.

The relationship between short-term $PM_{2.5}$ exposures and BP has also been examined in well-established cohorts including the Multi-Ethnic Study of Atherosclerosis (MESA), the Normative Aging Study (NAS), the Detroit Exposure and Aerosol Research Study (DEARS), and the Detroit Healthy Environments Partnership (DHEP) study. While Hicken et al. (2013), Mordukhovich et al.

(2009), and Wilker et al. (2009) did not find associations in participants from the MESA or NAS with 1-hour to 1-month concentrations of $PM_{2.5}$, Dvonch et al. (2009), Hicken et al. (2014), and Brook et al. (2011) found some evidence of a relationship in studies conducted in Detroit. While Brook et al. (2011) and Hicken et al. (2014) found positive associations between SBP and 1-day lag $PM_{2.5}$ concentrations or 48-hour averages, respectively, Dvonch et al. (2009) reported negative associations for SBP. Taken together, results from these panel studies in healthy populations do not provide strong support for a consistent relationship between BP and short-term exposures to $PM_{2.5}$.

In contrast, panel studies including older adult populations report consistent evidence for a relationship between $PM_{2.5}$ and BP, particularly studies including participants living in nursing homes or senior communities, allowing for improved exposure assessment. Jacobs et al. (2012) examined BP in nursing homes residents and found positive associations between 24-hour $PM_{2.5}$ concentrations and SBP, but only in participants on antihypertensive medication. No associations were found for DBP. Liu et al. (2009) and Wellenius et al. (2012b) also examined BP in nursing home residents or community dwelling seniors, respectively, and also reported positive associations between $PM_{2.5}$ and BP. While Liu et al. (2009) found increases in SBP relative to 24-hour $PM_{2.5}$ levels, Wellenius et al. (2012b) reported positive associations for both SBP and DBP across averaging times ranging from 1 to 28 days with the strongest associations for 7 and 14 day averages. In addition to older adult populations, Rich et al. (2012) examined associations between BP and $PM_{2.5}$ exposures in a panel of cardiac rehabilitation patients; positive associations were reported for SBP and the $PM_{2.5}$ levels in the preceding 6 hours.

Recent evidence is similar to that evaluated in the 2009 PM ISA (U.S. EPA, 2009) and studies continue to demonstrate inconsistent results across a variety of study designs. There is, however, some indication of associations between short-term exposures to $PM_{2.5}$ and changes in BP in subpopulations including older adults and individuals with pre-existing cardiovascular disease.

Table 6-14 Epidemiologic panel studies of short-term $PM_{2.5}$ exposure and blood pressure.

Study	Study Population and Design	Exposure Assessment	Effect Estimates 95% CI	Copollutants Examination
†Kubesch et al. (2014) Barcelona, Spain (February–November 2011)	n = 31 healthy, nonsmoking adults, 18−60 yr (28 completed all exposures) Participants exposed from 8:00−10:00 a.m. at a high and low traffic site, with and without moderate exercise. BP measurements taken before, during, and after exposure.	Monitoring conducted at site of exposure 2-h avg High traffic site Mean: 80.8 Max: 128.6 Low traffic site Mean: 30.0 Max: 80.0	Post-exposure SBP (mm Hg): 0.95 (0, 1.91) DBP (mm Hg): 0.26 (−0.4, 0.92) Intra-exposure SBP (mm Hg): 1.26 (−0.82, 3.34) DBP (mm Hg): 0.97 (−0.88, 2.83) IQR not reported	Correlation ® = 0.85 UFP, 0.93 BC, 0.91 NO_X, 0.58 PM coarse
†Liu et al. (2014b) Sault Ste. Marie, Ontario, Canada (May–August 2010)	N = 66 healthy, nonsmoking adults, 18−55 years (61 completed the study) Participants were randomly assigned to exposures that included 5 consecutive 8-h days with a 30-min exercise period near a steel plant or a college campus. BP measurements taken before, during, and after exposure.	Monitoring conducted at site of exposure Daily avg Near steel plant 11 (4.0−25.8) Near college campus 9.4 (3.3−25)	% Change SBP Lag 0: −0.38 (−1.29, 0.55) Lag 1: −0.05 (−0.98, 0.88) DBP Lag 0: −0.33 (−1.07, 0.41) Lag 1: −0.22 (−1.04, 0.60)	Correlations (*r*) NR
†Morishita et al. (2015a) Dearborn, MI (June−August 2009) (June−July 2010)	N = 25 healthy, nonsmoking adults, 18−50 yr Participants were transported from rural residence to a high PM exposure for 4−5 h on 5 consecutive days. BP measured daily after exposure.	Monitoring conducted at site of exposure Avg concentration during exposure periods: 10.8 ± 6.8	"$PM_{2.5}$ mass alone was not associated with other health outcomes"	Correlations (*r*): NR.

Table 6-14 (Continued): Epidemiologic panel studies of short-term $PM_{2.5}$ exposure and blood pressure.

Study	Study Population and Design	Exposure Assessment	Effect Estimates 95% CI	Copollutants Examination
†Weichenthal et al. (2014a) Montreal, Canada (Summer 2013)	N = 53 healthy, nonsmoking women, 18−45 yr Participants cycled continuously for 2 h in a high and low traffic setting. BP measured before and after exposure	2-h avg High Traffic: 15.7 (15.9) Low Traffic: 13.4 (13.8)	% change per 15.2 μg/m^3 $PM_{2.5}$ SBP: 0.358 (−0.970, 1.69) DBP: −0.717 (−2.54, 1.11)	Correlations (*r*): 0.080 UFP, 0.13 BC, 0.043 NO_2, 0.048 O_3
†Chung et al. (2015) Boston, MA (August 2009–June 2011)	Community Assessment of Freeway Exposure and Health study N = 270 adults living in either a community near a major freeway or community representing urban background BP measured at one (n = 50) or two clinic visits (220)	Fixed-site monitor located at clinic site; 7 km from participants' homes 24-h avg Mean (SD): 7.80(3.70) Max: 20.9	Null associations reported for 24-hour $PM_{2.5}$	Correlations (*r*): 0.79 BC, −0.01 PNC, 0.43 NO_2, 0.48 O_3
†Rich et al. (2012) Rochester, NY (June 2006–November 2009)	N = 76 patients in a 10-week cardiac rehabilitation program due to recent coronary event (83% ≥ 50 yr). BP measured at the beginning of each clinic visit	Fixed-site monitor for $PM_{2.5}$ located 1.2 km from clinic. UFPs measured at clinic site. 24-h avg Mean: 8.7 (6.1) 75th percentile: 11.1 Max: 42.9	% Change SBP 0−5 h avg: 1.31 (0.03, 2.61); IQR 7.2 DBP 96−119 h avg: 0.43 (−0.34, 1.20)	Correlations (*r*): NR.
†Jacobs et al. (2012) Antwerp, Belgium (June 2007–October 2009)	N = 88 individuals living in one of five older adult 'service flats'; 64.8% taking antihypertensive medication; 39% with past CVD BP measured at 2 clinic visits	Fixed-site monitor located 4−28 km from older adult 'service flats' 24-h avg Mean: 24.4 (19.0) Max: 100.6	SBP (mm Hg) No antihypertensives −1.49 (−5.00, 2.02) W/hypertensives 2.26 (0.53, 3.94) DBP No antihypertensive 0.77 (−1.54, 3.03) W/hypertensives 0.36 (−0.72, 1.44)	Correlations (*r*): NR.

Table 6-14 (Continued): Epidemiologic panel studies of short-term $PM_{2.5}$ exposure and blood pressure.

Study	Study Population and Design	Exposure Assessment	Effect Estimates 95% CI	Copollutants Examination
†Wellenius et al. (2012b) Boston, MA (2005−2008)	MOBILIZE study N = 747 healthy older adults, ≥70 yr; 20% adults with diabetes, 79% with hypertension, 47% with hyperlipidemia BP measured at 2 clinic visits with participants in supine and standing positions	Fixed-site monitor located <20 km from participants'' homes 24-h avg Mena: 8.6 ± 4.9	SBP (mm Hg, standing) 1 day: 0.20(−1.63, 2.04) 5 days: 2.31 (−0.77, 5.38) 7 days: 3.68 (0.00, 8.82) 14 days: 4.41 (0.00, 8.82) 21 days: 3.23 (−1.61, 8.06) 28 days: 2.76 (−2.76, 8.28) DBP (mm hg, standing) 1 day: 0.20 (−0.82, 1.22) 5 days: 1.03 (−0.77, 2.31) 7 days: 1.84 (0.00, 2.68) 14 days: 2.06 (0.00, 4.41) 21 days: 1.29 (−1.29, 3.87) 28 days: 0.69 (−2.07, 3.45)	Correlations (*r*): NR.
†Liu et al. (2009) Windsor, Ontario (February−March 2007)	N = 29 health, nonsmoking older adults recruited from 3 nursing homes, ≥65 yr BP collected from 5−16 24-h periods	Personal monitoring for 24-h before clinic visits Mean: 6.3 95th: 16.6 Outdoor monitoring at nursing homes, 24-h avg Mean: 15.3 95th: 24.2	Personal (IQR 7.1) SBP (mm Hg): 3.43 (1.43) DBP (mm Hg): 0.00 (1.26) Outdoor (IQR 9.5) SBP (mm Hg): 3.20 (1.46) DBP (mm Hg): 4.32 (1.33)	Correlations (*r*): 0.57 (outdoor $PM_{2.5}$ and BC)
†Brook et al. (2011) Detroit, MI (2005−2007)	Detroit Exposure and Aerosol Research Study (DEARS) N = 65 healthy nonsmoking adults residing in suburban neighborhoods impacted by various sources BP measured at participants' homes for up to 5 consecutive evenings	Personal and fixed-site monitoring 24-h avg Total personal Mean (SD): 21.9 ± 24.8 Max: 225.4 Ambient Mean (SD): 15.4 ± 7.5 Max: 41.0	Ambient, 1-day lag SBP (mm Hg): 0.32 (−1.052, 1.692) DBP (mm Hg): 0.02 (−1.019, 1.059) Personal, 1-day lag SBP (mm Hg): 1.41 (0.763, 2.057) DBP (mm Hg): 0.44 (−0.070, 0.950	Correlations (*r*): NR.

Table 6-14 (Continued): Epidemiologic panel studies of short-term $PM_{2.5}$ exposure and blood pressure.

Study	Study Population and Design	Exposure Assessment	Effect Estimates 95% CI	Copollutants Examination
†Dvonch et al. (2009) Detroit, MI (May 2001–April 2003)	Detroit Healthy Environments Partnership N = 347 participants residing in three communities BP measurements taken at 2 study visits	Community monitors located within 5 km of study participants Annual avg across sites: 15.0 (8.2)	Lag 2 SBP (mm Hg):3.24 DBP (mm Hg): −0.92 Per 10 μg/m^3 $PM_{2.5}$ 95% CIs NR	Correlations (*r*): NR.
†Wilker et al. (2009) Boston, MA (1995−2006)	Normative Aging Study N = 945 healthy men, 21−80 yr Blood pressure measurements taken at clinic visits every 3−5 yr	Fixed-site monitor 48-h avg Mean (SD): 11.9 (6.1)	48-h avg SBP (mm Hg): 0.69 (−0.15, 1.53) DBP (mm Hg): −0.018 (−0.45, 0.41)	Correlations (*r*): NR.
†Mordukhovich et al. (2009) Boston, MA (April 1999–December 2007)	Normative Aging Study N = 791 healthy men, 21−80 yr BP measured at clinic visits every 3−5 yr	Fixed-site monitor 7-day moving avg Mean (SD): 12.06 (4.93)	7-day moving avg SBP (mm Hg): 0.90 (−1.43, 3.23) DBP (mm Hg): 0.02 (−1.20, 1.22)	Correlations (*r*): NR.

avg = average, BC = black carbon, BP=blood pressure, CI=confidence interval, CO = carbon monoxide, DBP=diastolic blood pressure, EC = elemental carbon, ECG = electrocardiograph, hr = hour, ICD = implantable cardiac device, IQR=interquartile range, km = kilometer, mm Hg=millimeters of Mercury, NO_2 = nitrogen dioxide, NO_X = oxides of nitrogen, NR=not reported, O_3 = ozone, OC = organic carbon, PNC = particle number count, SBP=systolic blood pressure, SO_4^{2-} = sulfate, SO_2=sulfur dioxide, SD = standard deviation, yr=year(s).

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

6.1.6.3 Controlled Human Exposure Studies of Changes in Blood Pressure (BP)

Previous work in the 2004 AQCD reported decreased SBP in asthmatics and increased SBP in healthy subjects after exposure to $PM_{2.5}$ CAPS from Los Angeles while exercising (Jr et al., 2003). The same study found no significant change in DBP. In the 2009 PM ISA (U.S. EPA, 2009), a single study associated increases in DBP in healthy adults with $PM_{2.5}$ carbon content, but not with $PM_{2.5}$ mass (Urch et al., 2005). In the previous review, it was suggested that longer follow-up times may be needed after a CHE study to capture a response to slower activated BP control mechanisms. Thus, it is important to note that some of the CHE studies discussed in this review measured for potential changes in BP up to 24-hours post $PM_{2.5}$ exposure.

A few recent CHE studies have expanded our understanding of the relationship between exposure to $PM_{2.5}$ and changes in BP. Bellavia et al. (2013) reported significant elevations in SBP ($p = 0.001$), and an increase in DBP that was not statistically significant in healthy adults after exposure to fine CAP from Toronto, Canada relative to FA. Similarly, Brook et al. (2009) examined the effect of $PM_{2.5}$ CAP exposure on BP in healthy adults in Toronto, Canada. The authors reported that DBP increased linearly during the exposure resulting in a significant 2.9 mm Hg increase (CAPs; $p = 0.002$) upon completion of the exposure. A trend toward elevated SBP with CAP exposure was also reported. Tong et al. (2015) also found an association between $PM_{2.5}$ CAP exposure and BP. Adults in their upper 50s were randomization into either fish oil, olive oil, or naïve groups for a 28-day supplementation period. In the naïve group at 30 min post exposure, DBP increased by 2.1 mm hg relative to filtered-air exposure ($p = 0.04$). This same relative increase was observed 60 min after exposure in the fish oil ($p = 0.008$) and olive oil ($p = 0.03$) supplemented groups. Increases in SBP that were not statistically significant were also reported in all treatment groups.

In contrast to the studies described above, Lucking et al. (2011) found no differences in BP post DE, particle filtered DE, or FA exposure in healthy men. Similarly, in older overweight, but healthy participants, Hemmingsen et al. (2015b) found no significant changes in BP after exposure to filtered, or nonfiltered traffic related air pollution (TRAP) from Copenhagen, Denmark using a relatively low $PM_{2.5}$ exposure concentration (Table 6-15). Direct changes in blood pressure were also not reported in the FILTER-HF CHE study (Vieira et al., 2016b). This study tested whether introducing a respiratory filter could attenuate the cardiovascular effects of acute DE-exposure in patients with HF, or in healthy individuals. When the FILTER-HF patients and healthy controls exercised for 6 minutes, BP increased with exercise but there were no statistically significant differences with DE exposure with or without filtration, although it was noted that assessing changes in blood pressure in the HF group is difficult given beta-blocker use.

A few CHE studies in the current review indicate that $PM_{2.5}$ CAP has an effect on BP. However, these studies are not entirely consistent with respect to reporting changes in SBP versus DBP. That being said, it is notable that in studies where increases in one measure of BP (e.g., SBP), but not the other (e.g., DBP) was found to be statistically significant, that other measure of BP usually trended toward statistical significance. There is also some evidence that changes in blood pressure may be associated with the endotoxin present in the PM samples (Zhong et al., 2015). Taken as a whole, there is some evidence that short-term $PM_{2.5}$ exposure can result in changes in blood pressure following CAPS but not DE exposure. More information on studies published since the 2009 ISA can be found in Table 6-15 below.

Table 6-15 Study-specific details from CHE studies of short-term $PM_{2.5}$ exposure and BP.

Study	Population	Exposure Details (Concentration; Duration)	Endpoints Examined
(Bellavia et al., 2013)	Healthy adults n = 8 M, 7 F 18−60 yr old 27.7 ± NA	~242 µg/m^3 for 130 min at rest PM collected from a busy street in Toronto, Canada	BP: 10 min pre, 5 min post DNA methylation: 1 h post
(Brook et al., 2009) Toronto Cohort	Healthy adults n = 16 M; 15 F 27 ± 8	148.5 ± 54.4 µg/m^3 $PM_{2.5}$ CAP for 2 h CAP from Toronto	BP: during exposure
(Hemmingsen et al., 2015b)	Healthy overweight older adults n = 25 M, 35 F; 55−83 yr	24 ± 13 µg/m^3 (nonfiltered) 3.0 ± 1.2 µg/m^3 (filtered) $PM_{2.5}$ for 5 h at rest PM collected from a busy street in central Copenhagen, Denmark	BP: ≤1 h post
(Tong et al., 2015)	Healthy older adults n = 10 M, 32 F; 57.8 ± 1.3 yr	253 ± 16 µg/m^3 of $PM_{2.5}$ for 2 h at rest CAPs from Chapel Hill, NC Effect of supplementation with fish oil or olive oil	BP: 15 min intervals during 2 h exposure and 30 min intervals pre- and post

(Vieira et al., 2016b)	Healthy adults
	n = 8 M, 7 F;
	45 ± 10 yr; 7 with a history of smoking
	HF patients
	n = 16 M, 10 F;
	51 ± 9 yr; 19 white;
	17 with a history of smoking
		325 ± 31 µg/m^3 $PM_{2.5}$ DE generated from a diesel engine and conditioned through a refrigerated metal retainer
		25 ± 6 µg/m^3 $PM_{2.5}$ filtered DE
		21 min total exposure, 15 at rest and 6 while walking,
			BP: continuously during 6 min walking exposure

(Zhong et al., 2015)	Healthy adults n = 23 M, 27 F; 18−60 yrs	Endotoxin and B-1,3-d-glucan associated with: 250 µg/m^3 $PM_{2.5}$ CAPs (target)	BP: pre, 0.5 h and 20 h post

Table 6-15 (Continued): Study-specific details from CHE studies of short-term $PM_{2.5}$ exposure and BP.

Study	Population	Exposure Details (Concentration; Duration)	Endpoints Examined
		200 µg/m^3 Course CAPs (target) 7.07 and IQR 7.09 ng/m^3) for 130 min at rest CAPs collected from a heavy-traffic 4-lane street in Toronto	
(Lucking et al., 2011)	Healthy young men n = 19, 25 ± 3 yr	320 ± 10 µg/m^3 fine DA particles 7.2 ± 2.0 µg/m^3 particles filtered DA 1 h exposure 15 min exercise (25 L/min^2 per m^2 body) alternating with 15 min rest Particles generated with a Volvo diesel engine	BP: 2 h, 6 h, and 8 h post.

BP = blood pressure. CAP = concentrated ambient particle, DE = diesel exhaust; h = hour, F = female, IQR = interquartile range, M = male, n = number, SD = standard deviation,

6.1.6.4 Toxicological Studies of Changes in Blood Pressure (BP)

In the 2009 PM ISA, studies generally reported an increase in some measure of BP following short-term $PM_{2.5}$ exposure to CAPs (Bartoli et al., 2009; Ito et al., 2008; Chang et al., 2004). Since the publication of the 2009 PM ISA, Wagner et al. (2014b) reported statistically significant changes ($p < 0.05$) in SBP, DBP, and MAP in SH rats in three of four independent experiments compared to control animals. In an earlier study, this group similarly reported that Sprague Dawley rats with cardio-metabolic syndrome fed a high fructose diet had a statistically significant decrease ($p < 0.05$) in SBP, DBP and MAP during $PM_{2.5}$ exposure relative to control exposed animals (Wagner et al., 2014a). More information on studies published since the 2009 ISA can be found in Table 6-16 below.

Table 6-16 Study specific details from toxicological studies of short-term $PM_{2.5}$ exposure and blood pressure (BP).

Study	Study Population	Exposure Details	Endpoints Examined
(Wagner et al., 2014b)	Adult SH rats, M, n = 8/treatment group	Inhalation of $PM_{2.5}$ CAPs from Dearborn, MI collected in summer, four independent experiments $PM_{2.5}$ concentrations were 415 ± 99; 642 ± 294; 767 ± 256; and 364 ± 58 $\mu g/m^3$ respectively., 8 h/day for 4 days to air or CAPs.	BP during exposure
(Wagner et al., 2014a)	Adult Sprague-Dawley rats, M, n = 4−8 per treatment group, fed either a normal diet or a high-fructose diet.	Inhalation of 356 $\mu g/m^3$ $PM_{2.5}$ CAPs from Dearborn, MI; 8 h/day for 9 consecutive weekdays.	BP during exposure and during non-exposure times in the evening and weekend

BP = blood pressure, CAP = concentrated ambient particle, h = hour, M = male, n = number, week = week.

6.1.6.4.1 Renin-Angiotensin System

Renin is secreted by the juxtaglomerular apparatus of the kidney and converts angiotensinogen to angiotensin 1 (Ang1). In the lung, kidney, and vascular endothelium, angiotensin-converting enzyme (Ace) cleaves Ang1 to release AngII. AngII can bind the angiotensin type 1 receptor (At1r) and causes vasoconstriction and a subsequent increase in blood pressure. It can also stimulate the release of aldosterone, which also increases blood pressure. Given this direct link between changes in the renin-angiotensin system and increases in blood pressure, the effect of short-term $PM_{2.5}$ inhalation on this system was evaluated.

The 2009 ISA for PM included no short-term studies on the renin-angiotensin system following short-term exposure to $PM_{2.5}$ CAPS. Since the 2009 PM ISA, a study in rats has demonstrated that short-term exposure to $PM_{2.5}$ increased ($p < 0.05$) plasma Ang II levels (Ghelfi et al., 2010). In an additional study, Aztatzi-Aguilar et al. (2015) found a statistically significant increase ($p < 0.05$) in At1r, but not Ace mRNA in the heart. These authors also found a statistically significant increase ($p < 0.05$) in mRNA expression of the receptor B1r in the heart; this is interesting given that increases in this receptor are indicative of vasodilation rather than vasoconstriction. Taken together, there is some evidence that short-term $PM_{2.5}$ exposure can lead to changes in multiple pathways involved in the regulation of vasoconstriction/vasodilation, and thus, blood pressure. More information on studies published since the 2009 ISA can be found in Table 6-17 below. In summary, studies published since the conclusion of the 2009 PM ISA with respect to changes in BP measurements and the renin-angiotensin system provide some additional evidence that short-term exposure to $PM_{2.5}$ can result in changes in BP. These studies

also provide some evidence that genetic or dietary factor may influence the effect of $PM_{2.5}$ exposure on BP.

Table 6-17 Study-specific details from animal toxicological studies of the renin-angiotensin system.

Study	Study Population	Exposure Details	Endpoints Examined
(Ghelfi et al., 2010)	Adult Sprague Dawley rats, n = 80 total	Inhalation of 390 μg/m^3 $PM_{2.5}$ some groups pretreated with valsartan or benazepril 5 h exposure	Plasma angiotensin II immediately post
(Aztatzi-Aguilar et al., 2015)	Adult Sprague-Dawley rats, m, n = 4 per treatment group	Inhalation of 178 μg/m^3 $PM_{2.5}$ for 5 h/day for 3 days from a high traffic and industrial area north of Mexico City in early summer	Angiotensin and bradykinin system gene expression in heart tissue collected 24 h post

CAPs = concentrated ambient particles, d = day, h = hour, m = male, n = number, post = after-exposure.

6.1.7 Peripheral Vascular Disease, Venous Thromboembolism, Pulmonary Embolism

Thrombosis refers to the formation of a blood clot inside a blood vessel, while a blood clot that breaks free and travels from its initial site of formation is known as an embolus. This mass can then become lodged and occlude blood flow, thus resulting in an embolism. Thrombi typically form in the deep (i.e., popliteal, femoral, iliac) veins of the lower extremities and can give rise to emboli that lodge in the pulmonary arteries. These deep vein thromboses (DVTs) and pulmonary emboli (PE) are the most common subtypes of venous thromboembolism (VTE).

In the 2009 PM ISA, there were two hospital admission studies looking at the relationship between short-term $PM_{2.5}$ exposure and PVD. One of these studies found a positive association between hospital admissions for PVD and short-term $PM_{2.5}$ exposure while the other study observed a negative association. Thus, there was only limited evidence of an association between $PM_{2.5}$ exposure and PVD hospital admissions in the last review.

Some epidemiologic studies published since the 2009 PM ISA provide additional evidence that short-term $PM_{2.5}$ exposures may be associated with increased risk of hospital admissions for PVD. However, considerable uncertainties remain with respect to the potential for copollutant confounding given that copollutant analyses were generally lacking in these studies. That being said, the lack of copollutant analyses in epidemiologic studies is at least partially mitigated by CHE and animal toxicological studies that provide biological plausibility for these associations by demonstrating changes

in hemodynamics (e.g., an increase in coagulation factors) following short-term $PM_{2.5}$ exposure (Section 6.2.1). Nonetheless, the relationship between ED visit and hospital admissions studies for PVD and short-term $PM_{2.5}$ exposure is still considered to be uncertain.

6.1.7.1 Emergency Department (ED) Visits and Hospital Admission

The 2009 PM ISA reviewed a limited number of studies examining the association between $PM_{2.5}$ and peripheral vascular disease (PVD). The MCAPS study among U.S. Medicare beneficiaries by Dominici et al. (2006) reported a positive association between hospital admissions for PVD and $PM_{2.5}$ concentrations on the same day (lag 0). Conversely, a single-city study in Toronto observed a negative association between PVD and $PM_{2.5}$ (Burnett et al., 1999). Several recent studies evaluating $PM_{2.5}$ exposure and PVD, venous thromboembolism (VTE), pulmonary embolism, and deep vein thrombosis are now available, and provide emerging evidence that $PM_{2.5}$ may be associated with specific forms of PVD, but there is still a limited evidence base (Table 6-18).

Table 6-18 Epidemiologic studies of short-term $PM_{2.5}$ concentrations and hospital admission and emergency department visits for peripheral vascular disease.

Study	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m³	Effect Estimates 95% CI	Copollutant Examination
Dominici et al. (2006) 204 U.S. Urban Counties (1999−2002) Age ≥65 yr	Concentrations from monitors in county averaged Number NR. Study population reside an average of 5.9 miles from monitor. Median pairwise correlation between same-county monitors 0.91.	PVD	24-h avg: 13.4 (IQR 3.9) 75th: 15.2	No quantitative results presented; results presented graphically. Positive associations at lags 0 and 2.	Correlation (*r*): NA Copollutant models with: NA
Burnett et al. (1999) Toronto, Canada (1980−1994)	1 monitor $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$ values not available for full study period. Values estimated from single TSS monitor.	PVD	24-h avg: 18.0 75th: 22.0 Max: 90.0	No quantitative results presented. Authors state that there was a negative association.	Correlation (*r*): NO_2: 0.52, SO_2: 0.53, CO: 0.49, O_3: 0.10, PM_{10}: 0.91, $PM_{10-2.5}$: 0.47 Copollutant models with: NA

Table 6-18 (Continued): Epidemiologic studies of short-term $PM_{2.5}$ concentrations and hospital admission and emergency department visits for peripheral vascular disease.

Study	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m^3	Effect Estimates 95% CI	Copollutant Examination
†Bell et al. (2015) 140 U.S. Counties (1999−2010) Age ≥65 yr	Concentrations from monitors in county averaged	PVD	24-h avg: 12.3 Max: 20.2	RR Lag 0: 1.013 (1.005, 1.021)	Correlation (*r*): NA Copollutant models with: NA
†Haley et al. (2009) Eight New York Cities (2001−2005)	Weighted averages across monitors in each city 39 monitors in total.	PVD	24-h avg: 5.8 (IQR 5.9) 75th: 8.0 Max: 42.2	RR Lag 0: 1.036 (1.007, 1.066) Lag 1: 1.003 (0.989, 1.018)	Correlation (*r*): NA Copollutant models with: NA
†Talbott et al. (2014) Seven U.S. States (2001−2009)	Fused-CMAQ CMAQ model combined with monitoring data, downscaled to Census Tract resolution.	PVD	24-h avg: 6.46 to 12.83 (across seven states) 75th: 7.64 to 16.55 (across seven states)	Select ORs New Jersey Lag 0: 1.023 (0.996, 1.050) Lag 1: 1.030 (1.005, 1.056) Lag 2: 1.034 (1.040, 1.059) Lag 3: 1.059 (1.024, 1.059) New York Lag 0: 1.031 (1.015, 1.049)	Correlation (*r*): NA Copollutant models with: O_3
†Dales et al. (2010) Santiago, Chile (Apr. 1998−Aug. 2005)	Concentrations from monitors assigned to central and adjacent municipalities. 6 monitors	VTE, PE	24-h avg: 32.99 IQR: 20.02	Relative Risk VTE Lag 0−1: 1.023 (1.014, 1.031) PE Lag 0−1: 1.023 (1.016, 1.029)	Correlation (*r*): NO_2: 0.73−0.92, SO_2: 0.72−0.83, CO: 0.40−0.83, O_3: −0.32−−0.14, PM_{10}: 0.85−0.92 Copollutant models with: NA
†Shih et al. (2011) 40 U.S. Cities (1993−1998) Ages 50−79 yr	National scale spatial interpolation by kriging using U.S. EPA AQS monitors $PM_{2.5}$ data 1999−2004 only	VTE Women	24-h avg: 13.5	Hazard Ratio VTE Lag 0: 1.04 (0.89, 1.22)	Correlation (*r*): NA Copollutant models with: NA

Table 6-18 (Continued): Epidemiologic studies of short-term $PM_{2.5}$ concentrations and hospital admission and emergency department visits for peripheral vascular disease.

Study	Exposure Assessment	Outcome	Mean and Upper Percentile Concentrations µg/m³	Effect Estimates 95% CI	Copollutant Examination
†Kloog et al. (2015) Northeastern U.S. (13 States) (2000−2008) Age ≥65 yr	Spatiotemporal monitoring incorporating land use variables and AOD observations 10 × 10 km spatial resolution Cross-validation R^2 using monitors within 10 km: 0.82.	DVT, PE	2-day avg: 12.6 (6.8) 75th: 15.9 Max: 96.0	RR DVT Lag 0: 1.006 (1.001, 1.011) Lag 0−1: 1.006 (1.000, 1.013) Lag 0−2: 1.007 (1.000, 1.014) PE Lag 0: 1.007 (1.000, 1.014) Lag 0−1: 1.004 (0.993, 1.014) Lag 0−2: 1.006 (1.001, 1.011)	Correlation (*r*): NA Copollutant models with: NA
†Milojevic et al. (2014) †Milojevic et al. (2015) 15 Conurbations in England and Wales (2003−2009)	Nearest monitor to patient's residence (50 km). Number NR.	PE	24-hour avg Median: 10.0 (IQR 8.0) 75th: 15.0	RR PE Lag 0−4: 0.959 (0.927, 0.992)	Correlation (*r*): NA Copollutant models with: CO: 0.48, NO_2: 0.53, O_3: −0.10, PM_{10}: 0.86, SO_2: 0.41

CMAQ = Community Multiscale Air Quality Modeling System, CO = carbon monoxide, DVT = deep vein thrombosis, HR = hazard ratio, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, OR = odds ratio, PE = pulmonary embolism, PM_{10} = particulate matter with mean aerodynamic diameter 10 µm, $PM_{10-2.5}$ = particulate matter with mean aerodynamic diameter between 2.5 µm and 10 µm, $PM_{2.5}$ = particulate matter with mean aerodynamic diameter 2.5 µm, PVD = peripheral vascular disease, RR = relative risk, SO2 = sulfur dioxide, VTE = venous thromboembolism.

†Studies published since the 2009 PM ISA.

For the included epidemiologic studies, the focus is on those studies conducted in areas where mean $PM_{2.5}$ concentrations are <20 µg/m³ or in the case of a multi-city study where more than half of the cities have concentrations <20 µg/m³. Other studies maybe be included if they contribute to evaluating important uncertainties (see Preface).

Bell et al. (2015) considered PVD hospital admissions among U.S. Medicare beneficiaries in 140 U.S. counties. The authors observed a 1.26% (95% CI: 0.48, 2.05%) increase in hospital admissions associated with $PM_{2.5}$ concentrations on the same day (lag 0). This association was consistent with the results of the Dominici et al. (2006) MCAPS study reviewed in the 2009 PM ISA, and also a recent Medicare-based study in eight New York cities (Haley et al., 2009). A study of 7 U.S. states also reported an association in New York and in New Jersey, but did not observe an association in five other participating states (Talbott et al., 2014).

In addition to studies evaluating the association between $PM_{2.5}$ and PVD, a few recent studies specifically evaluated VTE, and related outcomes of deep vein and pulmonary embolism. With regard to VTE, studies reported inconsistent results. In Santiago, Chile, Dales et al. (2010) observed a positive association between hospital admissions for VTE and $PM_{2.5}$ concentrations at lag 0−1 (OR: 1.02 [95% CI: 1.01, 1.03]). However, a U.S. Women's Health Initiative study did not report evidence of a positive association (Shih et al., 2011).

Studies examining deep vein thrombosis and pulmonary embolism provide inconsistent evidence of an association. In a study of Medicare beneficiaries in the northeastern U.S. using spatiotemporal monitoring that incorporates land use variables and AOD to estimate $PM_{2.5}$ concentrations, Kloog et al. (2015) observed that $PM_{2.5}$ concentrations were associated with a 0.59% (95% CI: 0.07, 1.11%) higher risk of pulmonary embolism at lag 0−2 and a 0.64% (95% CI: 0.03, 1.25%) higher risk of hospital admissions for deep vein thrombosis at lag 0−1. In Santiago, Chile, Dales et al. (2010) also observed an association between $PM_{2.5}$ and pulmonary embolism. On the other hand, in a large study from England and Wales, (Milojevic et al., 2014) reported a decrease in risk of hospital admissions for pulmonary embolism at lag 0−4 (−4.11%, 95% CI: −7.29, −0.71%).

In summary, there is limited, but generally consistent evidence that short-term $PM_{2.5}$ exposure is associated with increased hospital admissions for PVD. However, the number of studies available for review is still limited and considerable uncertainties remain. Specifically, none of the reviewed studies evaluated potential copollutant confounding. Evidence regarding specific forms of PVD (i.e., VTE, deep vein thrombosis, and pulmonary embolism) is inconsistent and insufficient to determine the presence of an association.

6.1.8 Emergency Department Visits and Hospital Admission Studies of Combined Cardiovascular-Related Effects

In addition to individual cardiovascular diseases, epidemiologic studies examined cardiovascular diseases in aggregate where, in some cases, the aggregate represented all cardiovascular diseases while, in others, a specific combination of cardiovascular diseases was represented. For example, many epidemiologic studies consider hospital admissions and ED visits for combined cardiovascular-related effects, including diseases of the circulatory system. This endpoint encompasses ED visits and hospital admissions for ischemic heart disease, MI, PVD, heart failure, arrhythmia, CBVD and stroke, and diseases of pulmonary circulation. Fewer studies examine the endpoint of cardiac diseases, a subset of CVD that excludes hospitalizations for cerebrovascular disease, peripheral vascular disease, and other circulatory diseases not involving the heart or coronary circulation. The 2004 PM AQCD discussed time-series studies examining the association between ambient $PM_{2.5}$ concentrations and CVD ED visits and HA. The 2009 PM ISA further reviewed studies providing strong evidence of an association from multicity studies of adults ages 65 years and older (Bell et al., 2008; Host et al., 2008; Barnett et al.,

2006). A number of single-city studies also generally supported the presence of an association between $PM_{2.5}$ and CVD ED visits and HA. Recent studies tend to focus on overall CVD visits and continue to add to the available evidence supporting the presence of an association of daily changes in $PM_{2.5}$ with ED visits and hospital admissions for CVD. Study details and results are presented in Table 6-19.

Table 6-19 Epidemiologic studies of short-term $PM_{2.5}$ concentrations and cardiovascular-related hospital admission and emergency department (ED) visits.

Study	Exposure Assessment	Outcome ICD Codes	Mean and Upper Percentile Concentrations µg/m³	Copollutant Examination
Bell et al. (2008) 202 U.S. Counties (1999–2010) Age ≥65 yr	Concentrations from monitors in county averaged	CVD 438, 430–438, 410–414, 429, 440–449	NR	Correlation (*r*): NA Copollutant models with: NA
Host et al. (2008) Six French Cities (2000–2003)	Concentration from monitors in city averaged 4 monitors Paris, 1 Toulouse, 2 other cities. Residence within 20 km. Between-monitor $r > 0.6$	CVD, Cardiac Diseases I00–I99, I00–I52, I20–I25	24-h avg: 13.8 to 18.6 (across six cities) 95th: 25.0 to 33.0 (across six cities)	Correlation (*r*): $PM_{10-2.5}$: 0.28–0.73 Copollutant models with: NA
Barnett et al. (2006) Four Australian Cities (1998–2001)	Concentrations from monitors in city averaged 3 monitors Sydney, 2 monitors Melbourne and Perth, 1 monitor Brisbane.	CVD, Cardiac Diseases 390–459	24-h avg: 8.1 to 9.7 (across four cities) Max: 29.3 to 122.8 (across four cities)	Correlation (*r*): NA Copollutant models with: NA
†Bell et al. (2015) 213 U.S. Counties (1999–2010) Age ≥65 yr	Concentrations from monitors in county averaged	CVD 428, 426–427, 430–438, 410–414, 429, 440–448	24-h avg: 12.3 Max: 20.2	Correlation (*r*): NA Copollutant models with: NA
†Bell et al. (2014) Four Counties in Massachusetts and Connecticut (2000–2004) Age ≥65 yr	1 monitor per county for 3 counties, one CT county used populated weighted average of 2 monitors	CVD 428, 426–427, 430–438, 410–414, 429, 440–448	24-h avg: 14.0 Median: 11.7	Correlation (*r*): NA Copollutant models with: NA

Table 6-19 (Continued): Epidemiologic studies of short-term $PM_{2.5}$ concentrations and cardiovascular-related hospital admission and emergency department (ED) visits.

Study	Exposure Assessment	Outcome ICD Codes	Mean and Upper Percentile Concentrations µg/m^3	Copollutant Examination
†Kloog et al. (2012) Six New England States (2000−2008) Age ≥65 yr	Spatiotemporal monitoring incorporating land use variables and AOD observations 10 × 10 km spatial resolution Cross-validation R^2 = 0.85.	CVD 390−429	24-h avg: 9.6 75th: 11.7 Max: 72.6	Correlation (*r*): NA Copollutant models with: NA.
†Kloog et al. (2014) Seven Mid-Atlantic States and Washington, D.C. (2000−2006) Age ≥65 yr	Spatiotemporal monitoring incorporating land use variables and AOD observations 10 × 10 km spatial resolution Cross-validation R^2 = 0.81.	CVD 390−459	2-day avg: 11.92 75th: 14.65 Max: 95.85	Correlation (*r*): NA Copollutant models with: NA
†(Bravo et al., 2017) 708 U.S. Counties (2002−2006) Age ≥65 yr	Fused-CMAQ Downscaler Model CMAQ combined with monitoring data, census tract estimates used to predict county level 24 h $PM_{2.5}$.	CVD 390−459	Mean: 12.60	Correlation (*r*): NA Copollutant models with: NA
†Hsu et al. (2017) 4 New York Regions (1991−2006)	Adjusted CMAQ-simulated model (see Hogrefe et al. (2009)) 12 × 12 km grid resolution with patient residential address	CVD 393−396, 401−405, 410−414, 427, 428, 430−434, 436−438	NR	Correlation (*r*): NA Copollutant models with: O_3
†Peng et al. (2009) 119 U.S. Counties (2000−2006) Age ≥65 yr	Concentrations from monitors in county averaged Most counties contain 2 monitors, 12 counties with 1. Within county *r* = 0.85 (0.83−0.95)	CVD 428, 430−438, 410−414, 429, 440−448	24-h avg: 11.79 Median: 9.4	Correlation (*r*): NA Copollutant models with: NA
†Talbott et al. (2014) Seven U.S. States (2001−2009)	Fused-CMAQ Downscaler model combined with monitoring data, downscaled to census tract resolution.	CVD 390−459	24-h avg: 6.46 to 12.83 (across seven states) 75th: 7.64 to 16.55 (across seven states)	Correlation (*r*): NA Copollutant models with: O_3

Table 6-19 (Continued): Epidemiologic studies of short-term $PM_{2.5}$ concentrations and cardiovascular-related hospital admission and emergency department (ED) visits.

Study	Exposure Assessment	Outcome ICD Codes	Mean and Upper Percentile Concentrations $\mu g/m^3$	Copollutant Examination
†Ostro et al. (2016) Eight California Counties (2005−2009)	Nearest monitor Within 20 km of population-weighted centroid of zip code	CVD 390−459	Overall mean: 16.5 (IQR: 11.4) (across 8 counties)	Correlation (*r*): NA Copollutant models with: NA
†Zanobetti et al. (2009) 26 U.S. Cities (2000−2003) Age ≥65 yr	Concentrations from monitors in county averaged 1 to 4 monitors per county. Monitor data discarded if between-monitor correlation <0.8	CVD 390−429	2-day avg: 15.3 (across 26 cities)	Correlation (*r*): NA Copollutant models with: NA
†Milojevic et al. (2014) 15 Conurbations in England and Wales (2003−2009)	Nearest monitor to patient's residence (within 50 km). Number NR.	CVD I00−I99	24-h avg Median: 10.0 (IQR 8.0) 75th: 15.0	Correlation (*r*): CO: 0.48, NO_2: 0.53, O_3: −0.10, PM_{10}: 0.86, SO_2: 0.41 Copollutant models with: NA
†Stafoggia et al. (2013b) Eight European Cities (2001−2010) Age ≥15 yr	Concentrations from monitors in city averaged Number NR.	CVD 390−459/I00−I99	24-h avg: 17.2 to 34.4 (across eight cities)	Correlation (*r*): NO_2: >0.6 Copollutant models with: $PM_{10-2.5}$, O_3, NO_2.

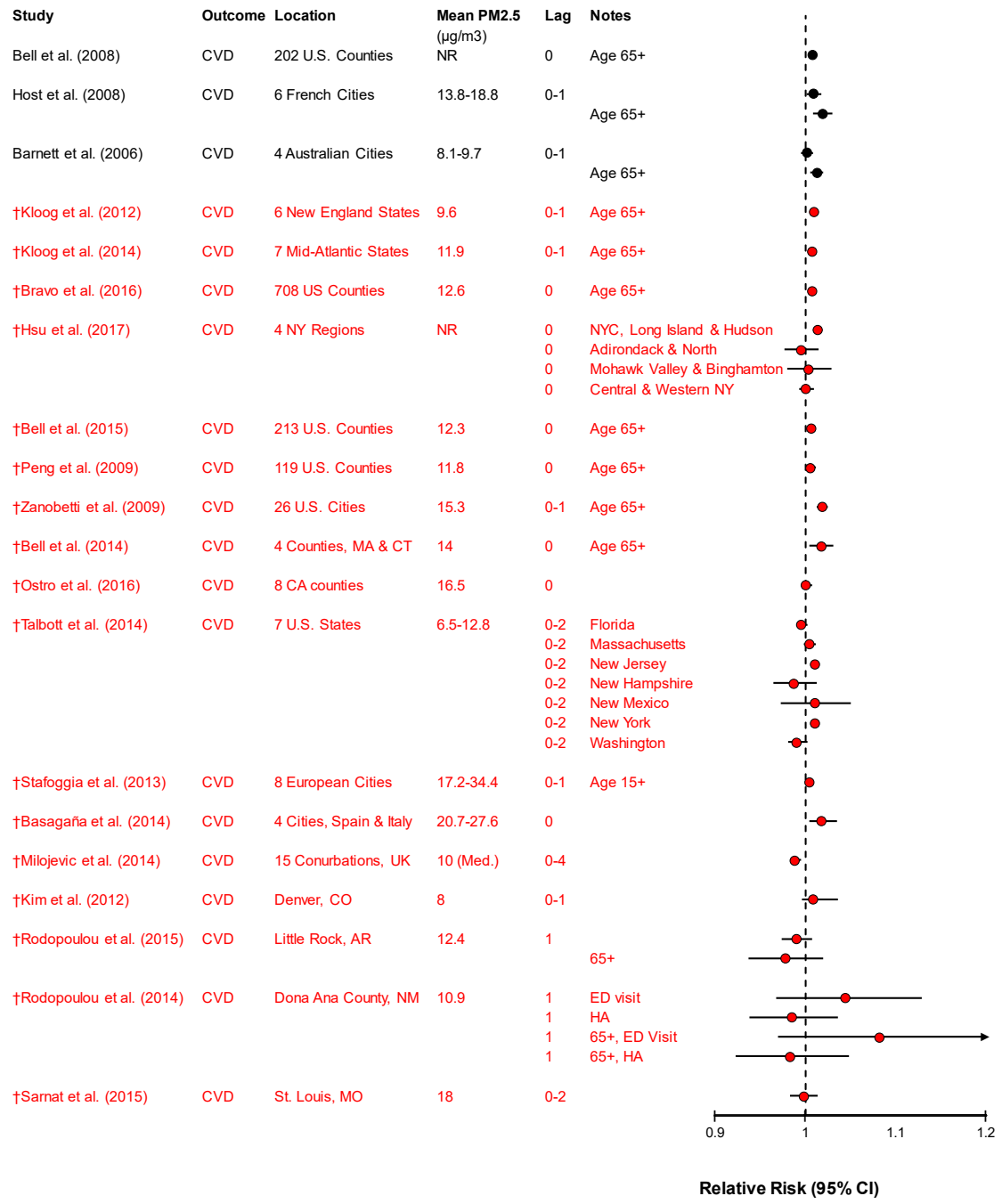
CMAQ = Community Multiscale Air Quality Modeling System, CVD = cardiovascular disease, CO = carbon monoxide, HR = hazard ratio, max = maximum, NR = not reported, NO_2 = nitrogen dioxide, OR = odds ratio, PM^{10} = particulate matter with mean aerodynamic diameter 10 μm, $PM_{10-2.5}$ = particulate matter with mean aerodynamic diameter between 2.5 μm and 10 μm, $PM_{2.5}$ = particulate matter with mean aerodynamic diameter 2.5 μm, RR = relative risk, SO_2 = sulfur dioxide.

For the included epidemiologic studies, the focus is on those studies conducted in areas where mean $PM_{2.5}$ concentrations are <20 $\mu g/m^3$ or in the case of a multi-city study where more than half of the cities have concentrations <20 $\mu g/m^3$. Other studies maybe be included if they contribute to evaluating important uncertainties (see Preface).

†Studies published since the 2009 PM ISA.

Epidemiologic studies that examined the effect of $PM_{2.5}$ on CVD ED visits and hospital admissions generally observed evidence of consistent positive associations. Several recent multicity studies in the U.S. and Europe provide additional support for positive associations between short-term $PM_{2.5}$ exposure and CVD ED visits and hospital admissions (Figure 6-6). While most studies of ED visits and hospital admissions rely on fixed-site monitoring, several recent studies assigned $PM_{2.5}$ exposure using spatiotemporal models of $PM_{2.5}$ concentration incorporating land use variables, AOD observations, and surface measurements. Studies utilizing Medicare hospital admissions in the Northeast and Mid-Atlantic reported a 1.03% (95% CI: 0.69, 1.45%) and 0.78% (95% CI: 0.54, 1.01%) increase in CVD

admissions over the previous two days (lag 0−1), respectively (Kloog et al., 2014; Kloog et al., 2012). A similar study of 708 urban and rural U.S. counties also reported a 0.79% (95% CI: 0.62, 0.97%) increased risk of CVD-related hospital admissions associated with $PM_{2.5}$ exposure over the previous two days (Bravo et al., 2017). Additionally, a study of seven U.S. states reported positive associations in Massachusetts, New Jersey, and New York, but did not observe a positive association in the other four states (Talbott et al., 2014), while a study of New York state observed a positive association near New York City at lag 0, but nulls results across the remaining regions of the state (Hsu et al., 2017).



Note: †Studies published since the 2009 PM ISA. CVD = cardiovascular disease, NR = not reported. Corresponding quantitative results are reported in Supplemental Table S6-8 (U.S. EPA, 2018).

Figure 6-6 Results of studies of short-term $PM_{2.5}$ exposure and hospital admissions and emergency department visits for cardiovascular-related effects.

There have been a number of recent multicity studies in the U.S. using $PM_{2.5}$ concentrations measured from single monitors or averaged across monitors to assign $PM_{2.5}$ exposure. The majority of these studies examined Medicare populations in cities across the U.S. Studies utilizing Medicare hospital admissions records for CVD in 213 (Bell et al., 2015), 119 (Peng et al., 2009), and 26 (Zanobetti et al., 2009) geographically diverse U.S. counties all reported increases in risk ranging from 0.6% to 1.9% (Figure 6-6). A Medicare study in four Northeastern counties also observed evidence of a positive association (Bell et al., 2014). In non-Medicare populations, a study of eight California counties reported a positive increase in risk with $PM_{2.5}$ at lag 2 (0.61%, 95% CI: −0.18%, 1.49%) (Ostro et al., 2016).

Multicity studies in Europe also provide generally consistent evidence of a positive association between short-term $PM_{2.5}$ exposure and cardiovascular-related ED visits and HA. The MED-PARTICLES study performed in eight southern European cities reported a 0.51% (95% CI: 0.12%, 0.90%) higher rate of cardiovascular-related hospital admissions for $PM_{2.5}$ concentrations averaged over the same and previous days (lag 0−1) (Stafoggia et al., 2013b). A four-city MED-PARTICLES study in Spain and Italy also observed a positive, but less precise (i.e., wider 95% CIs) association between $PM_{2.5}$ exposure and cardiovascular-related hospital admissions (1.18%, 95% CI: 0.32%, 2.04%) (Basagaña et al., 2015). On the other hand, Milojevic et al. (2014) considered cardiovascular-related hospital admissions in England and Wales and reported a negative association for PM2.5 concentrations at lag 0−4. Results from a number of single-city studies tended to be inconsistent, likely due to their generally smaller sample size and focus on a single location (Sarnat et al., 2015; Rodopoulou et al., 2014; Kim et al., 2012; Ito et al., 2011; Lall et al., 2011).

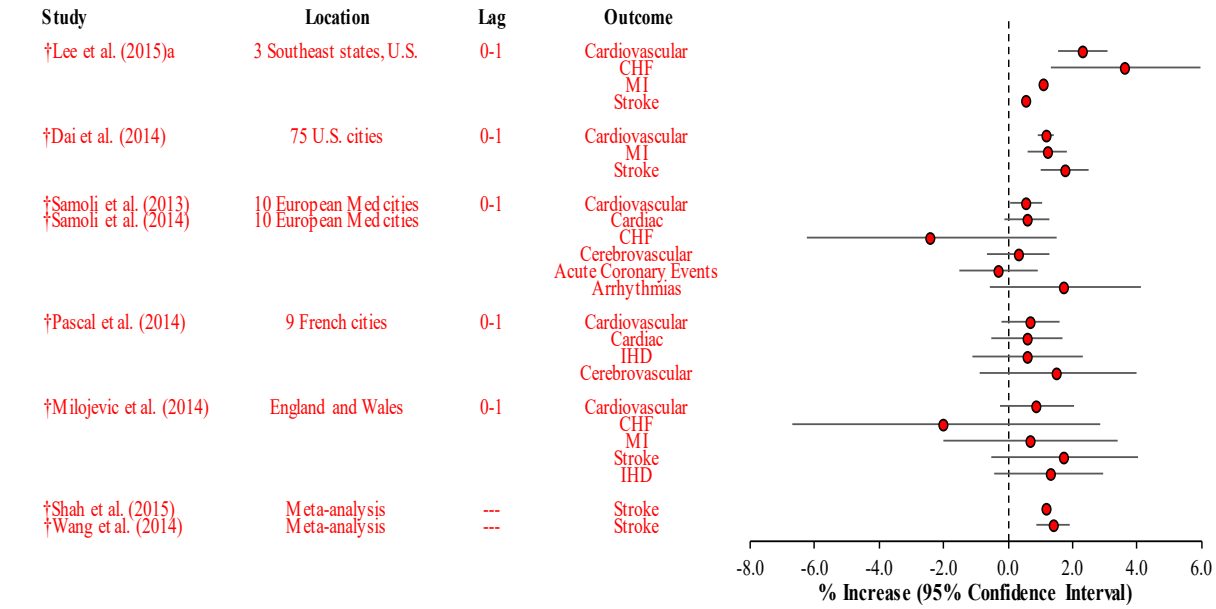
In summary, recent studies continue to provide evidence of a positive association between $PM_{2.5}$ exposure and cardiovascular-related ED visits and HA. Evidence of this association is provided by a number of multicity studies conducted across the U.S. and Europe. Single-city studies offer less consistent evidence.

6.1.9 Epidemiologic Studies of Cardiovascular Mortality

Studies that examine the association between short-term $PM_{2.5}$ exposure and cause-specific mortality outcomes, such as cardiovascular mortality, provide additional evidence for $PM_{2.5}$-related cardiovascular effects, specifically whether there is evidence of an overall continuum of effects. The multicity epidemiologic studies evaluated in the 2009 PM ISA provided evidence of consistent positive associations, ranging from 0.47–0.94% for a 10 $\mu g/m^3$ increase in 24-hour average $PM_{2.5}$ concentrations, between short-term $PM_{2.5}$ exposure and cardiovascular mortality (U.S. EPA, 2009). Across studies, the $PM_{2.5}$ effect on cardiovascular mortality was observed to be immediate with associations occurring in the range of lag 0 to 1 day(s). A limitation within the evidence was that multicity studies did not extensively examine potential copollutant confounding, but evidence from single city studies suggested that the $PM_{2.5}$-cardiovascular mortality relationship was not confounded by gaseous copollutants. In addition,

evidence from animal toxicological and controlled human exposure studies provided coherence and biological plausibility for the $PM_{2.5}$-related cardiovascular mortality associations reported in epidemiologic studies (U.S. EPA, 2009).

Recent multicity epidemiologic studies provide additional evidence of consistent positive associations between short-term $PM_{2.5}$ exposure and cardiovascular mortality at lags consistent with the 2009 PM ISA (i.e., lags 0 to 1 day) (Figure 6-7). Unlike the studies evaluated in the 2009 PM ISA, some recent studies have also further evaluated the $PM_{2.5}$-cardiovascular mortality relationship by examining cause-specific cardiovascular mortality outcomes (e.g., stroke, heart failure) (Figure 6-7). Across multicity studies there is evidence of a positive association for some of these cardiovascular mortality outcomes; however, the overall evidence is not as consistent as that observed when examining all cardiovascular mortality as detailed in Figure 6-7. This pattern of associations across cardiovascular mortality outcomes is also reflected in a single-city study conducted in Pittsburgh, PA that focused only on copollutant models including O_3 (i.e., authors did not report results of single pollutant models), but reported mean $PM_{2.5}$ concentrations similar to those observed in the multicity studies (i.e., 13.9 $\mu g/m^3$) (Dabass et al., 2016a). The difference in results across cardiovascular mortality outcomes can likely be attributed to the smaller number of mortality events observed when examining some cause-specific cardiovascular mortality outcomes, which results in unstable estimates with larger uncertainty. As a result, those studies included in the discussion of policy-relevant considerations in Section 6.1.14, specifically potential copollutant confounding, lag structure of associations, and effect modification by season and temperature focus on the combination of all cardiovascular mortality outcomes.



Note: †Studies published since the 2009 PM ISA. CHF = congestive heart failure; MI = myocardial infarction; IHD = ischemic heart disease. a = Lee et al. (2015b) did not provide 95% confidence intervals for the MI and stroke results. Corresponding quantitative results are reported in Supplemental Table S6-9(U.S. EPA, 2018).

Figure 6-7 Percent increase in cause-specific cardiovascular mortality outcomes for a 10 μg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations observed in multicity studies and meta-analyses.

6.1.10 Heart Rate (HR) and Heart Rate Variability (HRV)

Heart rate (HR), a key prognostic indicator, is modulated at the sinoatrial node of the heart by both parasympathetic and sympathetic branches of the autonomic nervous system. In general, increased sympathetic activation increases HR, while enhanced activation of parasympathetic, vagal tone, decreases HR, but HR does not, however, provide direct information on the relative contribution of each arm of the autonomic nervous system (Lahiri et al., 2008). Heart rate variability (HRV) represents the degree of difference in the inter-beat intervals of successive heartbeats and is an indicator of the relative balance of sympathetic and parasympathetic tone to the heart and their interaction (Rowan III et al., 2007). Low HRV is associated with an increased risk of cardiac arrhythmia (Corey et al., 2006) and an increased risk of mortality in people with previous myocardial infarction (Fauchier et al., 2004; Bigger et al., 1992),). In general, the two most common ways for measuring HRV are time domain measures of variability and frequency domain analysis of the power spectrum. With respect to time domain measures, the standard deviation of NN intervals (i.e., normal-to-normal or the interval between consecutive normal beats; SDNN) reflects total heart rate variability and root mean square of successive differences in NN intervals (rMSSD) reflect parasympathetic influence on the heart. In terms of frequency domain, high frequency (HF) domain is widely thought to reflect cardiac parasympathetic activity while the low frequency (LF) domain has been posited as an indicator of the interaction of the sympathetic and parasympathetic

nervous systems (Billman, 2013)although its linkage with sympathetic tone is controversial and uncertain (Notarius et al., 1999).

In the 2009 PM ISA (U.S. EPA, 2009), numerous epidemiologic panel studies observed positive associations between short-term $PM_{2.5}$ and changes in HRV indices. Some studies also reported stronger HRV decreases in individuals with pre-existing disease. In addition, CHE studies reported changes in HRV following $PM_{2.5}$ exposures more consistently in older adults.

Since the publication of the 2009 PM ISA, there have been a number of studies across disciplines indicating a relationship between short-term exposure to $PM_{2.5}$ and changes in HRV. A number of epidemiologic panel studies using quasi-experimental designs suggest that short-term exposure to $PM_{2.5}$ can elicit a change in HRV. In agreement with these panel studies is limited evidence from CHE studies reporting a shift toward sympathetic predominance following exposure to $PM_{2.5}$. Finally, there is also limited evidence for $PM_{2.5}$ effects on HRV that may be modified by seasonal/dietary/genetic factors from animal toxicological studies. Thus, in the current review there is additional evidence across disciplines that short-term exposure to $PM_{2.5}$, can lead to changes in HRV.

With respect to HR, in the current review epidemiologic panel studies generally reported inconsistent results across a handful of studies. That is, while some studies showed a change in HR following short-term exposure to $PM_{2.5}$, other panel studies did not. In addition, there was no evidence of changes in HR from CHE studies, but some evidence from animal toxicological studies indicating that short-term $PM_{2.5}$ exposure can result in changes in HR. Taken together, evidence for changes in HR in response to short-term $PM_{2.5}$ exposure is considered to be limited across disciplines.

6.1.10.1 Epidemiologic Panel Studies of Heart Rate (HR) and Heart Rate Variability (HRV)

The epidemiologic panel study evidence in the 2009 PM ISA (U.S. EPA, 2009) included numerous studies that observed associations between short-term $PM_{2.5}$ concentrations over hours to days and decreases in HRV (Table 6-20). Most of the studies reported associations between higher concentrations of $PM_{2.5}$ averaged over 24−48 hours and lower SDNN, rMSSD and HF. Some studies also reported stronger HRV decreases among individuals with pre-existing diabetes, glucose intolerance, ischemic heart disease, or hypertension and in subgroups defined by genetic polymorphisms in oxidative stress related genes, lower intake of dietary methyl nutrients and genetic polymorphisms of methionine metabolism and chronic lead exposure. The $PM_{2.5}$ associations with HRV were less marked in individuals on prescription beta-blocker medication or those who reported taking omega-3-fatty acid supplements. There were no epidemiologic panel studies that examined HR evaluated in the 2009 PM ISA.

Several panel studies published since the last review demonstrate the potential for $PM_{2.5}$ exposures to elicit a rapid change in HRV. These studies used quasi-experimental designs to evaluate the

relationship between HRV indices and well-defined $PM_{2.5}$ exposures primarily related to traffic. Weichenthal et al. (2014a) specifically evaluated effects related to 2-hour exposures in high and low traffic settings and found that time-domain measures of HRV (rMSSD and pNN50) were reduced in the 3 hours following exposures, but estimates for SDNN, LF, HF, and LF/HF were imprecise (i.e., wide confidence intervals around effect estimates). Another study evaluating traffic exposures monitored participants over the course of a day and examined 5-minute HRV measures relative to concurrent and up to very short lags of $PM_{2.5}$ concentrations with consideration of time spent commuting. In this study, (Hampel et al., 2014) observed consistent decreases in rMSSD and SDNN with concurrent and up to 30-minute lags of ambient $PM_{2.5}$ concentrations in nontraffic environments (−1.03% change in SDNN 95%CI (−1.61, −0.44); −1.37% change in rMSSD 95%CI (−2.03, −0.72) per 5.4 µg/m3, 15−19-minute lag), but generally found increases in SDNN with $PM_{2.5}$ concentrations during traffic exposures and varied estimates for rMSSD. Nyhan et al. (2014) and Liu et al. (2015b) conducted studies examining HRV in young healthy participants during different modes of commuting (e.g., subway, bus, cars, walking, cycling); however, results from these studies were not consistent. While Nyhan et al. (2014) did not observe associations between SDNN or rMSSD and ambient $PM_{2.5}$ concentrations, Liu et al. (2015b) reported consistent decreases in SDNN and rMSSD with increases in $PM_{2.5}$ concentrations for all commuters, with the strongest associations for walking commutes.

In two related studies, Brook et al. (2013b) and Morishita et al. (2015a) examined exposures to traffic-related $PM_{2.5}$ in Detroit. In both of these studies, 25 healthy rural residents in Michigan were transported to urban locations on a daily basis under controlled conditions so as to minimize ambient exposures for 5 consecutive days for 4−5 hours. 5-day averaged $PM_{2.5}$ exposures measured at home residence and the urban site were associated with 13 ms lower SDNN (95% CI: −25, −0.9) in the first published study (Brook et al., 2013b) whereas nonsignificant estimates were reported for same-day averaged $PM_{2.5}$ in a second publication (Morishita et al., 2015a).

Other recently available studies focused on associations between $PM_{2.5}$ exposure and changes in HRV in specific subpopulations, including those with pre-existing cardiovascular disease and older adults. Zanobetti et al. (2010) found decreases in rMSSD and HF with increases in PM averaged over 30 minutes up to five days in adults with ischemic heart disease. Furthermore, this study observed even larger reductions with traffic exposures in the two hours preceding HRV measures [−15.2% RMSSD (95% CI: −24.8, −4.4); −39.2% HF (95% CI: −58.0, −12.0)]. While Schneider et al. (2010) also found evidence for reductions in rMSSD and pNN50 with increasing $PM_{2.5}$ concentrations [−3.75% rMSSD (95% CI: −7.98, 0.68); −10.20% pNN50 (95% CI: −21.47, 0.25)], other studies conducted in panels with pre-existing cardiovascular disease did not find associations between $PM_{2.5}$ and SDNN, rMSSD, or pNN50 for averaging periods ranging from 1-hour up to 5-days (Bartell et al., 2013; Rich et al., 2012). In a panel of individuals with diabetes or glucose intolerance in Augsburg, very short averaging periods calculated from fixed-site monitors including concurrent time of ECG recording up to 6-hour lags of hourly averages were associated with 2−5% lower SDNN per 12.3 µg/m3 $PM_{2.5}$. Concurrent $PM_{2.5}$ was also associated with 7% lower rMSSD (95% CI: −12, −2) (Hampel et al., 2012). In a follow-up analysis, a

3.3% lower SDNN (95% CI: −5.8, −0.7) and 6.9% lower rMSSD (95% CI: −11.7, −1.7) were associated with 1-hour averages $PM_{2.5}$ per 12.3 µg/m3 (Peters et al., 2015).

HRV has also been examined in studies conducted with well-established cohorts including the MESA and the NAS. In the MESA, the strongest associations for HRV were reported between 2-day average $PM_{2.5}$ and reductions in rMSSD in repeated 10 second ECGs [−2.06% rMSSD (95% CI: −4.02, 0.0)] (Park et al., 2010). Similar associations were observed for SDNN (Park et al., 2010). Consistent with these results, the NAS used 7 minute ECGs and reported reductions in SDNN, LF, and HF [−3.8% (95% CI: −0.2, −7.4), −7.8% (95% CI: −0.4, −15.3), and −10.6% (95% CI: −1.8, −19.4)] for 2-day $PM_{2.5}$ exposures (Ren et al., 2010).

Changes in HR related to short-term exposures to $PM_{2.5}$ were generally inconsistent across the studies examining associations. While Lee et al. (2014) found decreases in HR associated with increases in 1-day lag $PM_{2.5}$ concentrations, Liu et al. (2009) found increases in HR with increasing 24-hour $PM_{2.5}$ concentrations. Increases in HR were also observed in a panel of adults with personal monitoring in Detroit relative to 1−10 hour averages of $PM_{2.5}$ exposure, but no associations were observed for 10−20 hour averages of $PM_{2.5}$ exposure or for a 1-day lag (Brook et al., 2011; Brook et al., 2010b). Morishita et al. (2015a) reported positive associations between HR and $PM_{2.5}$ in a quasi-experimental study in healthy adults transported to an urban exposure site for 5 consecutive days.

Table 6-20 Epidemiologic panel studies of short-term $PM_{2.5}$ exposure and heart rate variability.

Study	Study Population and Design	Exposure Assessment	HRV Parameters Examined	Copollutants Examined
†Morishita et al. (2015a) Dearborn, MI June−August 2009 June−July 2010	N = 25 healthy, nonsmoking adults, 18−50 yr Participants were transported from rural residence to a high PM exposure; exposures were for 4−5 h on 5 consecutive days. HRV (supine, resting) recorded for 6-min after exposure	Monitoring conducted at site of exposure Avg concentration during exposure periods: 10.8 ± 6.8	Same-day $PM_{2.5}$ SDNN, LF, HF, LF/HF	Copollutant models with: SO_4^{2-}, metals, and sources

Table 6-20 (Continued): Study-specific details from panel studies of heart rate variability and heart rate.

Study	Study Population and Design	Exposure Assessment	HRV Parameters Examined	Copollutants Examined
†Weichenthal et al. (2014a) Montreal, Canada Summer 2013	N = 53 healthy, nonsmoking women, 18−45 yr Participants cycled continuously for 2 h in a high and low traffic setting (approximately 11:00 a.m.−1:00 *p*.m.)	Personal monitoring 2-h avg High Traffic: 15.7 (15.9) Low Traffic: 13.4 (13.8)	pNN50, rMSSD, SDNN, LF, HF, LF/HF	Copollutant models with: BC, NO_2, O_3, and UFPs
†Brook et al. (2013b) Dearborn, MI June−August 2009, 2010	N = 25 healthy, nonsmoking adults (18−50 yr) Participants resided in locations with urban background levels of $PM_{2.5}$; transported to urban site for 4−5 h exposure blocks on 5 consecutive days. HRV measured (6-min recordings) 7-day before exposure, 3-h after last exposure, and 7-day after exposure	Monitoring conducted at exposure site and at 2 fixed-site monitor Urban site—averaged over exposure block Mean (SD): 11.5 (4.8) Fixed sites—7-day avg before end of exposure block Mean (SD): 9.7 (3.9) Fixed sites—7-day avg post exposure Mean (SD): 10.3 (2.7)	SDNN, HF, LF, HF/LF	Correlation (*r*): NR
†Hampel et al. (2014) Augsburg, Germany March 2008	N = 5 healthy, nonsmoking adults HRV measured in 5-min intervals over 23-h	Personal monitoring, $PM_{2.5}$ 5-min, Mean (SD) 13.2 (36.8) In traffic by car: 3.0 (1.0) In traffic by foot/bike: 6.6 (3.8) Not in traffic: 14.9 (40.0) Max: 387.1 Personal monitoring, UFPs 5-min, Mean (SD) 19,304 (32,651) In traffic by car: 7,507 (5,148) In traffic by foot/bike: 7,386 (5,462) Not in traffic: 21,674 (35,222)	HR, LF, HF, SDNN, rMSSD	Copollutant models with: UFPs, CO

Table 6-20 (Continued): Study-specific details from panel studies of heart rate variability and heart rate.

Study	Study Population and Design	Exposure Assessment	HRV Parameters Examined	Copollutants Examined
†Liu et al. (2015b) Taipei, Taiwan January–March, 2012–2014	N = 120 young, healthy students, 19–24 yr Participants monitored during 1-h (9:00 a.m.–10:00 a.m.) commutes by subway, bus, car, and walking. HRV measured during 1-h commute in 5-min segments	Personal monitoring Mean (SD); Max Subway: 22.3 (6.9); 42.1 Bus: 32.2 (12.4); 53.9 Car: 29.2 (11.3); 11.3 Walking: 42.1 (18.2); 88.1	SDNN, rMSSD	Copollutant models with: VOCs
†Nyhan et al. (2014) Dublin, Ireland	N = 32 young, healthy adults, 18–35 yr Participants monitored during 2–7 commutes (bus, train, walking, or cycling) from 8:00 a.m.–9:00 a.m. HRV measured during 1-h commute in 5-min segments	Personal monitoring Mean (SD) All: 31.2 (42.0) Bus: 18.2 (17.8) Train: 35.8 (29.0) Pedestrian: 28.7 (25.3) Cyclist: 39.1 (30.4)	SDNN, rMSSD	Correlation (*r*): NR
†Rich et al. (2012) Rochester, NY June 2006–November 2009	N = 76 patients in a 10-week cardiac rehabilitation program due to recent coronary event (83% ≥50 yr). HRV indices determined using Holter monitoring conducted during clinic visit (approx. 1-h)	Fixed-site monitor for $PM_{2.5}$ located 1.2 km from clinic. UFPs measured at clinic site. 24-h avg Mean: 8.7 (6.1) 75th percentile: 11.1 Max: 42.9	SDNN and rMSSD	Copollutant models with: UFP
†Schneider et al. (2010) Erfurt, Germany October 2000–April 2001	N = 56 patients with CAD, >50 yr HRV measured up to 12 times; 5-min ECG recordings used for HR, HF, LF, and rMSSD; 24-h recordings used for HR, SDNN, rMSSD, and pNN50	Fixed-site monitor 24-h Mean (SD) 20.3 (14.8) 75th: 26.2 Max: 84	HR, SDNN, rMSSD, LF, pNN50	Correlations (*r*): 0.5 UFP, 0.8 EC, 0.7 OC Copollutant models with: UFP, EC, OC
†Zanobetti et al. (2010) Boston, MA October 1999–January 2003	N = 46 patients with CAD, 43-75 yr, residences average of 16.7 km from monitor HRV measured over 24-h at 4 study visits; 30-min intervals used for SDNN and rMSSD.	Fixed-site monitor 72-h Mean: 9.93 95th: 19.31	SDNN, rMSSD, HF, TP	Correlations (*r*): 0.46 NO_2, 0.29 O_3 Copollutant models with: BC, O_3, NO_2

Table 6-20 (Continued): Study-specific details from panel studies of heart rate variability and heart rate.

Study	Study Population and Design	Exposure Assessment	HRV Parameters Examined	Copollutants Examined
†(Bartell et al., 2013) Los Angeles, CA 2005−2007	N = 50 adults with CAD, ≥71 yr, residing in four retirement communities HRV measured from Holter monitoring conducted for two 5-day periods; 1-h intervals used for SDNN and rMSSD	Residential monitoring 24-h avg Mean (SD): 21.1 (11.4) Max: 77.4	SDNN, rMSSD, pNN50	Correlations (*r*): 0.44 OC, 0.58 BC, 0.14 NO_X, 0.31CO, −0.38 O_3 Copollutant models with: BC, OC (primary and secondary), UFPs, NO_X, O_3, CO
†Lee et al. (2014) Boston, MA March−August 2004	N = 21 adults, 21−69 yr, residing in inner-city neighborhood HRV measured from two 24-h monitoring periods; 5-min intervals used for SDNN	Personal monitoring 5-min Mean (SD): 29.8 (77.7)	SDNN	Correlation (*r*): NR
†Brook et al. (2010b) Detroit, MI 2005−2007	Detroit Exposure and Aerosol Research Study (DEARS) N = 51 healthy nonsmoking adults residing in suburban neighborhoods impacted by various sources BP measured at participants' homes for up to 5 consecutive evenings	Personal and fixed-site monitoring 24-h avg Total personal Mean (SD): 18.0 ± 10.4 Max: 51.9 Ambient Mean (SD): 15.8 ± 7.6 Max: 38.9	HR	Correlation (*r*): NR
†Park et al. (2010) Six U.S. communities July 2000−August 2002	N = 5,465 adults, 45−85 yr HRV measured with three consecutive 10-sec recordings	Fixed-site monitoring 48-h avg 14.3	SDNN, rMSSD	Correlation (*r*): NR

Table 6-20 (Continued): Study-specific details from panel studies of heart rate variability and heart rate.

Study	Study Population and Design	Exposure Assessment	HRV Parameters Examined	Copollutants Examined
†Ren et al. (2010) Boston, MA November 2000−December 2007	N = 686 men, mean age 73 yr HRV measured over 7-min	Fixed-site monitoring 48-h Mean (SD): 11.32 (6.53)	SDNN, LF, HF	Correlation (*r*): NR.

avg = average, BC = black carbon, CO = carbon monoxide, EC = elemental carbon, ECG = electrocardiograph, HF=high frequency, HR=heart rate, hr = hour, ICD = implantable cardiac device, IQR=interquartile range, km = kilometer, LF=low frequency, LF/HF = ratio of low frequency to high frequency, NO_2 = nitrogen dioxide, NO_X = oxides of nitrogen, NR=not reported, O_3 = ozone, OC = organic carbon, PNC = particle number count, pNN50= mean number of times per hour in qhic change in consecutive normal sinus (NN) intervals exceeds 50 milliseconds, rMSSD= root mean square of successive differences in R-R intervals, SDNN= standard deviation of normal to normal R-R intervals, SO_4^{2-} = sulfate, SO_2=sulfur dioxide, SD = standard deviation, TP=total power, yr=year(s).

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

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6.1.10.2 Controlled Human Exposure Studies of Heart Rate (HR) and Heart Rate Variability (HRV)

In the 2009 PM ISA, a study examined healthy adults and adults with asthma exposed for two hours to $PM_{2.5}$ (Jr et al., 2003) and found significant increases in HR in both groups. With respect to HRV, in the 2009 PM ISA decreases in HRV in response to short-term $PM_{2.5}$ exposure were observed more consistently in CHE studies of older adults (Gong et al., 2004; Devlin et al., 2003).

Since the 2009 PM ISA, a few CHE studies have examined the effect of $PM_{2.5}$ on HR. Sivagangabalan et al. (2011) and Brook et al. (2009) reported that exposure to $PM_{2.5}$ CAP did not result in a significant difference in HR relative to FA. Similarly, in heart failure patients and healthy subjects, the FILTER-HF study indicated that HR was not significantly changed with exposure to DE or filtered DE when compared to clean air exposure. When the FILTER-HF patients exercised for 6 minutes, heart rate increased with exercise, but there were no significant differences with air pollution exposure with or without filtration (Vieira et al., 2016b).

Recent CHE studies have reported changes in indices of HRV following short-term $PM_{2.5}$ exposure. In Copenhagen, Denmark, Hemmingsen et al. (2015b) exposed older overweight, but healthy men and women to TRAP that was nonfiltered or particle filtered. HFn was statistically significantly decreased ($p < 0.05$) and LF was statistically significantly increased ($p = 0.027$) when nonfiltered TRAP was compared to particle filtered after 5 hours of exposure. In addition, SDNN was transiently reduced by 13% ($p = 0.045$) after first entering the nonfiltered TRAP chamber, but notably, this effect did not persist. Similarly, Brook et al. (2009) reported that exposure to $PM_{2.5}$ CAP resulted in significant reductions ($p < 0.05$) in both time and frequency domains of HRV. In a dietary intervention study, Tong et al. (2012) found that after a 28-day supplementation period with olive oil, there was a lower HF/LF ratio immediately after CAP exposure in older adults. This reflected an immediate increase in LF that persisted

20 hours post exposure. There were no changes in HRV time domain measurements in this study. In an additional CAP study, Huang et al. (2012) found no difference in measures of time or frequency domains of HRV when CAP exposure was compared to clean air, but noted that CAP concentrations were lower than those used in previous studies where cardiovascular effects were reported.

As previously noted, the FILTER-HF CHE study examined whether introducing a respiratory filter could attenuate the cardiovascular effects of acute DE-exposure in patients with heart failure. Results indicated that time and frequency metrics of HRV were not significantly changed with exposure to DE or filtered DE when compared to clean air exposure (Vieira et al., 2016a).

Considered as a whole, the CHE studies discussed above provide some evidence of a change in HRV following $PM_{2.5}$ CAP exposure, but not following exposure to DE. Moreover, there is no evidence from the studies discussed above since the 2009 PM ISA for changes in heart rate following short-term exposure to $PM_{2.5}$. More information on studies published since the 2009 ISA can be found in Table 6-21 below.

Table 6-21 Study specific details from controlled human exposure (CHE) studies of short-term $PM_{2.5}$ exposure and Heart Rate (HR) and Heart Rate Variability (HRV).

Study	Population	Exposure Details	Endpoints Examined
(Brook et al., 2009) Toronto Cohort	Healthy adults n = 16 M; 15 F 27 ± 8	148.5 ± 54.4 µg/m^3 $PM_{2.5}$ CAPs for 2 h CAPs from Toronto	HR: during exposure HRV time and frequency domains: pre- and just before end of exposure
(Hemmingsen et al., 2015b)	Healthy overweight older adults n = 25 M, 35 F; 55−83 yr	24 ± 13 µg/m^3 (nonfiltered) 3.0 ± 1.2 µg/m^3 (filtered) $PM_{2.5}$ for 5 h at rest PM collected from a busy street in central Copenhagen, Denmark	HRV: ≤1 h post
(Huang et al., 2012)	Healthy adults n = 7 M, 8 F; 20−36 yr	89.5 ± 10.7 µg/m^3 $PM_{2.5}$ CAPs for 2 h. During exposure, subjects completed 4 cycles of 15 minutes each rest or exercise.	HRV time-domain endpoints: 18 h post HRV frequency domain: 1 and 18 h post
(Tong et al., 2012)	Healthy adults n = 8 M 21 F; 50−72 yr 57.4 ± 1.4	278 ± 19 µg/m^3 CAP for 2 h at rest CAPs from Chapel Hill, NC Effect of supplementation with fish oil or olive oil	HRV frequency and repolarization metrics: 105 min pre, and 2 h, 20 h post HRV time domain: Holter device was wore for entire 48 period calculated from two 24-h periods

Table 6-21 (Continued): Study specific details from controlled human exposure (CHE) studies of short-term $PM_{2.5}$ exposure and Heart Rate (HR) and Heart Rate Variability (HRV).

Study	Population	Exposure Details	Endpoints Examined
(Vieira et al., 2016a)	Healthy adults n = 8 M, 7 F; 45 ± 10 yr; 14 white; 7 with a history of smoking HF patients n = 16 M, 10 F 51 ± 9 yr; 19 white; 17 with a history of smoking	325 ± 31 µg/m^3 $PM_{2.5}$ DE generated from a diesel engine and conditioned through a refrigerated metal retainer 25 ± 6 µg/m^3 $PM_{2.5}$ filtered DE 21 min total exposure, 15 at rest and 6 while walking	HRV: continuously during 21 min exposure, (15 min at rest and 6 min while walking)
(Sivagangabalan et al., 2011)	Healthy adults n = 11 M, 14 F 18−50 yr	150 µg/m^3 CAP for 2 h at rest CAPs from Toronto	HR

CAPs = concentrated ambient particle, DE = diesel exhaust, F = female, h = hour, HR = heart rate, HRV = heart rate variability, M = male, n = number, SD = standard deviation,

6.1.10.3 Toxicology Studies of Heart Rate (HR) and Heart Rate Variability (HRV)

In the 2009 PM ISA (U.S. EPA, 2009) there was some animal toxicological evidence for changes in HR following short-term exposure to $PM_{2.5}$ CAPS. Since the 2009 PM ISA, using data collected every 30 seconds or integrated over 8 hours, Rohr et al. (2011) reported that winter ($p < 0.05$), but not summer month short-term $PM_{2.5}$ exposure resulted in a statistically significant increase in HR in SH rats. Similarly, Farraj et al. (2015) also reported that during winter, but not summer $PM_{2.5}$ CAPs exposure statistically significantly decreased ($p < 0.05$) HR in SH rats compared to controls. Wagner et al. (2014b) also found a statistically significant increase in HR in two of four independent experiments in SH rats. In a separate study that evaluated diet, Wagner et al. (2014a) reported a statistically significant decrease ($p < 0.05$) in HR in Sprague Dawley rats fed a normal or high fructose chow following $PM_{2.5}$ exposure when compared to controls. However, Kurhanewicz et al. (2014) found no change in HR following $PM_{2.5}$ exposure in mice when compared to filtered air controls.

Considered as a whole, there is some evidence that exposure to $PM_{2.5}$ could lead to changes in HR, although the direction of these HR changes are not entirely consistent. This could be due to differences in study parameters such as species, strain, diet, or the season in which the $PM_{2.5}$ was collected. More information on studies published since the 2009 ISA can be found in Table 6-22 below.

6.1.10.3.1 Heart Rate Variability (HRV)

The 2009 PM ISA provided some evidence of changes in HRV following short-term $PM_{2.5}$ CAPs exposure in SH rats, but not in wild-type or $ApoE^{-/-}$ mice (U.S. EPA, 2009). Since the publication of the 2009 PM ISA, Rohr et al. (2011) collected $PM_{2.5}$ data every 30 minutes during exposure and reported that in the summer, there was a statistically significant reduction in SDNN ($p = 0.003$), but not rMSSD in SH rats, whereas a statistically significant change ($p = 0.027$) in rMSSD, but not SDNN was reported in the winter. Interestingly, these authors also reported no significant effects on rMSSD or SDNN in summer or winter using 8-hour integrated $PM_{2.5}$ measurements. In addition, Wagner et al. (2014a) found that changes in HRV metrics in Sprague Dawley rats were dependent upon diet; that is, SDNN and rMSSD both increased ($p < 0.05$) following short-term exposure to $PM_{2.5}$ CAPs in animals fed a high fructose diet. However, SDNN and rMSSD both decreased ($p < 0.05$) in normal chow fed rats (Wagner et al., 2014a) following short-term $PM_{2.5}$ exposure.

In addition to the studies presented above, Kurhanewicz et al. (2014)and Farraj et al. (2015) reported that short-term $PM_{2.5}$ exposure did not alter time or frequency measures of HRV. Similarly, in SH rats exposed to $PM_{2.5,}$ Wagner et al. (2014b) found no statistically significant change in rMSSD in four independent experiments and no statistically significant changes in SDNN in three of four of these experiments.

Taken together, there is at least some evidence from animal toxicology studies that short-term exposure to $PM_{2.5}$ may lead to changes in HRV. Moreover, these studies demonstrate that changes in HRV may be dependent upon the season in which $PM_{2.5}$ is collected and the diet of the animal being exposed. More information on studies published since the 2009 ISA can be found in Table 6-22 below.

Table 6-22 Study specific details from toxicological studies of short-term $PM_{2.5}$ exposure and heart rate (HR) and heart rate variability (HRV).

Study	Population	Exposure Details	Endpoints Examined
(Farraj et al., 2015)	Adult SH rats (12 weeks) M, n = 6/group	Inhalation of 168.7 µg/m^3 summer or 78.5 µg/m^3 winter $PM_{2.5}$ CAPS collected from Durham NC. 4 h exposure	HR, HRV time and frequency domains, in the time period immediately post to 6 h post
(Kurhanewicz et al., 2014)	Adult, C57BL/6 mice, F, (10−12 weeks), n = 5−8/group	Inhalation of 190 µg/m^3 $PM_{2.5}$ from Research Triangle Park, NC Exposed for 4 days, 4 h/day.	HR, HRV time and frequency domains continuously pre- to post exposure

Table 6-22 (Continued): Study specific details from toxicological studies of short-term $PM_{2.5}$ exposure and heart rate (HR) and heart rate variability (HRV).

Study	Population	Exposure Details	Endpoints Examined
(Rohr et al., 2011)	SH rats, male, 13−14 weeks old, n = 8 per treatment group	Inhalation of 518 μg/m^3 and 357 μg/m^3 $PM_{2.5}$ CAPs in the summer and winter, respectively from Detroit, Mi, 8 h/day for 13 days	HR, HRV time and frequency domains during exposure
(Wagner et al., 2014b)	Adult SH rats, m n = 8/treatment group	Inhalation of $PM_{2.5}$ CAPs from Dearborn, MI collected in summer, four independent experiments $PM_{2.5}$ concentrations were 415 ± 99; 642 ± 294; 767 ± 256; and 364 ± 58 μg/m^3 respectively., 8 h/day for 4 days to air or CAPs	HR, HRV time domains during exposure
(Wagner et al., 2014a)	Adult Sprague-Dawley rats, M, n = 4−8 per treatment group, fed either a normal diet or a high-fructose diet	Inhalation of 356 μg/m^3 $PM_{2.5}$ CAPs from Dearborn, MI; 8 h/day for 9 consecutive weekdays	HR, HRV time domains during exposure and during nonexposure times in the evening and weekend

CAPs = concentrated ambient particles, d = day, F = female, h = hour, HR = heart rate, HRV = heart rate variability, M = male, n = number, SH = spontaneously hypertensive.

6.1.11 Systemic Inflammation and Oxidative Stress

As discussed in detail above (Section 6.1.1), systemic inflammation has been linked to a number of CVD-related outcomes. For example, circulating cytokines such as IL-6 can stimulate the liver to release inflammatory proteins (e.g., CRP) and coagulation factors that can ultimately increase the risk of thrombosis and embolism. Similarly, oxidative stress can result in damage to healthy cells and blood vessels and further increase the inflammatory response. Thus, this section discusses the evidence for changes in markers of systemic inflammation and oxidative stress following short-term $PM_{2.5}$ exposures.

In the 2009 PM ISA (U.S. EPA, 2009), the evidence for systemic inflammation following short-term exposure to $PM_{2.5}$ was limited. This remains the case in the current ISA. That is, while some epidemiologic panel, CHE, and animal toxicological studies report changes in markers of inflammation such as IL-6 and inflammatory proteins such as CRP following short-term exposure to $PM_{2.5}$, other studies do not show changes in these and other markers of inflammation. However, it should be noted that markers of systemic inflammation such as cytokines are often transiently expressed, thus making it difficult to consistently find changes across studies using a variety of methodological approaches.

With respect to oxidative stress, in the 2009 PM ISA there were a few animal toxicological studies that provided mostly positive evidence of an effect of short-term $PM_{2.5}$ CAP exposure on markers of oxidative stress. Since the 2009 PM ISA, there are a couple of additional toxicological studies in animals reporting changes in measures of oxidative stress following short-term $PM_{2.5}$ exposure. Thus, there is additional evidence for oxidative stress following short-term exposure to $PM_{2.5}$, that adds to similar evidence from the previous review.

6.1.11.1 Epidemiologic Panel Studies of Systemic Inflammation and Oxidative Stress

There are numerous recently published epidemiologic studies examining associations between inflammatory biomarkers in circulation and short-term exposure to $PM_{2.5}$ (Table 6-23), but overall, across study designs and populations, results are inconsistent. Strak et al. (2013a) and Steenhof et al. (2014) provide some evidence of positive associations in healthy populations in a study of healthy volunteers in Utrecht, the Netherlands that were exposed to five different sites that differed appreciably in $PM_{2.5}$ concentrations. Results demonstrate that increases in $PM_{2.5}$ concentrations were associated with increased CRP as well as higher white blood count, particularly neutrophils (Steenhof et al., 2014).

However, contrary to the results just discussed, in the Heinz Nixdorf Recall study from the Ruhr Area in Germany, associations were not observed between $PM_{2.5}$ and CRP. The study included almost 4,000 population-based participants and used a chemistry transport model with a spatial resolution of 1 × 1 km grid to estimate $PM_{2.5}$ exposures Hertel et al. (2010 2010, 1075921) also observed null associations between $PM_{2.5}$ and CRP in healthy individuals in Utah based on measurements taken on days with low, moderate, and high $PM_{2.5}$ concentrations. Karottki et al. (2014) conducted a study including 78 adults from 58 homes and found that 48-hour average concentrations of $PM_{2.5}$ were associated with increased CRP. Null associations were observed for IL-6, IL1B, IL-8, white blood counts or IFN-γ (Karottki et al., 2014).

Several studies focused on populations with pre-existing cardiovascular disease, which provide some evidence for $PM_{2.5}$-associated changes in inflammatory biomarkers. Huttunen et al. (2012) conducted a study with 52 older adults with ischemic heart diseases, and found that bi-weekly measures of IL12 and CRP for a 6-month period were associated with ambient $PM_{2.5}$. Other, well-conducted studies demonstrated similar associations between $PM_{2.5}$ and inflammatory IL6 and TNF in a panel of older adults, with the strongest associations being observed for 5-day averages (Wittkopp et al., 2013; Delfino et al., 2009b). However, other studies in panels of older adults, including some with pre-existing cardiovascular conditions, did not find evidence for associations with inflammatory markers. In a panel of patients with recent myocardial infarction or unstable angina participating in a cardiac rehabilitation program in Rochester, New York, null associations were observed between CRP and $PM_{2.5}$ levels averaged over 5 hours up to 5 days (Wang et al., 2016; Rich et al., 2012), with the exception of a positive association with 72−95 hour lag concentrations. Short-term $PM_{2.5}$ exposure was not associated with CRP

or myeloperoxidase, markers of systematic inflammation, in a panel of adults with acute coronary syndrome or nonemergent cardiac catheterization (Croft et al., 2017). Similarly, Liu et al. (2009) conducted a repeated measures study with a panel of older adults residing in three nursing homes and did not observe evidence for associations between $PM_{2.5}$ and markers for inflammation and oxidative stress. $PM_{2.5}$ was also not associated with CRP, IL6, or serum amyloid A in a study of 115 postmenopausal women residing in the Seattle, WA area (Williams et al., 2011).

Table 6-23 Epidemiologic panels studies of short-term $PM_{2.5}$ exposure and systemic inflammation and oxidative stress.

Study	Study Population and Design	Exposure Assessment	Endpoints Examined	Copollutants Examined
†Strak et al. (2013a) †Steenhof et al. (2014) Utrecht, the Netherlands March–October 2009	N = 31 healthy, adult university students Participants were randomly assigned to five different exposure sites (underground train station, farm, continuous and stop/go traffic, and urban background); 5-h exposures with intermittent exercise; Endpoints examined 2 and 18-h after exposure	Monitoring conducted at exposure site 5-h mean $PM_{2.5}$ (range) Underground: 140 (123−167) Continuous traffic: 23 (17−39) Stop/go traffic: 20 (13−63) Farm: 36 (18−95) Urban background: 16 (8−30)	CRP, WBCs	Correlations (*r*): 0.22 coarse PM, 0.07 UFP, 0.17 EC, 0.39 OC, 0.72 SO_4^{2-}, −0.15 O_3, 0.45 NO_2
†O'Toole et al. (2010) Provo, Utah January–March 2009	N = 16 healthy adults, 18−25 yr Endpoints examined on days with high, moderate, and low PM concentrations	$PM_{2.5}$ concentrations reported graphically High days: >40 µg/m^3 Moderate days: 20−40 µg/m^3 Low days: <10 µg/m^3	CRP	Correlations (*r*): NR.
†Huttunen et al. (2012) November 2005–May 2006	N = 52 adults with ischemic heart disease, >50 yr Participants followed for 24 weeks	Fixed-site monitor 24-h mean (SD): 7.2 (10.4) 75th: 8.1 Max: 128.0	IL12, IL8, CRP, MPO, WBCs	Correlations (*r*): 0.34 UFPs, 0.57 $PM_{10-2.5}$

Table 6-23 (Continued): Study-specific details from panel studies of systemic inflammation.

Study	Study Population and Design	Exposure Assessment	Endpoints Examined	Copollutants Examined
†Rich et al. (2012) Rochester, NY June 2006–November 2009	N = 76 patients in a 10-week cardiac rehabilitation program due to recent coronary event (83% ≥50 yr. Up to 10 repeated measurements from weekly visits	Fixed-site monitor for $PM_{2.5}$ located 1.2 km from clinic. UFPs measured at clinic site. 24-h mean (SD): 8.7 (6.1); 8.0 (5.2) 75th percentile: 11.1; 10.7	WBCs, CRP	Correlations (*r*): NR>
†Croft et al. (2017) November 2011 – December 2013 (winter months) Rochester, NY	N = 135 patients with acute coronary syndrome or nonemergent cardiac catheterization, >18 yrs Blood draws at time of catheterization	Fixed-site monitoring 24-h mean (SD): 6.9 (3.1) Max: 15.3	CRP, MPO	Correlations (*r*): 0.65 BC, 0.44 UFPs
†Liu et al. (2009) Windsor, Ontario February−March 2007	N = 29 health, nonsmoking older adults recruited from 3 nursing homes, ≥65 yr Blood samples collected 2−3 times from each subject during study	Personal monitoring for 24-h before clinic visits Mean: 6.3 95th: 16.6 Outdoor monitoring at nursing homes, 24-h avg Mean: 15.3 95th: 24.2	CRP, IL6, TNF-α, TBARS, 8-isoprostane	Correlations (*r*): 0.48 BC
†Wittkopp et al. (2013) Los Angeles, CA	N = 60 adults with coronary artery disease residing in four retirement communities, >60 yr Blood samples collected weekly for 12 weeks	Residential monitor 24-h Mean (SD): 11.37 (9.40)	CRP, TNF-α sTNF-RII, IL6, IL6sr	Correlations (*r*): NR.
†Karottki et al. (2014) October 2011–February 2012	N = 78 nonsmoking, healthy adults, 41−68 yr, from 58 residences Blood samples collected after 2-day monitoring period	Fixed-site monitor 48-h Median: 14.4 95th: 40.5	CRP, WBCs	Correlations (*r*): 0.32 UFPs

Table 6-23 (Continued): Study-specific details from panel studies of systemic inflammation.

Study	Study Population and Design	Exposure Assessment	Endpoints Examined	Copollutants Examined
†Hertel et al. (2010) Ruhr area, Germany 2000−2003	N = 3,999 participants, 45−75 yr, with risk factors for CVD Blood samples collected at baseline assessment	Fixed-site monitor 24-h 17.23 (10.81) Max: 187	CRP	Correlations (*r*): NR.

avg = average, BC = black carbon, CI=confidence interval, CO = carbon monoxide, pressure, CRP=c-reactive protein, EC = elemental carbon, ECG = electrocardiograph, hr = hour, ICD = implantable cardiac device, IL6=interleukin 6, IL6sr=interleukin 6 soluble receptor, IL8=interleukin 8, IL12=interleukin 12, IQR=interquartile range, km = kilometer, MPO=myeloperoxidase, NO_2 = nitrogen dioxide, NO_X = oxides of nitrogen, NR=not reported, O_3 = ozone, OC = organic carbon, PNC = particle number count, SO_4^{2-} = sulfate, SO_2=sulfur dioxide, SD = standard deviation, sTNF RII=soluble tumor necrosis factor receptor 2, TBARS=thiobarbituric acid reactive substances, TNFα=tumor necrosis factor alpha, WBC=white blood cell, yr=year(s).

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

6.1.11.2 Controlled Human Exposure Studies of Short-Term $PM_{2.5}$ Exposure and Systemic Inflammation and Oxidative Stress

In the 2004 PM AQCD, exposure to $PM_{2.5}$ CAPs was not found to effect IL-6, TNF-α, WBC count, or CRP (Ghio et al., 2003). In addition, exposure to $PM_{2.5}$ CAPs was found to not effect serum amyloid A levels (Jr et al., 2003). However, Gong et al. (2004) reported the number of peripheral basophils increased in healthy, but not in COPD subjects after short-term exposure to $PM_{2.5}$.

A few CHE studies published since the 2009 PM ISA found at least some evidence of inflammation following short-term exposure to $PM_{2.5}$. Behbod et al. (2013) reported that exposure to $PM_{2.5}$ CAP resulted in healthy adults having increased blood leukocytes and neutrophils at 24 hours, but not 3-hour post exposure due in part to the endotoxin content of the sample. Similarly, Brook et al. (2009) reported that blood neutrophils and total white blood cells, but not TNF-α were higher immediately after ($p < 0.01$ vs. pre-exposure value for the same visit), but not 24-hour post CAP exposure. Notably however, these changes were not statistically significant when compare to FA exposure (Brook et al., 2009). In an additional study, Urch et al. (2010) used two different $PM_{2.5}$ CAP exposure levels and reported a statistically significant increase ($p < 0.05$) in blood IL-6 levels for the higher CAP (140 ± 6 μg/m^3) condition ($p < 0.0001$) at 3-hour, but not immediately after or the day after exposure. In addition, no significant effects were observed at the lower CAP level (64 ± 3 μg/m^3).

Although the studies mentioned above include some evidence for increases in inflammatory markers following short-term exposure to $PM_{2.5}$, some of these and other studies also reported no statistical change in a number of inflammatory markers (Vieira et al., 2016a; Hemmingsen et al., 2015a; Liu et al., 2015a; Tong et al., 2015; Behbod et al., 2013; Hazucha et al., 2013; Tong et al., 2012; Lucking et al., 2011; Urch et al., 2010). For example, relative to baseline Tong et al. (2015) reported no statistical difference in serum levels of CRP, ICAM-1, VCAM-1, IL-6, and TNF-α following $PM_{2.5}$ exposure.

Similarly, Liu et al. (2015a) did not report a statistically significant change in Il-6 or CRP and Hemmingsen et al. (2015a) did not report an increase in CRP or inflammatory cells following short-term $PM_{2.5}$ exposure.

Overall, the evidence presented above is inconsistent. This is not unexpected however, given the variability in design and subjects across these studies (Table 6-24). Thus, it can still be concluded that the studies presented above provide limited evidence that short-term exposure to $PM_{2.5}$ can result in an increase in inflammation. Moreover, these results also provide evidence that the amount of endotoxin present in $PM_{2.5}$ exposure appreciably contributes to inflammatory potential.

With respect to markers of oxidative stress, Liu et al. (2015a) reported increased levels ($p < 0.05$) of the lipid peroxidation biomarker malondialdehyde (MDA) in urine, but not blood following short-term exposure to $PM_{2.5}$. However, in the same study there was little post-exposure change in urine levels of the DNA oxidative damage biomarker OHdG. Similarly, Hemmingsen et al. (2015a) did not report changes in blood markers of oxidative stress when $PM_{2.5}$ exposure was compared to FA exposure. Thus, there is little evidence from CHE studies of a relationship between markers of oxidative stress and $PM_{2.5}$. However, given the potential transient nature for markers of oxidative stress, results of these studies may have been different if additional time points had been selected for blood and urine collection. More information on studies published since the 2009 ISA can be found in Table 6-24.

Table 6-24 Study-specific details from controlled human exposure (CHE) studies of short-term $PM_{2.5}$ exposure and inflammation and oxidative stress.

Study	Population	Exposure Details	Endpoints Examined
(Behbod et al., 2013)	Healthy adults N = 19 M; 16 F 18−60 yr old	~250 µg/m^3 fine CAP (0.1 to 2.5 microns) ~200 µg/m^3 course CAP (2.5 to 10 microns) For 130 min CAP from busy Toronto street Correlated effects with presence of endotoxin	Inflammatory cells and markers of inflammation ~45 pre- and 3 h and 24 h after start of each exposure
(Brook et al., 2009) Toronto Cohort	Healthy adults n = 16 M; 15 F 27 ± 8	148.5 ± 54.4 µg/m^3 $PM_{2.5}$ CAP for 2 h CAP from Toronto	Markers of inflammation: pre, post, and 24 h post
(Hemmingsen et al., 2015b)	Healthy overweight older adults n = 25 M, 35 F; 55−83 yr	24 ± 13 µg/m^3 (nonfiltered) 3.0 ± 1.2 µg/m^3 (filtered) $PM_{2.5}$ for 5 h at rest PM collected from a busy street in central Copenhagen, Denmark	Markers of inflammation and oxidative stress: ≤1 h post

Table 6-24 (Continued): Study-specific details from controlled human exposure (CHE) studies of short-term $PM_{2.5}$ exposure and inflammation and oxidative stress.

Study	Population	Exposure Details	Endpoints Examined
(Liu et al., 2015a)	Healthy adults n = 50; 18−60 yr 28 ± 9	238.4 ± 62.0 µg/m^3 fine cap 212.9 ± 52 µg/m^3 course cap 135.8 ± 67.2 µg/m^3 ultrafine cap for 130 min individually	Markers of inflammation: 1 h, and 21 h post
(Ramanathan et al., 2016)	Healthy adults	Used stored plasma samples from: 148.5 ± 54.4 µg/m^3 $PM_{2.5}$ (652,259 ± 460,843 particles ≥0.3 µm, 2,987 ± 1,918 particles ≥2.0 µm) 2 h exposure at rest	HDL antioxidant and anti-inflammatory capacity: pre, 1 h, and 20 h post
(Tong et al., 2012)	Healthy adults n = 8 M 21 F 50−72 yr 57.4 ± 1.4	278 ± 19 µg/m^3 CAP for 2 h at rest CAPS from Chapel Hill, NC Effect of supplementation with fish oil or olive oil	Inflammatory cells: 2 h pre, post and next day follow-up
(Tong et al., 2015)	Healthy older adults n = 10 M, 32 F	253 ± 16 µg/m^3 of $PM_{2.5}$ for 2 h at rest CAPs from Chapel Hill, NC Effect of supplementation with fish oil or olive oil	Markers of inflammation markers immediately after or 20 h post-exposure
(Urch et al., 2010)	13 non-asthmatics and 10 mild asthmatics n = 11 M 13 F 18−40 yr	150 µg/m^3 $PM_{2.5}$ for 2 h at rest	Inflammatory cells and cytokines in blood: pre, 10 min, 3 h, 20 h, post
(Lucking et al., 2011)	Healthy young men	320 ± 10 µg/m^3 fine DA particles 7.2 ± 2.0 µg/m^3 particles filtered DA 1 h exposure 15 min exercise (25 L/min^2 per m^2 body) alternating with 15 min rest Particles generated with a Volvo diesel engine	Markers of inflammation
(Hazucha et al., 2013)	Current and ex-smokers; n = 11; 3 M, 8 F 35−74 yr	108.7 ± 24.8 µg/m^3 $PM_{2.5}$ for 2 h at rest	Markers of inflammation: 3 h and 22 h post

CAP = concentrated ambient particle, DE = diesel exhaust, F = female, h = hour, HDL = high density lipoproteins, M = male, n = number, SD = standard deviation.

6.1.11.3 Toxicology Studies of Systemic Inflammation and Oxidative Stress

Toxicological studies in the 2009 PM ISA (U.S. EPA, 2009) that evaluated inflammation reported inconsistent results. Although Kodavanti et al. (2005) reported no increase in WBCs after short-term

$PM_{2.5}$ exposure, an additional study reported a significant decrease in WBC following short-term $PM_{2.5}$ exposure (Kooter et al., 2006).

Since the 2009 PM ISA, Xu et al. (2013) investigated the pulmonary and systemic inflammatory effects of $PM_{2.5}$ in mice at 5, 14, and 21 days post-exposure. PM statistically significantly increased ($p < 0.05$) monocyte chemoattractant protein-1 levels at 5 days only, while TNF-α, and IL-12 were not statistically significantly altered. However, short-term $PM_{2.5}$ exposure significantly ($p < 0.05$) increased leukocyte ($p < 0.05$) adhesion (14 day) and rolling (21 day) in the mesenteric microvasculature compared to FA. Davel et al. (2012) also reported that pulmonary arterial tissue TNF-α protein statistically significantly increased ($p < 0.05$), while IL-1-β and IL-6 protein were not modified following $PM_{2.5}$ exposure in rats. They also reported no statistically significant differences in plasma levels of TNF-α, IL-1β, and IL-6, nor did they report appreciable differences in a number of inflammatory cell types between $PM_{2.5}$ exposed and control animals. Taken together, there is at least some evidence from toxicological studies of an effect of short-term $PM_{2.5}$ exposure on markers of systemic inflammation and the ability to observe these effects are likely highly influenced by study design (e.g., exposure duration and sample collection times post-exposure). More information on these studies and their design can be found in Table 6-25.

6.1.11.3.1 Oxidative Stress

The 2009 PM ISA (U.S. EPA, 2009) evaluated the effects of short-term $PM_{2.5}$ CAPs exposure on markers of oxidative stress in animal toxicological studies and generally reported increases in these markers (Ghelfi et al., 2008; Rhoden et al., 2005; Gurgueira et al., 2002). Since the publication of the 2009 PM ISA, Davel et al. (2012) used hydroethidine fluorescence (a probe that detects superoxides) to show that short-term exposure to $PM_{2.5}$ can induce oxidative stress in pulmonary arteries of rats when compared to FA control. Similarly, Ghelfi et al. (2010) found that short-term exposure to $PM_{2.5}$ resulted in changes in markers of oxidative stress. Thus, there is limited additional evidence that short-term exposure to $PM_{2.5}$ can result in oxidative stress.

Table 6-25 Study-specific details from toxicological studies of short-term $PM_{2.5}$ exposure and systemic inflammation and oxidative stress.

Study	Population	Exposure Details	Endpoints Examined
(Xu et al., 2013)	Adult C57Bl/6 mice, lacking Adrb1, Adrb2, both, or neither	Inhalation of 143.8 μg/m^3 $PM_{2.5}$ CAPs, for 6 h/day, 5 days/week for 5, 14, and 21 days from Columbus, OH	Leukocyte rolling post 14 and 21 days exposure and blood markers of inflammation post 5, 14, and 21 days exposure
(Davel et al., 2012)	3-mo old Wistar rats, M	Inhalation of 600 μg/m^3 $PM_{2.5}$ CAPs for 3 h/day for two weeks from Sao Paulo City, Brazil	Protein markers of inflammation in the pulmonary artery post exposure Markers of inflammation in the blood post-exposure Detection of superoxide in the pulmonary artery using hydroethidine fluorescence
(Ghelfi et al., 2010)	Adult Sprague Dawley rats, n = 80 total	Inhalation of $PM_{2.5}$ some groups pretreated with valsartan or benazepril 5 h exposure	Markers of oxidative stress measured by chemiluminescence and TBARS

CAPs = concentrated ambient particle, d = day, DE = diesel exhaust, h = hour, M = male, TBARS = thiobarbituric acid reactive substances, week = week.

6.1.12 Coagulation

Coagulation refers to the process by which blood changes from a liquid to a semi-solid state in order to form a clot. Increases in coagulation factors (e.g., fibrinogen, thrombin) or decreases in factors that promote fibrinolysis such as tissue plasminogen activator (tPA) can promote clot formation, and thus, increase the potential for an embolism.

In previous reviews, evidence from epidemiologic panel, CHE, and animal toxicological studies were inconsistent, with some studies showing changes in markers of coagulation following $PM_{2.5}$ exposure while other studies did not. In general, this remains to be the case in the current review. In epidemiologic panel studies, the evidence for associations with fibrinogen was limited across studies, and the evidence for other biomarkers was similarly limited. Likewise, CHE studies provide inconsistent evidence across these studies of an effect of short-term $PM_{2.5}$ exposure on indicators for thrombosis and coagulation. Notably however, there was some evidence for changes in markers of coagulation following short-term exposure to $PM_{2.5}$ from toxicological studies in mice, but not rats. Specifically, these studies provide evidence from genetic mouse models that activation of the β-adrenergic pathway or the sympathetic nervous system contributes to changes in markers of coagulation following short-term $PM_{2.5}$ exposures (Chiarella et al., 2014). When considered as a whole, these recent studies do provide additional evidence that short-term exposure to $PM_{2.5}$ can promote clot formation. Although in some cases evidence

for increases or decreases in clotting factors is inconsistent across studies, this is largely expected given the differences in study design and the transient nature of clotting factor expression.

6.1.12.1 Panel Epidemiologic Studies of Coagulation

Several recently available studies have examined associations between short-term exposures to $PM_{2.5}$ and biomarkers related to coagulation, with fibrinogen being the most commonly studied (Table 6-26). As in the 2009 PM ISA (U.S. EPA, 2009), the evidence for associations for fibrinogen with short-term exposures to $PM_{2.5}$ remains inconsistent across studies, and the evidence for other biomarkers remains limited.

Of the recent studies, one was quasi-experimental in design. Strak et al. (2013a) conducted a study with 31 healthy volunteers in Utrecht, the Netherlands where participants were assigned in random order to five locations to capture distinct pollutant exposures including two traffic sites, an underground train station, a farm, and an urban background site. In two-pollutant models, 5-hour exposures to $PM_{2.5}$ at outdoor sites were associated with increases in vWF and platelet counts but not fibrinogen or tPA/PAI-1 complex (Strak et al., 2013a). In a follow-up analysis using an alternative determination of coagulation status, null associations were observed for $PM_{2.5}$ concentrations and FXII-mediated (intrinsic) thrombin generation (Strak et al., 2013b).

O'Toole et al. (2010) conducted a study designed to capture gradients in $PM_{2.5}$ concentrations. Blood samples were collected from young, healthy adults on a day with high $PM_{2.5}$ concentrations, a day with moderate concentrations, and two days with low concentrations. Results from this study demonstrated an increase in platelet-monocyte aggregates with increasing $PM_{2.5}$ concentrations; however, associations were not observed for pro-coagulation factor fibrinogen.

Other studies have evaluated associations for fibrinogen, lipoprotein-associated phospholipase A2, and vWF in panels with pre-existing cardiovascular conditions. Results across these studies are inconsistent (Croft et al., 2017; Wang et al., 2016; Huttunen et al., 2012; Rich et al., 2012; Brüske et al., 2011; O'Toole et al., 2010; Peters et al., 2009). Croft et al. (2017) reported positive associations between fibrinogen and 1, 12, and 24-hour lags of $PM_{2.5}$ exposure, but found no evidence of associations for d-Dimer or vWF in a panel of adults with acute coronary syndrome or nonemergent cardiac catheterization. Huttunen et al. (2012), Rich et al. (2012), Brüske et al. (2011), and Peters et al. (2009) did not observe associations for fibrinogen or other biomarkers examined.

Overall these panel studies do not provide strong support for associations between short-term $PM_{2.5}$ exposures and fibrinogen. Similarly, studies for other biomarkers of coagulation remain limited, as was the case in the last review. More information on these studies can be found in Table 6-26.

Table 6-26 Epidemiologic panel studies of short-term $PM_{2.5}$ exposure and coagulation.

Study	Study Population and Design	Exposure Assessment	Endpoints Examined	Copollutants Examined
†Strak et al. (2013a) †Strak et al. (2013b) Utrecht, the Netherlands March–October 2009	N = 31 healthy, adult university students Participants were randomly assigned to five different exposure sites (underground train station, farm, continuous and stop/go traffic, and urban background); 5-h exposures with intermittent exercise. Endpoints examined 2 and 18-h after exposure	Monitoring conducted at exposure site 5-h mean $PM_{2.5}$ (range) Underground: 140 (123−167) Continuous traffic: 23 (17−39) Stop/go traffic: 20 (13−63) Farm: 36 (18−95) Urban background: 16 (8−30)	Fibrinogen, platelet counts, vWF, thrombin potential, FXII-mediated thrombin generation	Correlations (*r*): 0.22 coarse PM, 0.07 UFP, 0.17 EC, 0.39 OC, 0.72 SO_4^{2-}, −0.15 O_3, 0.45 NO_2
†O'Toole et al. (2010) Provo, Utah January–March 2009	N = 16 healthy adults, 18−25 yr Endpoints examined on days with high, moderate, and low PM concentrations	$PM_{2.5}$ concentrations reported graphically High days: >40 µg/m^3 Moderate days: 20−40 µg/m^3 Low days: <10 µg/m^3	Platelet-monocyte aggregates and fibrinogen	Correlations (*r*): NR.
†Huttunen et al. (2012) November 2005–May 2006	N = 52 adults with ischemic heart disease, >50 yr Participants followed for 24 weeks	Fixed-site monitor 24-h mean (SD): 7.2 (10.4) 75th: 8.1 Max: 128.0	Fibrinogen	Correlations (*r*): NR.
†Peters et al. (2009) May 2003−July 2004 5 European cities	AIRGENE study N = 854 patients with history of MI, mean age 63 yr	Fixed-site monitor 24-h mean (range): 16.4 (0−95)	Fibrinogen	Correlations (*r*): NR.

Table 6-26 (Continued): Epidemiologic panel studies of short-term $PM_{2.5}$ exposure and coagulation.

Study	Study Population and Design	Exposure Assessment	Endpoints Examined	Copollutants Examined
†Brüske et al. (2011) Augsburg, Germany May 2003–February 2004	AIRGENE study N = 200 patients with history of MI, mean age 62 yr Up to 6 repeated measurements from visits every 4−6 weeks	Fixed-site monitor 24-h mean (SD): 17.4 (6.2) Max: 36.7	Lipoprotein-associated phospholipase A2	Correlations (*r*): 0.58 CO, 0.57 NO_2, 0.42 SO_2, −0.08 O_3
†Rich et al. (2012) Rochester, NY June 2006–November 2009	N = 76 patients in a 10-week cardiac rehabilitation program due to recent coronary event (83% ≥50 yrs). Up to 10 repeated measurements from weekly visits	Fixed-site monitor for $PM_{2.5}$ located 1.2 km from clinic. UFPs measured at clinic site. 24-h mean (SD): 8.7 (6.1); 8.0 (5.2) 75th percentile: 11.1; 10.7	Fibrinogen	Correlations (*r*): 0.65 BC, 0.44 UFPs
†Croft et al. (2017) Rochester, NY November 2011–December 2013 (winter months)	N = 135 patients with acute coronary syndrome or nonemergent cardiac catheterization, >18 yr Blood draws at time of catheterization	Fixed-site monitoring 24-h mean (SD): 6.9 (3.1) Max: 15.3	Fibrinogen, vWF	Correlations (*r*): 0.65 BC, 0.44 UFPs

avg = average, BC = black carbon, CI=confidence interval, CO = carbon monoxide, pressure, EC = elemental carbon, ECG = electrocardiograph, FXII=coagulation factor XII, hr = hour, ICD = implantable cardiac device, IQR=interquartile range, km = kilometer, NO_2 = nitrogen dioxide, NO_X = oxides of nitrogen, NR=not reported, O_3 = ozone, OC = organic carbon, PNC = particle number count, SO_4^{2-} = sulfate, SO_2=sulfur dioxide, SD = standard deviation, vWF= von Willebrand factor, yr=year(s).

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

6.1.12.2 Controlled Human Exposure Studies of Coagulation

Previous reviews described multiple CHE studies that evaluated the potential for thrombosis and coagulation following exposure to fine particles. Studies exposed healthy adults to $PM_{2.5}$ CAP and reported increased levels of fibrinogen (a marker for increased tendency for blood to coagulate) in both studies (Ghio et al., 2003; Ghio et al., 2000). However, in an additional study Jr et al. (2003) did not find an increase in fibrinogen, or two other coagulation markers: factor VII, or vWF. A later study by the same group in the same location evaluated older adults with COPD and also reported no associations between these coagulation indices and $PM_{2.5}$ exposure (Gong et al., 2004).

Recent studies have also examined the relationship between short-term $PM_{2.5}$ exposure and the potential for increased coagulation. Lucking et al. (2011) exposed healthy young men to FA, DE, and DE filtered using a particle trap (filtered DE). Results indicated no statistically significant difference in platelet levels. Results also indicated no statistically significant difference in tPA release (i.e., an anticoagulant) when comparing DE to FA exposures in response to the blood vessel dilator bradykinin. However, exposure to filtered DE revealed enhanced tPA release in response to bradykinin when compared to unfiltered DE ($P = 0.03$), suggesting that $PM_{2.5}$ from DE can suppress tPA release.

In the same study, Lucking et al. (2011) also performed ex vivo analyses using a Badimon chamber model 2 hours after each exposure. The procedure was designed to mimic the rheological conditions of people with mild coronary artery disease (low-shear) and more severe coronary stenosis (high-shear). When study participant's blood was pumped from the antecubital vein through the low-shear, and then the high-shear chambers, there was thrombus formation after unfiltered DE exposure compared to FA exposure in both stress chambers: 21.8% (low); $P = 0.001$ and 14.8% (high); $P = 0.02$. Exposure to filtered DE significantly reduced thrombus formation in the low-shear chamber by 15.7% ($P = 0.023$), thereby indicating that particles were at least partially responsible for thrombus formation under low-shear conditions.

In contrast to the results presented above, following $PM_{2.5}$ exposure Hazucha et al. (2013) found no change in plasminogen, vWF, tPA, D-dimer, or PAI-1 relative to pre-exposure levels in adults who currently or previously smoked. Similarly, in a dietary supplementation study, Tong et al. (2015) reported no difference in plasminogen, vWF, or fibrinogen levels immediately after, or 20 hour post exposure in naïve or subjects supplemented with olive or fish oil for four weeks prior to $PM_{2.5}$ exposure. However, these authors also reported that in volunteers supplemented with olive oil that there was a statistically significant ($p < 0.05$) increase in tPA and a decrease in D-dimer levels relative to baseline (Tong et al., 2015). In a prior dietary intervention study, these authors (Tong et al., 2012) also reported no changes in platelets immediately after or 20 hour post $PM_{2.5}$ exposure in groups supplemented with olive or fish oil. Finally, Vieira et al. (2016a) also did not report that exposure to DE or filtered DE increased platelets or other indicators of coagulation.

Taken together, the recent evidence from CHE studies appears to be inconsistent with respect to an effect of $PM_{2.5}$ exposure on indicators of thrombosis and coagulation. However, this is not particularly unexpected given variability in study design and subjects across these studies (Table 6-27). Thus, it can be concluded from the information presented above that there is some evidence that short-term exposure to $PM_{2.5}$ can result in changes in coagulation/fibrinolysis factors that can promote thrombosis. More information on studies published since the 2009 ISA can be found in Table 6-27.

Table 6-27 Study-specific details from controlled human exposure (CHE) studies of short-term $PM_{2.5}$ exposure and coagulation.

Study	Population	Exposure Details	Endpoints Examined
(Hazucha et al., 2013)	Current and ex-smokers; n = 11; 3 M, 8 F 35−74 yr	108.7 ± 24.8 μg/m^3 $PM_{2.5}$ for 2 h at rest	Markers of coagulation: 3 h and 22 h post
(Lucking et al., 2011)	Healthy young men	320 ± 10 μg/m^3 fine DA particles 7.2 ± 2.0 μg/m^3 particles filtered DA 1 h exposure 15 min exercise (25 L/min^2 per m^2 body) alternating with 15 min rest Particles generated with a Volvo diesel engine	Fibrinolytic function markers: 2 h, 6 h, and 8 h post Ex vivo thrombus formation: 2 h post in Badimon chamber Arterial stiffness: 5 m 20 m 30 m 50 m post
(Tong et al., 2012)	Healthy adults n = 8 M 21 F; 50−72 yr 57.4 ± 1.4	278 ± 19 μg/m^3 CAPs for 2 h at rest CAPS from Chapel Hill, NC Effect of supplementation with fish oil or olive oil	Platelets 2 h pre, immediately after and 20 h post
(Tong et al., 2015)	Healthy older adults n = 10 M, 32 F; 57.8 ± 1.3 yr	253 ± 16 μg/m^3 of $PM_{2.5}$ for 2 h at rest CAPs from Chapel Hill, NC Effect of supplementation with fish oil or olive oil	Markers of fibrinolysis: pre, post, and 20 h post

CAPs = concentrated ambient particle, DA = diesel exhaust, F = female, h = hour, M = male, n = number, SD = standard deviation.

6.1.12.3 Toxicology Studies of Coagulation and Thrombosis

In the 2009 PM ISA, (Sun et al., 2008a) reported that $PM_{2.5}$ increased tissue factor (TF) expression in aortas and in the atherosclerotic plaques of $ApoE^{-/-}$ mice fed a high-fat diet compared to filtered air controls.

Since the publication of the 2009 ISA, additional rodent studies have specifically measured the effects of CAPs on hemostasis and thrombosis. In rats, exposure to ambient $PM_{2.5}$ did not alter fibrinogen, platelet counts, partial thromboplastin time to activation, or prothrombin time (Davel et al., 2012). In mice however, Budinger et al. (2011) reported that short-term $PM_{2.5}$ exposure increased ($p < 0.05$) the formation of thrombin-anti-thrombin complexes in the plasma of wild type, but not $IL\text{-}6^{-/-}$ mice. In a follow-up mechanistic study, Chiarella et al. (2014) found that in mice, $PM_{2.5}$-induced increases in plasma thrombin-antithrombin complexes were reduced in the presence of the catecholamine transport inhibitor reserpine, whereas treatment with the β2-agonist albuterol exacerbated PM-dependent indicators of thrombosis. Furthermore, these $PM_{2.5}$ mediated effects were lost by pharmacological inhibition or genetic

loss of the β2-adrenergic receptor in murine alveolar macrophages. In summary, there is additional animal toxicological evidence in the current review that short-term exposure to $PM_{2.5}$ can result in an increase of factors consistent with coagulation and thrombosis in mice, but not rats. Moreover, a mechanistic study provides evidence that the β-adrenergic receptor is involved in this process in mice. More information on studies published since the 2009 ISA can be found in Table 6-28.

Table 6-28 Study-specific details from toxicological studies of short-term $PM_{2.5}$ exposure and coagulation.

Study	Population	Exposure Details	Endpoints Examined
(Budinger et al., 2011)	Adult, C57BL/6 and IL6$^{-/-}$ mice, M	Inhalation of 88.5 μg/m^3 $PM_{2.5}$ CAPs for 8 hours/day for 3 days	Formation of thrombin anti thrombin complexes post 3 days exposure
(Chiarella et al., 2014)	Adult, C57BL/6, and Adrb1$^{-/-}$, Adrb2$^{-/-}$, or Adrb1 and Adrb$^{-/-}$mice	Inhalation $PM_{2.5}$ CAP (109 μg/m^3), exposed for 8 h/day for 3 days	Plasma thrombin-anti-thrombin and thrombus formation time, TF mRNA levels post 3 days exposure
(Davel et al., 2012)	3-mo old Wistar rats, M	Inhalation of 600 μg/m^3 $PM_{2.5}$ CAPs for 3 h/day for 2 weeks from Sao Paulo City, Brazil	Hematological variables, coagulation outcomes, post 15-day exposure

CAP = concentrated ambient particle, d = day, F = female, h = hour, M = male, n = number, SD = standard deviation, TF = tissue factor

6.1.13 Endothelial Dysfunction and Arterial Stiffness

Endothelial dysfunction is the physiological impairment of the inner lining of blood vessels. Endothelial dysfunction is typically measured by flow mediated dilation percent (FMD%). It is a noninvasive technique involving measurement of the percent change in brachial artery diameter (BAD) after reactive hyperemia (increased blood flow following removal of an artery-occluding blood pressure cuff) (Thijssen et al., 2011) or pharmacological challenge. In addition to measuring FMD or BAD, experimental studies often examine biomarkers that may be indicative of endothelial dysfunction or vascular damage. These biomarkers include endothelin 1 (ET-1), and changes in the number of circulating endothelial progenitor cells (EPCs).

In the previous review, there was limited evidence from animal toxicological studies for a relationship between short-term $PM_{2.5}$ exposure and increased molecular markers of endothelial dysfunction, but a single CHE study did not show a relationship between short-term $PM_{2.5}$ exposure and clinical measures of endothelial dysfunction (e.g., BAD). In contrast, there is considerable and consistent recent evidence of endothelial dysfunction following short-term PM2.5 exposure. Specifically, there is at

least some evidence from more recent epidemiologic panel studies and consistent evidence from CHE and animal toxicological studies of endothelial dysfunction or markers of endothelial dysfunction following short-term exposure to $PM_{2.5}$.

Arterial stiffness is associated with a variety of cardiovascular risk factors and outcomes (Laurent et al., 2006). Carotid-femoral pulse wave velocity (PWV) is used to directly and noninvasively measure arterial stiffness. PWV measures the velocity at which the pulse generated by the heart travels through the arteries, typically measured by the foot-to-foot method (end diastole of the wave in the carotid artery to end diastole of the wave in the femoral artery). There is no recent evidence that short-term exposure to $PM_{2.5}$ can result in changes in arterial stiffness.

6.1.13.1 Panel Epidemiologic Studies of Impaired Vascular Function

Several epidemiologic studies examined the relationship between ambient $PM_{2.5}$ and vasomotor function, particularly for brachial artery diameter and flow-mediated or nitroglycerin-mediated dilation (Table 6-29).

A series of analyses were done using the Detroit Exposure and Aerosol Research Study (DEARS) data focused on personal measures of $PM_{2.5}$ and vascular measurements in nonsmoking adults. In these studies, positive associations were observed between 2-hour $PM_{2.5}$ and vasoconstriction, as indicated by brachial artery diameter (BAD); however, vasodilation was observed relative to $PM_{2.5}$ concentrations with a 2-day lag (Brook et al., 2011; Brook et al., 2010b). Flow-mediated dilation (FMD) and nitroglycerin-mediated dilation (NMD) were also measured in these studies, but associations were only observed for 2-hour averages of $PM_{2.5}$ and decreases in FMD. Other studies examining BAD, FMD, and NMD did not provide evidence of associations in either older or younger adults (Liu et al., 2014b; Liu et al., 2009).

6.1.13.1.1 Digital Vascular Function

By measuring the microvessel pulse-wave amplitude of the index finger in resting state and after cuff-induced occlusion, short-term $PM_{2.5}$ changes can be studied in relation to resting pulse-wave amplitude and to endothelium dependent reactive hyperemia. In roughly 2,400 participants of the Framingham Heart Study living in Boston, MA higher 1, 2, and 3-day averages of ambient $PM_{2.5}$ concentrations were associated with higher microvessel dilation (Ljungman et al., 2014). Another measure of microvascular function is central retinal arterial and venous diameter, where narrower arterial equivalents and wider venular equivalents are linked, with increased risk for more severe cardiovascular events including myocardial infarction and stroke. In the MESA study, preceding day $PM_{2.5}$ levels were associated with smaller central retinal arteriolar equivalents, and null associations were observed for venular equivalents (Adar et al., 2010).

6.1.13.1.2 Arterial Stiffness

Arterial stiffness can be measured using the augmentation index (Aix). Increases in this index indicate greater arterial stiffness and may represent increased risk of an adverse cardiovascular event. Stiffening of the elastic arteries has been associated with premature mortality and morbidity (Avolio et al., 2009; Laurent et al., 2001) plausibly increasing the cardiac load and leading to higher pulse pressure into the peripheral circulation and contributing to end-organ damage in the brain and kidneys (Mitchell, 2008). Several different measures of arterial stiffness are available including carotid femoral pulse wave velocity (CFPWV), augmentation index (AI), and aortic pulse pressure. CFPWV is generally considered to be the gold standard approach (Mitchell, 2009).

Morishita et al. (2015a) examined changes in AIX relative to ambient $PM_{2.5}$ in small panel of healthy adults and found no evidence of an association with same day $PM_{2.5}$ exposures.

6.1.13.1.3 Biomarkers of Endothelial Injury

Two studies reviewed in the 2009 PM ISA reported positive associations between short-term levels of PM and endothelial biomarkers (Delfino et al., 2008; O'Neill et al., 2007). Higher mean $PM_{2.5}$ during the preceding 1−6 days was associated with higher inter-cellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in 92 Boston residents with Type 2 diabetes (O'Neill et al., 2007). ICAM-1, VCAM-1, endothelial-leucocyte adhesion molecule (E-selectin) and *P*-selectin are specific markers of endothelial activation. Markers of vasodilation include vascular endothelial growth factor (VEGF), and markers of vasoconstriction include endothelin-1 (ET-1).

Other recently published studies have examined the relationship between short-term $PM_{2.5}$ concentration sand adhesion molecules. Madrigano et al. (2010) and Wilker et al. (2011) conducted analyses as part of the Normative Ageing Study from Boston, MA and examined 7-day and 2-day average $PM_{2.5}$ exposures, respectively. Results from these studies demonstrate that seven-day, but not 2-day, average level of $PM_{2.5}$ are associated with both higher VCAM-1 (6.0%, 95% CI 1.4, 10.9) and ICAM-1 (7.4%, 95% CI 3.8, 11.1).

Liu et al. (2009) also examined biomarkers related to vascular function in 28 nonsmoking seniors in nursing homes in Windsor, Ontario with residential monitoring. Positive associations were observed for personal $PM_{2.5}$ exposures and VEGF, but not for personal exposures and ET-1 or with ambient $PM_{2.5}$ concentrations (Liu et al., 2009).

In summary these studies overall indicate possible PM effects on adhesion molecules (VCAM-1 and ICAM-1), but the evidence base is limited. More information on these studies can be found in Table 6-29.

Table 6-29 Epidemiologic panel studies of short-term $PM_{2.5}$ exposure and endothelial dysfunction.

Study	Study Population and Design	Exposure Assessment	Effect Estimates (95% CI)	Copollutants Examined
†Weichenthal et al. (2014a) Montreal, Canada Summer 2013	N = 53 healthy, nonsmoking women, 18−45 yr Participants cycled continuously for 2 h in a high and low traffic setting (approximately 11:00 a.m.−1:00 *p*.m.) RHI measured 3 h after exposures (nitroglycerin-mediated)	Personal monitoring 2-h avg High Traffic: 15.7 (15.9) Low Traffic: 13.4 (13.8)	RHI 1.56% (−2.89, 6.02) per 15.2 µg/m^3	Correlations (*r*): NR.
†Brook et al. (2013b) Dearborn, MI June−August 2009, 2010	N = 25 healthy, nonsmoking adults (18−50 yr) Participants resided in locations with urban background levels of $PM_{2.5}$; transported to urban site for 4−5 hr exposure blocks on 5 consecutive days. Measurements taken 7-day before exposure, 3-hour after last exposure, and 7-day after exposure	Monitoring conducted at exposure site and at 2 fixed-site monitor Urban site—averaged over exposure block Mean (SD): 11.5 (4.8) Fixed sites—7-day avg before end of exposure block Mean (SD): 9.7 (3.9) Fixed sites—7-day avg post exposure Mean (SD): 10.3 (2.7)	RHI, AI, PWV "No other CV outcome or blood biomarker (cytokines, PBMC) beyond HOMA-IR and SDNN was associated with the 5-day $PM_{2.5}$ exposure levels."	Correlations (*r*): NR.
†Morishita et al. (2015a) Dearborn, MI June−August 2009 June−July 2010	N = 25 healthy, nonsmoking adults, 18−50 yr Participants were transported from rural residence to a high PM exposure; exposures were for 4-5 hr on 5 consecutive days. Reactive hyperemia determined by finger pulse amplitude tonometry each day after exposure	Monitoring conducted at site of exposure Avg concentration during exposure periods: 10.8 ± 6.8	RHI, AI, PWV "$PM_{2.5}$ mass alone was not associated with other health outcomes"	Correlations (*r*): 0.59 EC, 0.47 OC

Table 6-29 (Continued): Epidemiologic panel studies of short-term $PM_{2.5}$ exposure and endothelial dysfunction.

Study	Study Population and Design	Exposure Assessment	Effect Estimates (95% CI)	Copollutants Examined
†Liu et al. (2014b) Sault Ste. Marie, Ontario, Canada May–August 2010	N = 66 healthy, nonsmoking adults, 18−55 yr (61 completed the study) Participants were randomly assigned to exposures that included 5 consecutive 8-h days with a 30-min exercise period near a steel plant	Monitoring conducted at site of exposure Daily avg (5−95th) 11 (4.0−25.8)	% Change Lag 0: 0.04 (−0.11, 0.18) Lag 1: −0.01 (−0.14, 0.12) Per 9.6 μg/m^3 $PM_{2.5}$	Correlations (*r*): NR.
†Liu et al. (2009) Windsor, Ontario February−March 2007	N = 29 health, nonsmoking older adults recruited from 3 nursing homes, ≥65 yr	Personal monitoring for 24-h before clinic visits Mean: 6.3 95th: 16.6 Outdoor monitoring at nursing homes, 24-h avg Mean: 15.3 95th: 24.2	BAD: 0.02 (0.02) FMD: 0.13 (0.24) Per IQR: 7.1 μg/m^3 $PM_{2.5}$	Correlations (*r*): 0.57 BC
†Adar et al. (2010) Six U.S. communities July 2000−August 2002	MESA N = 5,465 adults, 46−87 yr CRAE measured at second MESA examine	Fixed-site monitoring 24-h avg 15.4 (9.1)	24-h lag CRAE −0.6 μm (−1.0, −0.2) CRVE −0.1 (−0.7, 0.5)	Correlations (*r*): NR.
†Ljungman et al. (2014) Boston, MA 2003−2008	Framingham Heart Study Offspring and Third Generation Cohorts N = 2,369 participants residing within 50 km of monitor Peripheral arterial tonometry hyperemic response measured at clinic visit	Fixed-site monitoring 24-h avg Mean (SD): 9.6 (5.3)	PAT Results reported graphically; 1 to 5-day avg null, 7-day avg positive PWA 2-day avg 5.9% (1.9, 10.0) 3-day avg 6.4% (2.0, 10.9) Per 5 μg/m^3 $PM_{2.5}$	Correlations (*r*): 0.69 BC, −0.16 UFPs, 0.86 SO_4^{2-}, 0.37 NO_X, 0.20 O_3
†Madrigano et al. (2010) Boston, MA 1999−2008	Normative Aging Study N = 809 white men Blood drawn at 1−5 visits per participant, visits occurred every 3−5 yr	Fixed-site monitoring 24-h avg 10.67 (6.49)	Biomarkers examined: sICAM-1, sVCAM-1	Correlations (*r*): NR.

Table 6-29 (Continued): Epidemiologic panel studies of short-term $PM_{2.5}$ exposure and endothelial dysfunction.

Study	Study Population and Design	Exposure Assessment	Effect Estimates (95% CI)	Copollutants Examined
†Wilker et al. (2011) Boston, MA 1999−2008	Normative Aging Study N = 723 white men Blood drawn at 1−5 visits per participant, visits occurred every 3−5 yr	Fixed-site monitoring IQR: 4.7	Biomarkers examined: sICAM-1, sVCAM-1	Correlations (*r*): NR.
†Brook et al. (2010b) Detroit, MI 2005−2007	Detroit Exposure and Aerosol Research Study (DEARS) N = 51 healthy nonsmoking adults residing in suburban neighborhoods impacted by various sources CV measurements taken on five consecutive evenings	Personal and fixed-site monitoring 24-h avg Total personal Mean (SD): 18.0 ± 10.4 Max: 51.9 Ambient Mean (SD): 15.8 ± 7.6 Max: 38.9	Results reported graphically. BAD: Positive association for 2-h lag FMD: Negative association for 2-h lag	Correlations (*r*): NR.
†Brook et al. (2011) Detroit, MI 2005−2007	Detroit Exposure and Aerosol Research Study (DEARS) N = 65 healthy nonsmoking adults residing in suburban neighborhoods impacted by various sources BP measured at participants' homes for up to 5 consecutive evenings	Personal and fixed-site monitoring 24-h avg Total personal Mean (SD): 21.9 ± 24.8 Max: 225.4 Ambient Mean (SD): 15.4 ± 7.5 Max: 41.0	Lag 2, personal exposure BAD (mm) −0.08 (−0.158, −0.002) NMD (%) 0.13 (−1.771, 2.031) FMD (%) −0.59 (−1.629, 0.449)	Correlations (*r*): NR.

AI = augmentation index, avg = average, BAD = brachial artery diameter, BC = black carbon, CRAE = central retinal artery equivalent, CRVE = central retinal vein equivalent, CV = cardiovascular, EC = elemental carbon, FMD = flow mediated dilation, h = hour, IQR = interquartile range, MESA = multiethnic study of atherosclerosis, NMD = nitroglycerin-mediated dilation, NO_X = oxides of nitrogen, NR=not reported O_3 = ozone, OC = organic carbon, PAT = pulse amplitude tonometry, PWV = pulse wave velocity, RHI = reactive hyperemia index, SD = standard deviation, SO_4^{2-} = sulfate, UFPs = ultrafine particles, yr=year(s).

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

6.1.13.2 Controlled Human Exposure Studies of Short-Term $PM_{2.5}$ Exposure and Impaired Vascular Function

In the 2009 PM ISA (U.S. EPA, 2009), a CHE study examined the relationship between $PM_{2.5}$ exposure and vascular function. Bräuner et al. (2008) found no changes in vasoconstriction following a 24-hour exposure to unfiltered or particle filtered $PM_{2.5}$ urban traffic particles. In the current review, additional CHE studies have explored the relationship between exposure to $PM_{2.5}$ and vascular function.

As described below, these studies generally report decreases in vascular function following $PM_{2.5}$ CAP and unfiltered DE exposure.

Studies using ambient particles, Hemmingsen et al. (2015b), (Tong et al., 2015), and Brook et al. (2009) found at least some measure of impaired vascular function following $PM_{2.5}$ exposure. Hemmingsen et al. (2015b) reported a 12% significant decrease in brachial artery flow following nitroglycerin ($p = 0.033$) administration and a 5% decrease (not statistically significant) after reactive hyperemia when comparing nonfiltered to particle filtered air from Copenhagen, Denmark. Similarly, in a dietary supplementation study, healthy older adults were randomized to fish oil, olive oil, or naïve treatment groups for a 28-day supplementation period followed by exposure to FA then CAP (Tong et al., 2015). In response to reactive hyperemia, the authors reported significantly decreased FMD of the brachial artery immediately after CAP exposure in both the naïve; ($p = 0.03$) and fish oil ($p = 0.01$) groups relative to baseline measurement before treatment. Notably, at 20-hour post exposure, FMD for the fish oil group remained lower ($p = 0.01$). Finally, Brook et al. (2009) examined the effects of $PM_{2.5}$ from Toronto, Canada on vascular function in healthy adults. Immediately after exposure there was not a decrease in FMD or NMD, but the authors did report that FMD, but not NMD was statistically significantly decreased 24 hours after CAP exposure compared to baseline for the same visit ($p < 0.05$), but not relative to filter air exposure.

A PM effect on vascular function was also reported in a filtered DE study by Lucking et al. (2011). Healthy young men were exposed to FA, unfiltered DE, and filtered DE. When unfiltered DE was compared to FA, forearm blood flow was found to be impaired in response to the endothelium dependent vasoactive substances acetylcholine ($p = 0.01$) and bradykinin ($p = 0.009$), as well as the endothelium independent (and nitric oxide (NO) independent) vasoactive substance verapamil ($p = 0.03$). Importantly, there was not an impaired response when comparing filtered DE to FA, thereby indicating that it was likely the particles were responsible for the impaired blood flow following administration of the vasoactive agents. Finally, there was no statistically significant difference in forearm blood flow between DE and FA in response to the endothelial-independent vasodilator sodium nitroprusside (SNP), but interestingly, there was increased blood flow in response to SNP when comparing filtered DE to unfiltered DE ($p = 0.04$). Similarly, in the FILTER-HF study, healthy adult controls and HF patients were exposed to DE or filtered DE. A statistically significant 21% decrease in blood flow was demonstrated in the HF group only ($p < 0.05$) after reactive hyperemia, and this effect was almost completely attenuated ($p = 0.019$) with particle filtration (Vieira et al., 2016a).

With respect to biomarkers of endothelial dysfunction, Tong et al. (2015) did report a statistically significant ($p < 0.05$) increase in the vasoconstrictor ET-1 in blood 20 hours post-exposure in the naïve treatment group relative to baseline. In addition, Liu et al. (2015a) examined the potential for $PM_{2.5}$ CAP exposure to increase blood and urine levels of VEGF and ET-1. Statistically significant increases in ET-1 and VEGF were not found in the blood, but urine sampling revealed a statistically significant increase for VEGF at 1 hour, but not 21 hours (although still elevated). The authors also provided evidence that CAP

endotoxin content may contribute to the observed effects. Similarly, Zhong et al. (2015) reported that increases in VEGF in response to PM exposure are also associated with the amount of endotoxin present in the sample.

Taken together, recent CHE studies do show evidence of a $PM_{2.5}$ effect on vascular function. In contrast to the results reported in the single study from the previous review, all of the current studies report some effect of $PM_{2.5}$ ambient particles or DE particles on measures of blood flow. However, the timing of the response varied among studies. Studies were also not completely consistent with respect to the decreased blood flow response when comparing endothelial dependent to endothelial independent mechanisms. In addition, there was some evidence for an increase in markers associated with endothelial dysfunction in blood and urine.

6.1.13.2.1 Arterial Stiffness

Arterial stiffness can be measured using the augmentation index (Aix). Increases in this index indicate greater arterial stiffness and may represent increased risk of an adverse cardiovascular event. In the FILTER-HF study, HF and healthy control patients were exposed to FA, DE or filtered DE and decreases in Aix were not attenuated with particle filtration (Vieira et al., 2016a). Thus, DE-dependent decreased arterial stiffness in HF patients is related to exposure to the entire DE mixture and is not $PM_{2.5}$-dependent. Similarly, Lucking et al. (2011) examined the potential for arterial stiffness following FA, DE, and filtered DE exposure in healthy young men. There were no differences in indicators of arterial stiffness among any of the treatment groups. Thus, there is no evidence from CHE studies of a relationship between increased arterial stiffness and exposure to filtered DE. More information on studies published since the 2009 ISA can be found in Table 6-30.

Table 6-30 Study-specific details from CHE studies of short-term $PM_{2.5}$ exposure and impaired vascular function.

Study	Population	Exposure Details (Concentration; Duration)	Endpoints Examined
(Brook et al., 2009) Toronto Cohort	Healthy adults n = 16 M; 15 F 27 ± 8	148.5 ± 54.4 µg/m^3 $PM_{2.5}$ CAP or 132.4 ± 38.7 µg/m^3 $PM_{2.5}$ CAP and 109 ± 5.6 ppb O_3 for 2 h CAP from Toronto	Reactive hyperemia and Nitroglycerine Induced vasodilation post exposure: pre, post, and 24 h post Markers of vascular constriction: pre, post, and 24 h post
(Hemmingsen et al., 2015b)	Healthy overweight older adults n = 25 M, 35 F; 55−83 yr	24 ± 13 µg/m^3 (nonfiltered) 3.0 ± 1.2 µg/m^3 (filtered) $PM_{2.5}$ for 5 h at rest	Reactive hyperemia and nitroglycerine induced vasodilation post exposure

Table 6-30 (Continued): Study-specific details from CHE studies of short-term $PM_{2.5}$ exposure and impaired vascular function.

Study	Population	Exposure Details (Concentration; Duration)	Endpoints Examined
		PM collected from a busy street in central Copenhagen, Denmark	
(Liu et al., 2015a)	Healthy adults n = 50; 18−60 yr 28 ± 9	238.4 ± 62.0 μg/m^3 fine cap from Toronto for 130 min	Biomarkers of vascular function measured pre, 1 h, and 21 h post
(Lucking et al., 2011)	Healthy young men	320 ± 10 μg/m^3 fine DA particles 7.2 ± 2.0 μg/m^3 particles filtered DA 1 h exposure 15 min exercise (25 L/min^2 per m^2 body) alternating with 15 min rest Particles generated with a Volvo diesel engine	Vascular function: 6−8 h post, Arterial stiffness
(Tong et al., 2015)	Healthy older adults n = 10 M, 32 F; 57.8 ± 1.3 yr	253 ± 16 μg/m^3 of $PM_{2.5}$ for 2 h at rest CAPs from Chapel Hill, NC Effect of supplementation with fish oil or olive oil	Reactive hyperemia: pre, post, 20 h post Markers of vasoconstriction: pre, post, and 20 h post

(Vieira et al., 2016b)	Healthy adults
	n = 8 M, 7 F;
	45 ± 10 yr; 7 with a history of smoking)
	HF patients
	n = 16 M, 10 F;
	51 ± 9 yr; 19 white; 17 with a history of smoking)
		325 ± 31 μg/m^3 $PM_{2.5}$ DE generated from a diesel engine (Branco BD-2500 CFE, Toyama, Sao Paulo, SP, Brazil) and conditioned through a refrigerated metal retainer
		25 ± 6 μg/m^3 $PM_{2.5}$ filtered DE
		21 min total exposure, 15 at rest and 6 while walking
			Reactive hyperemia and Aix: during exposure

(Zhong et al., 2015)	Healthy adults n = 23 M, 27 F; 18−60 yr	Endotoxin and B-1,3-d-glucan associated with: 250 μg/m^3 $PM_{2.5}$ CAPs (target) 200 μg/m^3 Course CAPs (target) 7.07 and IQR 7.09 ng/m^3) for 130 min at rest CAPs collected from a heavy-traffic 4-lane street in Toronto, Canada.	Biomarkers of vascular function: >8 h post

Note: SD = standard deviation, M = male, F = female, n = number, h = hour, DA = diesel exhaust, CAP = concentrated ambient particle, IQR = interquartile range, Aix = augmentation index.

1

6.1.13.3 Toxicology Studies of Impaired Vascular Function

2 Since the publication of the 2009 PM ISA, studies have evaluated the short-term effects of $PM_{2.5}$
3 exposure on endothelial dysfunction. Specifically, O'Toole et al. (2010) found that short-term $PM_{2.5}$
4 exposure reduced ($p < 0.05$) the level of circulating endothelial progenitor cells (EPCs). Haberzettl et al.

(2012) confirmed this finding, and identified that the reduction in circulation was not due to EPC death or tissue deposition. Instead, they found that CAP exposure increased ($p < 0.05$) the number of resident EPCs in the bone marrow and that this was at least in part due to impaired VEGF signaling resulting in decreased translocation into the blood. In an additional study, Davel et al. (2012) reported that short-term exposure to $PM_{2.5}$ impaired acetylcholine, but not NTP induced relaxation ($p < 0.05$) in pulmonary arterial rings from $PM_{2.5}$-exposed rats when compared to FA controls. Similarly, compared to control animal serum, Aragon et al. (2015) reported that treatment of naïve aortic rings with serum from mice exposed to the particle portion of mixed vehicle emissions (i.e., mixture of gas and diesel exhaust), but not $PM_{2.5}$ from road dust, resulted in impaired acetylcholine induced relaxation ($p < 0.05$). When considered as a whole, these toxicological studies report consistent evidence that short-term exposure to $PM_{2.5}$ can result in indicators of endothelial dysfunction. More information on studies published since the 2009 ISA can be found in Table 6-31.

Table 6-31 Study-specific details from toxicological studies of short-term $PM_{2.5}$ exposure and impaired vascular function.

Study	Population	Exposure Details	Endpoints Examined
(Davel et al., 2012)	3-mo old Wistar rats, M	Inhalation of 600 µg/m^3 $PM_{2.5}$ CAPs for 3 h/day for 2 weeks from Sao Paulo City, Brazil	Acetylcholine and NTP induced relaxation of pulmonary artery segments post exposure
(O'Toole et al., 2010)	C57BL/6 mice n = 28	Inhalation of 30−100 µg/m^3 $PM_{2.5}$ for 6 h/day for 9 days from Louisville, KY	Number of circulating endothelial progenitor cells in blood post exposure using flow cytometry post exposure
(Haberzettl et al., 2012)	Adult C57BL/6 mice, M, 8−12 weeks	Inhalation of 30−100 µg/m^3 $PM_{2.5}$ for 4, 9, or 30 days from Louisville, KY during August or June 2009	Number of circulating endothelial progenitor cells VEGF signaling post exposure
(Aragon et al.)	Adult C57BL/6 mice, M, 6−8 weeks	Inhalation of $PM_{2.5}$ road dust for 6 h from Phoenix and Tucson, AZ	Acetylcholine-induced relaxation of aortic rings

CAP = concentrated ambient particle, d = day, DE = diesel exhaust, h = hour, NTP = sodium nitroprusside, VEGF = vascular endothelial growth factor, w = week.

6.1.14 Policy-Relevant Considerations

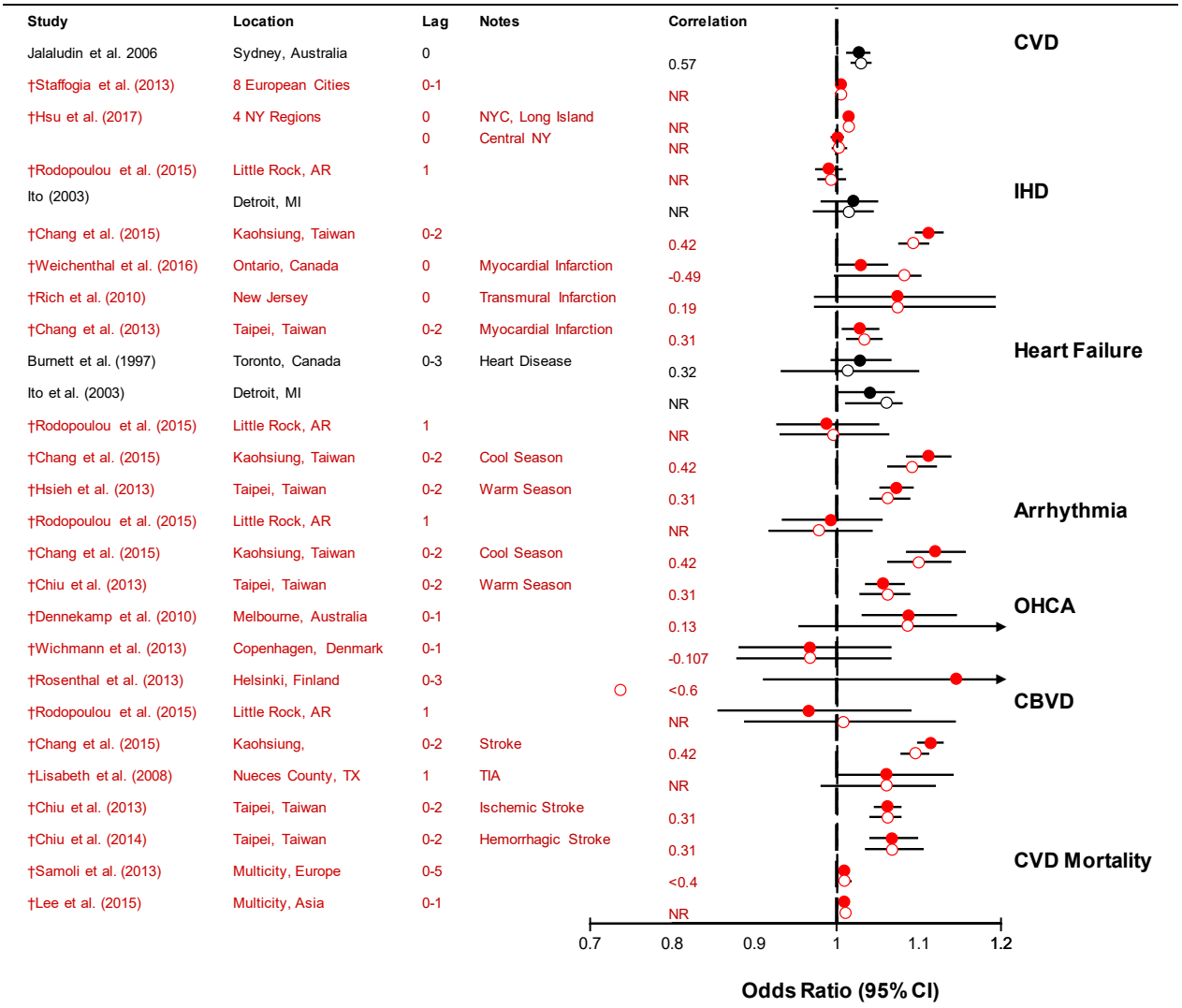
Epidemiologic studies that examined short-term $PM_{2.5}$ exposure and cardiovascular-related effects often conduct additional analyses to assess whether the associations observed are due to chance, confounding, or other biases. Within this section, evidence is evaluated across epidemiologic studies to further assess the association between short-term $PM_{2.5}$ exposure and cardiovascular-related effects, focusing specifically on those analyses that address policy-relevant issues: copollutant confounding

(Section 6.1.14.1), the role of season and temperature on $PM_{2.5}$ associations (Section 6.1.14.2), and lag structure (Section 6.1.14.3). The studies that inform these issues are primarily epidemiologic studies that conducted time-series or case-crossover analyses focusing on cardiovascular-related ED visits and hospital admissions and cardiovascular mortality. Studies examining additional endpoints, such as subclinical markers of a PM-related cardiovascular effect (e.g., heart rate variability, inflammation, etc.), may also examine some of these issues, but are not the focus of this evaluation.

6.1.14.1 Potential Copollutant Confounding of the $PM_{2.5}$-Cardio Vascular Disease (CVD) Relationship

In the examination of potential confounding effects of copollutants on the relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects, it is informative to evaluate whether $PM_{2.5}$ risk estimates are changed in copollutant models. Compared to the evidence available at the time of the 2009 PM ISA, there are many additional studies that conducted analyses that inform the potential of confounding effects of copollutants. Recent studies have examined the potential for copollutant confounding by evaluating copollutant models that include O_3 (Figure 6-8), NO_2, (Figure 6-9), SO_2 (Figure 6-10), CO (Figure 6-11) and $PM_{10–2.5}$ (Figure 6-12). These recent studies address a previously identified data gap by informing the extent to which effects associated with exposure to $PM_{2.5}$ are independent of co-exposure to correlated copollutants. Generally, these studies provide evidence for a direct relationship between $PM_{2.5}$ exposure and cardiovascular-related health effects independent of other copollutants.

The results for associations between short-term $PM_{2.5}$ exposure and cardiovascular effects in single pollutant models and copollutant models adjusted for O_3 are shown in Figure 6-8. The correlations between $PM_{2.5}$ and O_3 exposures in the studies that conducted copollutant analyses were generally positive and low to moderate, ranging from $r = -0.49$ to 0.57. Across studies, the $PM_{2.5}$ effect estimates remained relatively unchanged in copollutant models adjusted for O_3. The trend persisted for aggregate CVD outcomes, as well as specific cardiovascular endpoints, such as IHD, heart failure, arrhythmia, cerebrovascular disease, and cardiovascular mortality. There were several exceptions to the trend. The effect of short-term $PM_{2.5}$ exposure on out-of-hospital cardiac arrest (Rosenthal et al., 2013) decreased substantially and became negative after adjusting for O_3 in the model. Conversely, the effect of short-term $PM_{2.5}$ exposure on MIs (Weichenthal et al., 2016b) increased after adjusting for O_3 in the model.

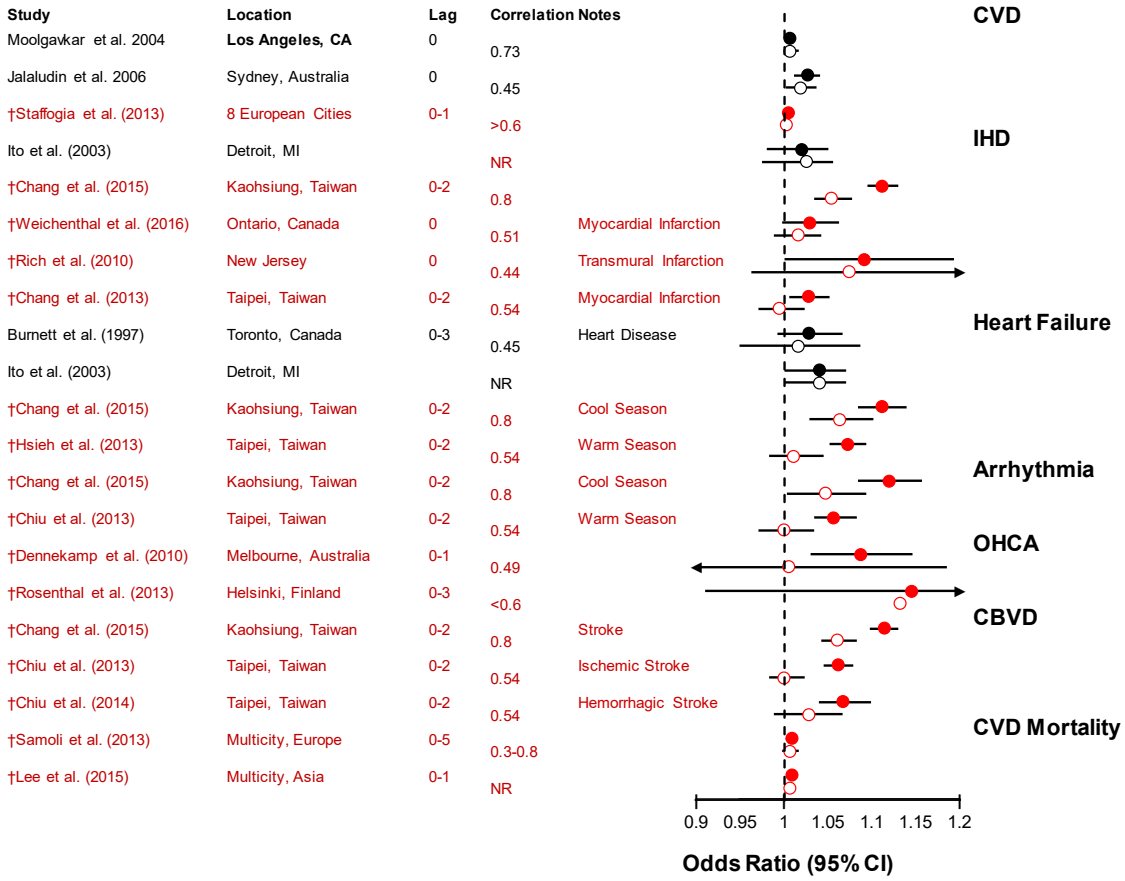


Associations are presented per 10 μg/m^3 increase in pollutant concentration. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Filled circles represent effect of $PM_{2.5}$ in single pollutant models, white circles represent effect of $PM_{2.5}$ adjusted for O_3. Supplemental Table S6-11 (U.S. EPA, 2018). TIA: transient ischemic attack; CVD: cardiovascular; IHD: ischemic heart disease; OHCA: out-of-hospital cardiac arrest; CBVD: cerebrovascular disease; NR: not reported. †Studies published since the 2009 PM ISA.

Figure 6-8 Associations between short-term exposure to $PM_{2.5}$ and cardiovascular effects in single pollutant models and models adjusted for O_3.

The results for associations between short-term $PM_{2.5}$ exposure and cardiovascular effects in single pollutant models and copollutant models adjusted for NO_2 are presented in Figure 6-9. For this pair of pollutants, the correlations were generally positive and moderate to high, ranging from $r = -0.45$ to 0.80. Generally, the $PM_{2.5}$ effect estimates remained relatively unchanged in copollutant models adjusted for NO_2 across CVD effects. However, there were several exceptions to the trend, and in each of these

cases the effect of short-term $PM_{2.5}$ exposure decreased after adjusting for NO_2 in the model (Chang et al., 2015; Chang et al., 2013; Chiu and Yang, 2013; Dennekamp et al., 2010). There were no instances when the inverse was observed (i.e., higher $PM_{2.5}$ associations after adjusting for NO_2).

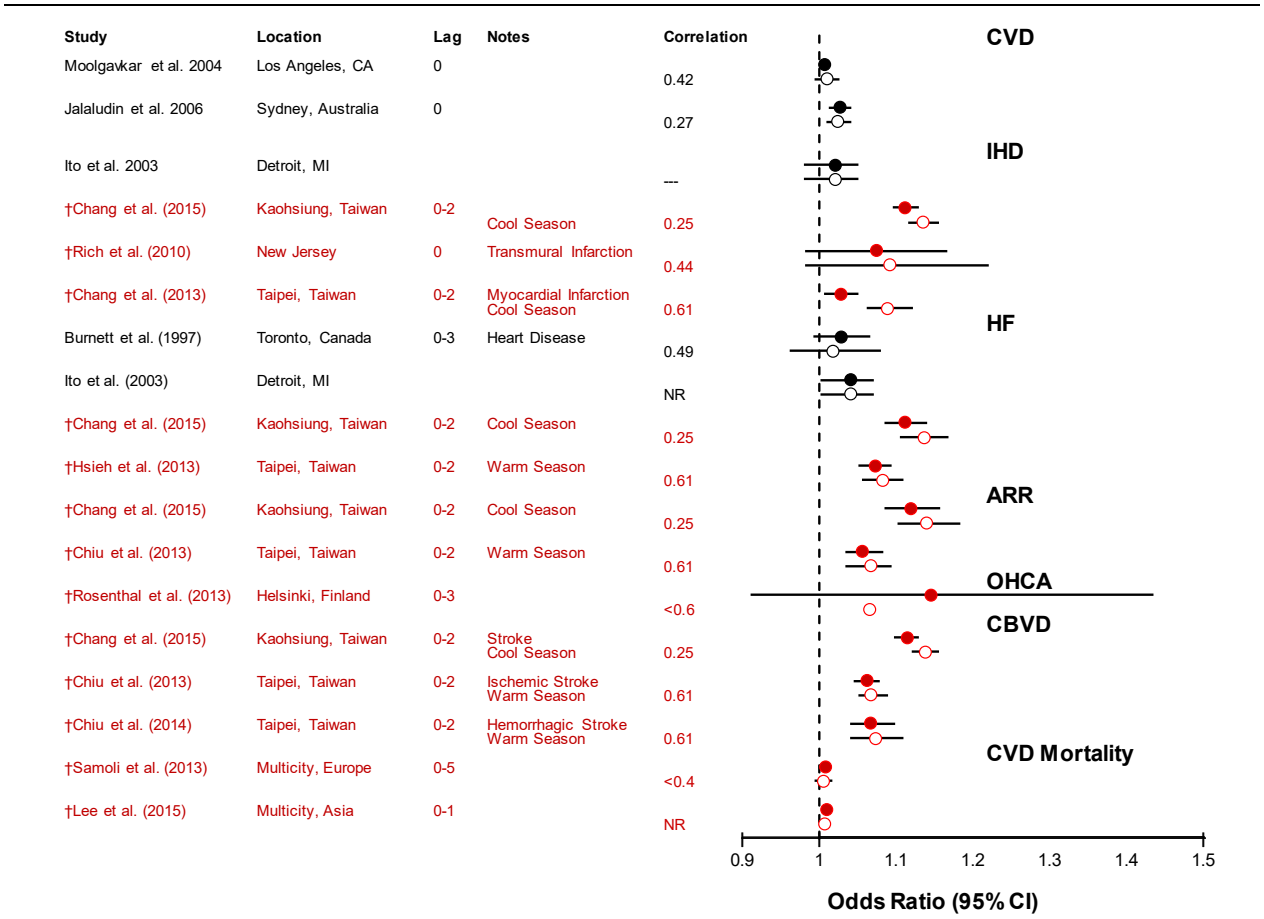


Associations are presented per 10 $\mu g/m^3$ increase in pollutant concentration. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Filled circles represent effect of $PM_{2.5}$ in single pollutant models, white circles represent effect of $PM_{2.5}$ adjusted for NO_2. Supplemental Table S6-12 (U.S. EPA, 2018). CVD: cardiovascular; IHD: ischemic heart disease; OHCA: out-of-hospital cardiac arrest; CBVD: cerebrovascular disease; NR: not reported. †Studies published since the 2009 PM ISA.

Figure 6-9 Associations between short-term exposure to $PM_{2.5}$ and cardiovascular effects in single pollutant models and models adjusted for NO_2.

The results for associations between short-term $PM_{2.5}$ exposure and cardiovascular effects in single pollutant models and copollutant models adjusted for SO_2 are presented in Figure 6-10. For this pair of pollutants, the correlations were generally positive and low to moderate, ranging from $r = -0.25$ to 0.61. Similar to ozone, the $PM_{2.5}$ effect estimates generally remained relatively unchanged in copollutant

models adjusted for SO_2 across CVD effects. In some instances, the magnitude of the $PM_{2.5}$ association increased slightly after adjusting for SO_2.

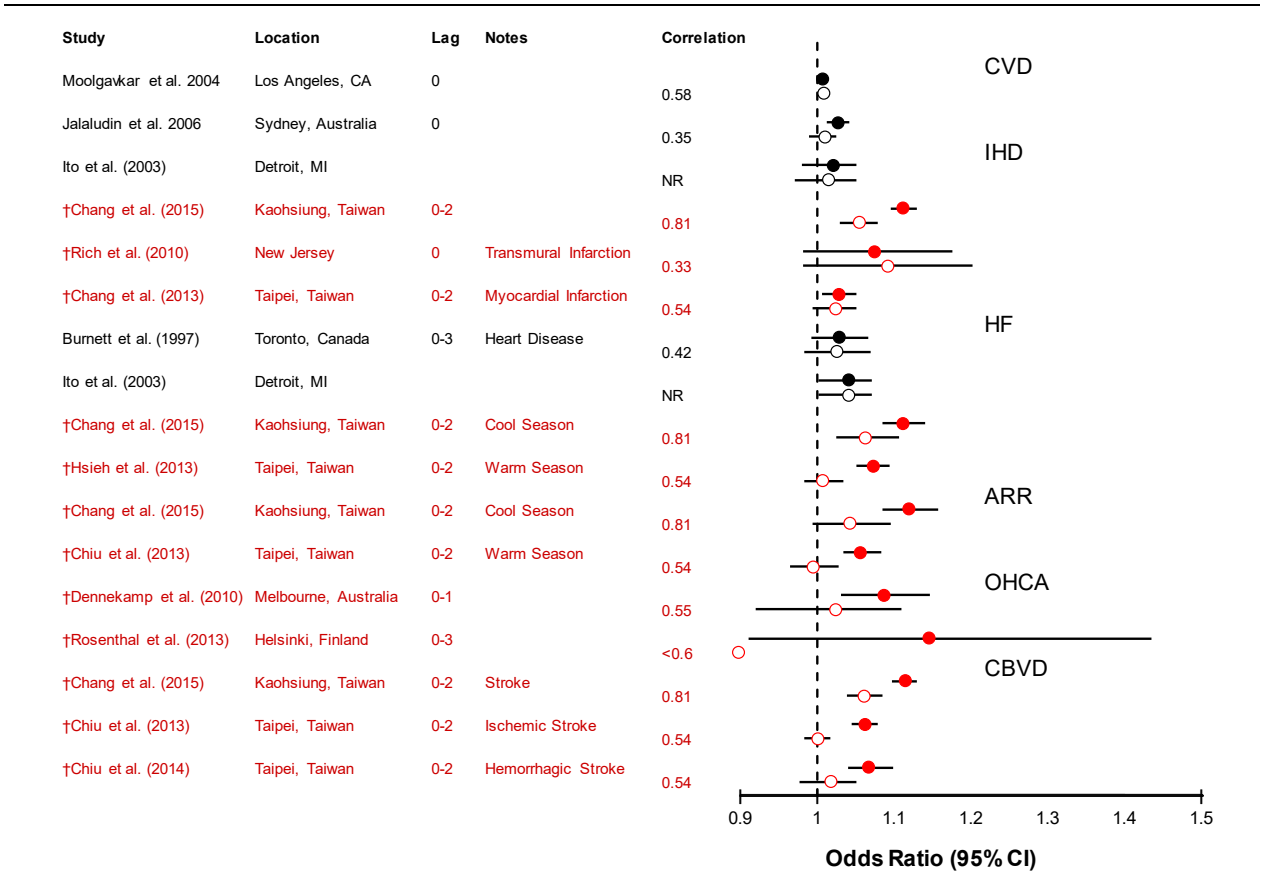


Associations are presented per 10 µg/m^3 increase in pollutant concentration. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Filled circles represent effect of $PM_{2.5}$ in single pollutant models, white circles represent effect of $PM_{2.5}$ adjusted for SO_2. Supplemental Table S6-13 (U.S. EPA, 2018). CVD: cardiovascular; IHD: ischemic heart disease; HF: heart failure; ARR: arrhythmia; OHCA: out-of-hospital cardiac arrest; CBVD: cerebrovascular disease; NR: not reported. †Studies published since the 2009 PM ISA.

Figure 6-10 Associations between short-term exposure to $PM_{2.5}$ and cardiovascular effects in single pollutant models and models adjusted for SO_2.

The results for associations between short-term $PM_{2.5}$ exposure and cardiovascular effects in single pollutant models and copollutant models adjusted for CO are presented in Figure 6-11. For this pair of pollutants, the correlations were generally positive and moderate to high, ranging from $r = -0.33$ to 0.81. Generally, the $PM_{2.5}$ effect estimates remained relatively unchanged in copollutant models adjusted

for CO across CVD effects. However, there were several exceptions to the trend. Similar to NO_2, there were several instances in which the effect of short-term $PM_{2.5}$ exposure decreased after adjusting for CO in the model (Chang et al., 2015; Chiu et al., 2014; Chiu and Yang, 2013; Hsieh et al., 2013; Dennekamp et al., 2010). There were no instances when the inverse was observed (i.e., higher $PM_{2.5}$ associations after adjusting for NO_2).

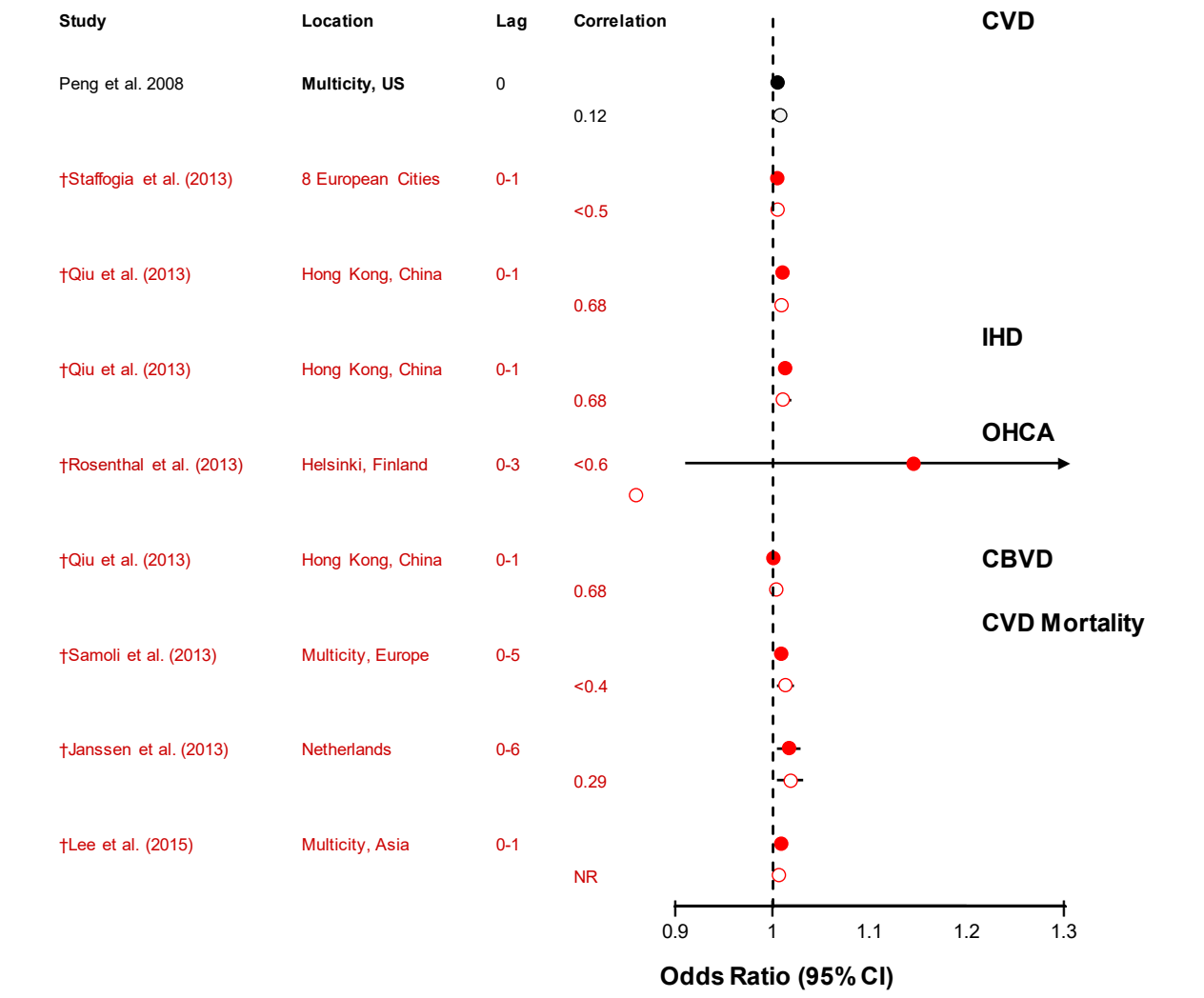


Associations are presented per 10 μg/m^3 increase in pollutant concentration. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Filled circles represent effect of $PM_{2.5}$ in single pollutant models, white circles represent effect of $PM_{2.5}$ adjusted for CO. Supplemental Table S6-14 (U.S. EPA, 2018). CVD: cardiovascular; IHD: ischemic heart disease; HF: heart failure; ARR: arrhythmia; OHCA: out-of-hospital cardiac arrest; CBVD: cerebrovascular disease; NR: not reported. †Studies published since the 2009 PM ISA.

Figure 6-11 Associations between short-term exposure to $PM_{2.5}$ and cardiovascular effects in single pollutant models and models adjusted for CO.

The results for associations between short-term $PM_{2.5}$ exposure and cardiovascular effects in single pollutant models and copollutant models adjusted for $PM_{10-2.5}$ are presented in Figure 6-12. For this

pair of pollutants, the correlations were generally positive and low to moderate, ranging from $r = -0.12$ to 0.68. Similar to ozone and SO_2, the $PM_{2.5}$ effect estimates generally remained relatively unchanged in copollutant models adjusted for SO_2 across CVD effects, except for in the study by (Rosenthal et al., 2013), for which the association was attenuated and became negative after adjusting for $PM_{10-2.5}$.



Associations are presented per 10 μg/m^3 increase in pollutant concentration. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Filled circles represent effect of $PM_{2.5}$ in single pollutant models, white circles represent effect of $PM_{2.5}$ adjusted for $PM_{10-2.5}$. Supplemental Table S6-15 (U.S. EPA, 2018). TIA: transient ischemic attack; CVD: cardiovascular; IHD: ischemic heart disease; OHCA: out-of-hospital cardiac arrest; CBVD: cerebrovascular disease; NR: not reported. †Studies published since the 2009 PM ISA.

Figure 6-12 Associations between short-term exposure to $PM_{2.5}$ and cardiovascular effects in single pollutant models and models adjusted for $PM_{10-2.5}$.

Overall, there are many more studies evaluating potential copollutant confounding using two-pollutant models than were available in the 2009 PM ISA. This new evidence generally demonstrates that the associations observed with $PM_{2.5}$ and cardiovascular effects in single pollutant models remain relatively unchanged in copollutant models, indicating that the observed associations with $PM_{2.5}$ are not artifacts due to confounding of another air pollutant. We did not observe any difference in the trend or pattern of these results across cardiovascular endpoints (e.g., aggregate CVD endpoints, IHD, heart failure, cardiovascular mortality). While the evidence is generally consistent across the copollutants evaluated, it was especially consistent for air pollutants that are not typically associated with traffic (i.e., ozone, SO_2, $PM_{10–2.5}$). While few, some inconsistencies were observed for the traffic-related pollutants (i.e., NO_2, CO), which generally had high correlations with $PM_{2.5}$ than the other copollutants. Due to these higher correlations, it is difficult to distinguish if any attenuation in $PM_{2.5}$ associations after adjusting for copollutants could be due to confounding, or if collinearity may play a role.

6.1.14.1.1 $PM_{2.5}$ within the Multipollutant Mixture

Although copollutant models are important in assessing potential copollutant confounding, it is well known that collinearity between pollutants can result in unstable estimates and that air masses are not limited to just two pollutants (Dominici et al., 2010). Therefore, in addition to copollutant models, studies that examine multipollutant exposures can provide additional information on the role of $PM_{2.5}$ within the complex air pollution mixture.

Analyses of pollutant mixtures use an array of statistical methods and pollutant combinations while examining cardiovascular-related effects, and were recently reviewed by (Luben et al., 2018). Luben et al. (2018) conducted a cross-disciplinary evaluation of the multipollutant effects on cardiovascular disease, integrating results from epidemiologic studies with controlled human exposure and animal toxicological studies. Overall, the review demonstrated a paucity of evidence available to characterize the multipollutant effects of air pollution on cardiovascular outcomes. Across the limited number of studies, the evidence neither consistently nor coherently indicated a stronger or weaker effect of combined exposure to $PM_{2.5}$ and another pollutant compared to exposure to a single pollutant alone.

6.1.14.2 The Role of Season and Temperature on $PM_{2.5}$ Associations

The examination of seasonal differences in $PM_{2.5}$ associations within studies that focus on cardiovascular-related hospital admissions and ED visits, as well as cardiovascular mortality, can provide information that could be used to assess whether specific sources that vary by season are contributing to the $PM_{2.5}$ associations observed in all-year analyses. Additional studies that examine potential modification of $PM_{2.5}$ associations by temperature can further elucidate the impact of season on observed associations. Studies evaluated in the 2009 PM ISA, demonstrated seasonal variability in $PM_{2.5}$

associations with cardiovascular-related effects, which is further supported by recent studies, while fewer studies have examined potential modification of $PM_{2.5}$ associations by temperature.

Different trends are observed when the role of season or temperature is evaluated across different cardiovascular endpoints (Figure 6-6). For example, among studies that evaluated short-term $PM_{2.5}$ exposure and ischemic heart disease, several studies observed no seasonal differences in associations (Rich et al., 2010; Szyszkowicz, 2009; Zanobetti et al., 2009), while Talbott et al. (2014) observed stronger associations during the cool season in some regions of New York. Similarly, there was no consistent trend for the effect of $PM_{2.5}$ on cerebrovascular disease across different seasons, with some studies observing stronger associations in the warm season (Chen et al., 2014b; Villeneuve et al., 2012), some studies observing strong associations in the cool season (Talbott et al., 2014), and others observing no seasonal differences in the association with $PM_{2.5}$ (O'Donnell et al., 2011).

Season had a more consistent effect on the relationship between short-term $PM_{2.5}$ exposure and other cardiovascular endpoints, such as heart failure, arrhythmias and aggregate cardiovascular disease (Figure 6-6). For both heart failure and arrhythmias, each of the limited number of studies reported stronger associations with short-term $PM_{2.5}$ exposure during the cool season. This general trend was also observed in studies evaluating aggregate CVD endpoints, with the majority of these studies observing stronger associations in the cool season. Conversely, the majority of studies evaluating the role of season or temperature on the effect of short-term $PM_{2.5}$ exposure on cardiovascular mortality observed stronger associations in the warm season. This trend was consistent across studies conducted in North America and Europe, whereas studies conducted in Asia tended to report stronger associations during the cool season or with lower temperatures.

Overall, there is no consistent role of season or temperature on the effect of short-term $PM_{2.5}$ exposure on cardiovascular morbidity or mortality. There is a limited number of studies that evaluate each of the different cardiovascular endpoints, and the evidence from these limited studies indicates inconsistent or no seasonal effects for some endpoints (i.e., ischemic heart disease, cerebrovascular disease), while the limited evidence more consistently indicates stronger associations during the cool season (for heart failure, arrhythmia, aggregate cardiovascular disease) or warm season (for cardiovascular mortality). In addition to the limited number of studies available to inform the role of season on the effect of short-term $PM_{2.5}$ exposure on cardiovascular effects, there are other factors the contribute uncertainty to this body of evidence. Variability in season-stratified results for different single-day lags make it difficult to draw inferences from this body of evidence. For example, Ito et al. (2011) observed no seasonal differences in the associations with CVD mortality for Lag day 1, but when evaluating Lag day 0, the authors reported strong positive associations in the warm season and strong negative associations during the cool season. Additionally, there is evidence of regional heterogeneity in the role of season on the effect of short-term $PM_{2.5}$ exposure on cardiovascular endpoints. Regional heterogeneity in results was observed both within studies that included multiple geographic study locations (e.g., (Talbott et al., 2014)) and across studies conducted in geographic locations (e.g., among

studies of CVD mortality, more likely to observe stronger associations in warm season for studies conducted in North America and Europe, but more likely to see stronger associations during cool season/cooler temperatures for studies conducted in Asia). Overall, the evidence across studies is inconclusive as to whether season or temperature modifies the association between short-term $PM_{2.5}$ exposure and cardiovascular endpoints.

6.1.14.3 The Effect of Lag Structure on Associations of Short-Term $PM_{2.5}$ Exposure and Cardiovascular Effects

An examination of the association between short-term $PM_{2.5}$ exposure and cardiovascular effects across different Lag days can inform whether $PM_{2.5}$ elicits an immediate, delayed, or prolonged effect on these endpoints, and whether the effect of $PM_{2.5}$ is consistent across cardiovascular endpoints. Recent studies provide evidence that allows for the comparison of immediate (single or multiday lags including lags 0−1), delayed (single or multiday lags including lags 2−5) or prolonged (multiday lags spanning at least four days, e.g., lag 0−5) exposure periods. Generally, evidence from studies that evaluate cardiovascular hospital admissions and ED visits indicates positive associations within the first few days after exposure, specifically for immediate single-day lags (i.e., Lag days 0 or 1) and multiday lags (i.e., Lag days 0−1, 0−2, or 0−3), with greater magnitude and precision of the association for multiday lags compared to single-day lags.

Generally, among studies that compared different single-day or multiday lag periods in evaluations of aggregate CVD hospital admissions and ED visits, stronger associations were observed for immediate Lag days, especially lag 0, compared to delayed or prolonged lag periods (Bell et al., 2014; Talbott et al., 2014; Qiu et al., 2013; Stafoggia et al., 2013a; Kim et al., 2012; Ito et al., 2011). For example, the left panel of Figure 6-13 (single day lag figure from Kim et al. 2012) demonstrates the stronger positive association for aggregate CVD hospital admissions with exposure on lag 0 compared to other single-day lags reported by Kim et al. (2012). Among studies that compared single-day lags and multiday lag periods, stronger associations were observed with multiday lag periods (e.g., lag 0−1, 0−2) and aggregate CVD hospital admissions and ED visits (Talbott et al., 2014; Qiu et al., 2013), though Bravo et al. (2017) observed generally similar effects for both single-day and multiday lag periods spanning immediate, delayed and prolonged exposure windows. Also, Milojevic et al. (2014) observed no difference in effects when examining immediate (i.e., 0−1) or prolonged (i.e., 0−4) multiday lags.

Similar to the results for studies focusing on aggregate CVD outcomes, comparison of lag periods in studies of several cause-specific CVD hospital admission and ED visits reported the strongest associations with immediate lag periods. Studies that examined the lag structure of associations between $PM_{2.5}$ and IHD (including MI and MI subtypes) largely provide evidence of immediate $PM_{2.5}$ effects with null or negative associations when examining delayed lags (Weichenthal et al., 2016b; Talbott et al., 2014; Kim et al., 2012; Rich et al., 2010; Haley et al., 2009; Stieb et al., 2009). For example, the right panel of Figure 6-13 demonstrates the stronger positive association for IHD hospital admissions with

exposure on lag 0 compared to other single-day lags reported by Kim et al. (2012). The observed risks were generally greater in magnitude for multiday lags (i.e., lag 0−1) compared to single-day lags (i.e., lag 0, lag 1). Similar results were observed for studies investigating short-term $PM_{2.5}$ exposure and heart failure (Talbott et al., 2014; Haley et al., 2009; Stieb et al., 2009), though Kim et al. (2012) observed positive associations for delayed lags (single day lags 2, 3, and 4) and a negative association for Lag day 0. Among recent studies evaluating the relationship between short-term $PM_{2.5}$ exposure and OHCA, authors generally observed the strongest associations for immediate lag periods (Ensor et al., 2013; Rosenthal et al., 2013; Dennekamp et al., 2010; Silverman et al., 2010), though some found delayed associations days (Wichmann et al., 2013).

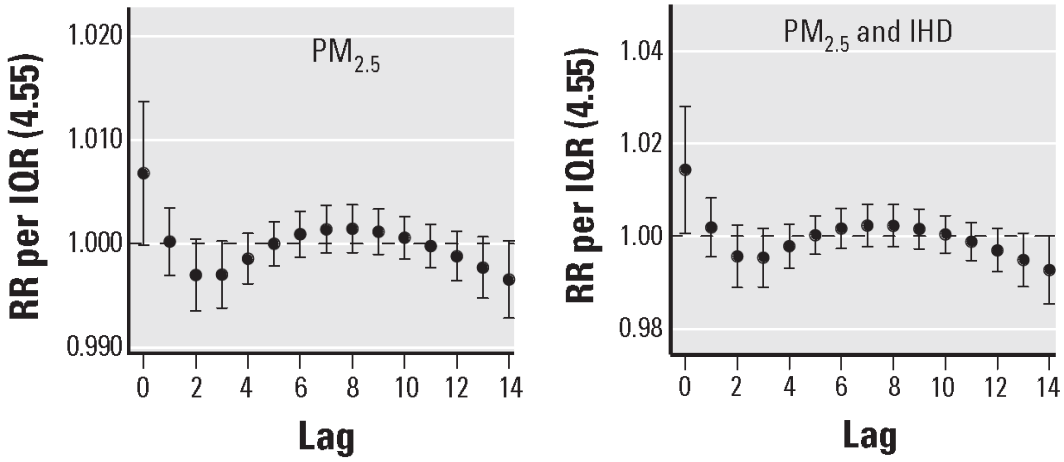


Figure 6-13 Pattern of RRs for single day lags 0−14 for aggregate cardiovascular disease (CVD) hospitalizations (left) and IHD hospitalizations (right) reported by Kim et al. (2012).

Most of the studies that examined multiple lag periods reported no evidence of a positive association between short-term $PM_{2.5}$ exposure and hospital admissions and ED visits for CBVD at any of the lag periods evaluated (Qiu et al., 2013; Kim et al., 2012; O'Donnell et al., 2011; Haley et al., 2009). However, when evaluating specific stroke subtypes, Lisabeth et al. (2008) and Wing et al. (2015) observed positive associations between $PM_{2.5}$ concentrations and ischemic stroke for immediate Lag days (lags 0 or 1), but not for delayed lags (single day lags 2, 3,4, 5). Limited evidence was inconsistent when comparing different lag periods in studies of ED visits and hospital admissions for arrhythmia. Talbott et al. (2014) reported positive associations for immediate lag periods (lag 0, 1, 0−1) with stronger associations observed for multiday lags compared to single-day lags. In contrast, Haley et al. (2009) observed negative associations for both immediate (i.e., 0,1) and delayed (i.e., 2, 3,4) single day lags in their evaluation of arrhythmia ED visits.

Recent multicity studies of short-term $PM_{2.5}$ exposure and cardiovascular mortality have conducted extensive examinations of the lag structure of associations. Of these studies, some only examined single-day lags (Lippmann et al., 2013c) or multi-day lags (Milojevic et al., 2014), while a few examined multi-day lags aimed at specifically addressing whether there is evidence of an immediate (lag 0−1 days), delayed (lag 2−5 days), or prolonged (lag 0−5 days) effect of $PM_{2.5}$ on cardiovascular mortality. Several studies provide evidence of an immediate $PM_{2.5}$ effect on cardiovascular mortality with associations largest in magnitude at lag 0 (Stafoggia et al., 2017; Janssen et al., 2013; Lippmann et al., 2013c; Samoli et al., 2013). Lanzinger et al. (2016a) and Samoli et al. (2013) provide some evidence indicating the potential for stronger associations with short-term $PM_{2.5}$ exposure averaged over delayed (e.g., lag 2−5) and prolonged (e.g., lag 0−5) lag periods and CVD mortality. Overall, recent multicity studies that examined the lag structure of associations, generally support the immediate effect of $PM_{2.5}$ on cardiovascular mortality, but also provide some evidence that associations may exist for exposures averaged over longer durations. However, the initial studies examining multi-day lags providing evidence of a delayed or prolonged effect are not supported when examining a series of single-day lags over the same duration.

Additionally, few studies examined subdaily averaging times, or exposures averaged over one or multiple hours during Lag day 0. In Rochester, New York, Gardner et al. (2014) observed positive associations between STEMI and $PM_{2.5}$ at lags of 0 hours and 0−2 hours, with evidence of positive associations for multi-hours lags up to 24 hours. Several studies investigating OHCA also examined subdaily averaging times, and generally observed positive associations, though the associations were consistently higher in magnitude for daily lags (single and multiday lags 0−4) compared to the subdaily lags (Straney et al., 2014; Ensor et al., 2013; Rosenthal et al., 2013). For example, Ensor et al. (2013) observed a small increase in risk of OHCA consistent with an increase in $PM_{2.5}$ concentrations in the hour preceding the OHCA event (1.84% [95% CI: −2.16, 5.90%]), but a larger magnitude association corresponding to an increase in 2-day moving average $PM_{2.5}$ (6.58% [95% CI: 0.83, 12.64%]). Wellenius et al. (2012a) considered subdaily averaging times when evaluating CBVD endpoints and observed positive associations for ischemic stroke at hourly lags ranging from 0 to 26 hours, with the largest magnitude of associations for lags from 8 to 20 hours. Overall, these evaluation of subdaily lags provide additional support for the immediate effect of short-term $PM_{2.5}$ exposure on cardiovascular hospital admissions, ED visits, and mortality.

In summary, there is evidence to support an immediate effect of short-term $PM_{2.5}$ exposure on hospital admissions and ED visits for aggregate CVD outcomes, IHD, HF and OHCA, as well as for cardiovascular mortality. This evidence comes from the evaluation of both single-day and multiday lags, as well as studies that evaluated subdaily lag periods. In contrast, the evidence was less consistent across studies, as well as across different lag periods within the same study, for associations between short-term $PM_{2.5}$ exposure and hospital admissions and ED visits for CBVD or arrhythmia. Overall, stronger associations were observed for immediate lags for most CVD outcomes, and the associations tended to be

stronger for immediate multiday lag periods (i.e., 0−1, 0−2) compared to immediate single-day lag periods (i.e., 0, 1).

6.1.15 Associations between $PM_{2.5}$ Components and Sources and Cardiovascular Effects

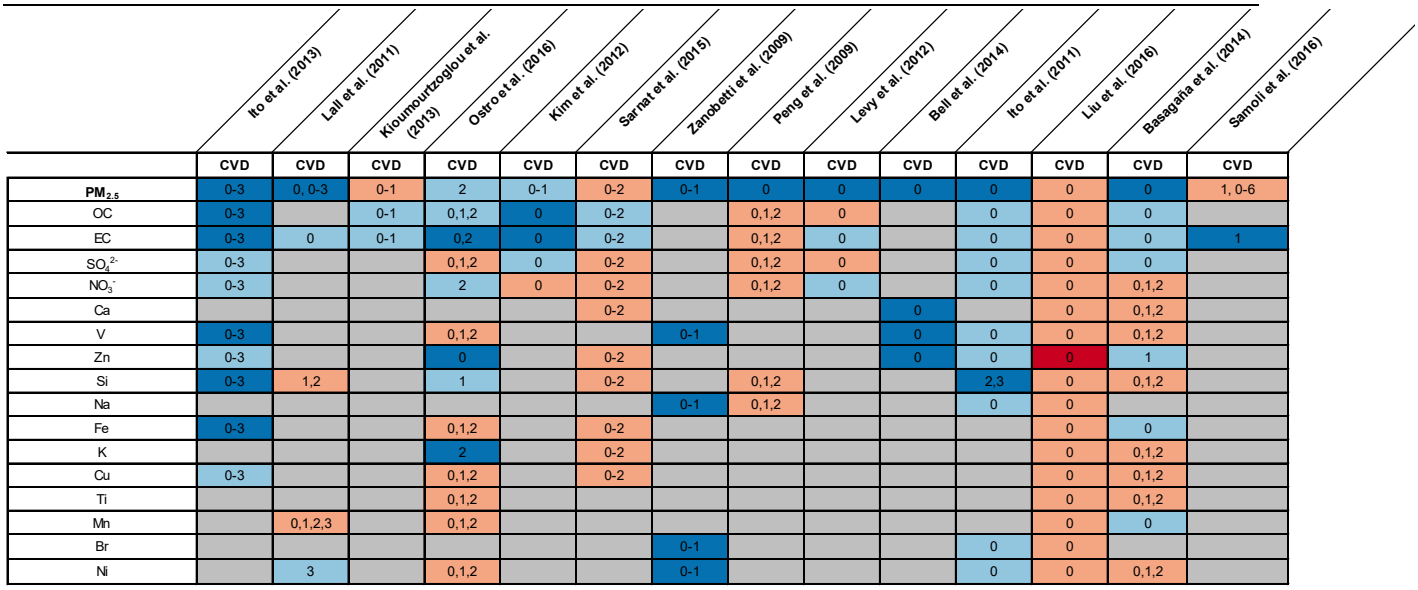
While many PM components are associated with a range of health effects, the 2009 PM ISA concluded that there was not sufficient evidence to differentiate between the PM components or sources that more closely related to health effects than $PM_{2.5}$ mass (U.S. EPA, 2009). However, there was some evidence for associations between increases in cardiovascular effects (e.g., hospital admissions and cardiovascular mortality) with sulfate particles and EC. In addition, several PM sources (i.e., crustal/soil/road dust and traffic) were associated with increased cardiovascular mortality and ST-segment changes. Generally, studies evaluated in the 2009 PM ISA that evaluated individual PM components and sources observed inconsistent results, with no apparent trend or pattern of effect across $PM_{2.5}$ components or across CVD endpoints.

Numerous recent studies examine short-term exposure to $PM_{2.5}$ sources or components and cardiovascular effects and the results are generally consistent with those reported in the 2009 PM ISA. To clearly illustrate the uncertainty in attributing cardiovascular effects to individual $PM_{2.5}$ components or sources versus $PM_{2.5}$ mass, this section is organized by component or source and discussed in the context of associations with $PM_{2.5}$ mass. In cases where studies examined short-term exposure to a $PM_{2.5}$ component or source and any cardiovascular health outcome, the evidence for the relationship is evaluated and synthesized below. This allows for integration across cardiovascular health endpoints in the evaluation of $PM_{2.5}$ components and sources. In each case, the evidence for the $PM_{2.5}$ component or source was evaluated in the context of the available evidence for the relationship with $PM_{2.5}$ mass.

The examination of the relationship between $PM_{2.5}$ components and CVD can generally be divided into two types of analyses: (1) those that examine whether specific components modify the $PM_{2.5}$-cardiovascular effects association, or (2) those that examine whether an individual component is associated with cardiovascular effects and potentially a better indicator of PM toxicity compared to PM mass. Although approach 1 is considered one of the techniques used to assess component toxicity as detailed in Mostofsky et al. (2012), these studies are often used to examine heterogeneity in $PM_{2.5}$-CVD risk estimates. As a result, the focus of this section is on those techniques that fall under approach 2, which includes assessing $PM_{2.5}$ component effect by component concentration or component concentration adjusted for $PM_{2.5}$ mass. Other techniques identified by Mostofsky et al. (2012) that would fall under approach 2 (i.e., component residual or $PM_{2.5}$ residual) were not used in the evaluation of $PM_{2.5}$ components and CVD health effects.

Taking this approach, the evidence does not demonstrate an individual PM component or source that is more consistently associated with CVD health endpoints. The largest body of evidence examining

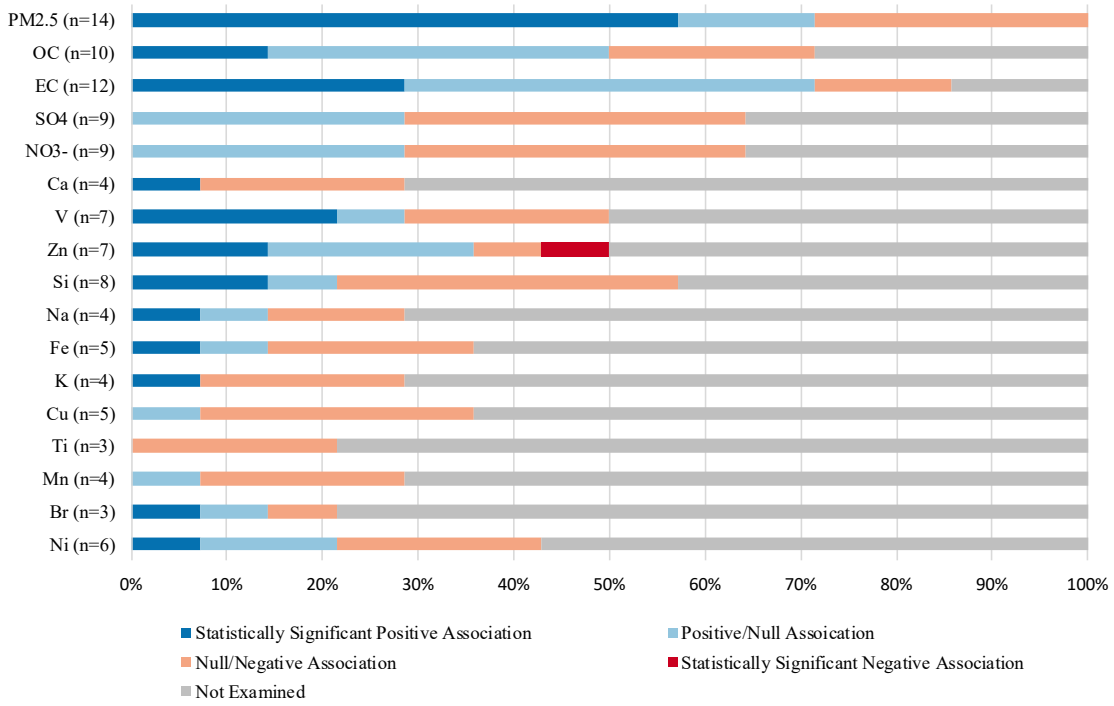
the association with $PM_{2.5}$ components is for ED visits or hospital admissions for aggregate CVD, and these results are summarized in Figure 6-14 and Figure 6-15. Figure 6-14 provides a snapshot of the evidence from studies of aggregate CVD ED visits and hospital admissions that evaluated associations with both $PM_{2.5}$ and $PM_{2.5}$ components. The evidence varies among components, with some studies finding positive associations between almost all $PM_{2.5}$ components evaluated and various cardiovascular health outcomes. The figure demonstrates the most consistent, positive associations with $PM_{2.5}$ mass, though similar patterns of associations are observed with EC, OC and, though evaluated in fewer studies, several metals (e.g., V, Zn, Si, Ni). Overall, associations with aggregate CVD ED visits and hospital admissions are not more clearly linked to a particular $PM_{2.5}$ component compared with $PM_{2.5}$ mass, and within-study comparisons do not show a consistent difference in association between $PM_{2.5}$ mass and a particular component (Figure 6-14). While the number of studies is more limited for other CVD endpoints (e.g., cause-specific ED visits and hospital admissions, measures of blood pressure, HRV, vascular function, and biomarkers of inflammation and oxidative stress), similar trends in associations are observed within and across studies evaluating these endpoints. Several sources of uncertainty common among studies of $PM_{2.5}$ components and sources limit their ability to contribute to causal inference. These include measurement error due to spatiotemporal heterogeneity and poorly addressed potential confounding by other components in the $PM_{2.5}$ mixture. The evidence for $PM_{2.5}$ components and sources is detailed below.



	Ito et al. (2013)	Lall et al. (2011)	Kioumourtzoglou et al. (2013)	Ostro et al. (2016)	Kim et al. (2012)	Sarnat et al. (2015)	Zanobetti et al. (2009)	Peng et al. (2009)	Levy et al. (2012)	Bell et al. (2014)	Ito et al. (2011)	Liu et al. (2016)	Basagaña et al. (2014)	Samoli et al. (2016)
	CVD	CVD	CVD	CVD	CVD	CVD	CVD	CVD	CVD	CVD	CVD	CVD	CVD	CVD
$PM_{2.5}$	0-3	0, 0-3	0-1	2	0-1	0-2	0-1	0	0	0	0	0	0	1, 0-6
OC	0-3		0-1	0,1,2	0	0-2		0,1,2	0		0	0	0	
EC	0-3	0	0-1	0,2	0	0-2		0,1,2	0		0	0	0	1
SO_4^{2-}	0-3			0,1,2	0	0-2		0,1,2	0		0	0	0	
NO_3^-	0-3			2	0	0-2		0,1,2	0		0	0	0,1,2	
Ca						0-2				0		0	0,1,2	
V	0-3			0,1,2			0-1			0	0	0	0,1,2	
Zn	0-3			0		0-2				0	0	0	1	
Si	0-3	1,2		1		0-2		0,1,2			2,3	0	0,1,2	
Na							0-1	0,1,2			0	0		
Fe	0-3			0,1,2		0-2						0	0	
K				2		0-2						0	0,1,2	
Cu	0-3			0,1,2		0-2						0	0,1,2	
Ti				0,1,2								0	0,1,2	
Mn		0,1,2,3		0,1,2								0	0	
Br							0-1				0	0		
Ni		3		0,1,2			0-1				0	0	0,1,2	

Note: Cells represent associations examined for studies of $PM_{2.5}$ mass and $PM_{2.5}$ components and aggregated cardiovascular hospital admissions or emergency department visits. Numbers within cells represent lag(s) at which association was observed. Dark blue = statistically significant positive association; light blue = positive association; light orange = null or negative association; red = statistically significant negative association; grey = component not examined. Only $PM_{2.5}$ components for which there were at least three studies available were included in the table. $PM_{2.5}$ = particulate matter with mean aerodynamic diameter 2.5 μm, OC = organic carbon, EC = elemental carbon, SO_4^{2-} = sulfate, NO_3^- = nitrate.

Figure 6-14 Heat map of associations observed between short-term $PM_{2.5}$ and $PM_{2.5}$ component exposure and hospital admissions and emergency department visits for cardiovascular-related effects.



Note: Bars represent the percent of associations across studies for $PM_{2.5}$ mass or $PM_{2.5}$ components for aggregated cardiovascular hospital admissions and emergency room visits where dark blue = statistically significantly positive, light blue = positive, light orange = null/negative, red = statistically significantly negative, and grey hatch = not examined. N = number of studies that provided an estimate. $PM_{2.5}$ = particulate matter with mean aerodynamic diameter 2.5 μm, OC = organic carbon, EC = elemental carbon, SO_4^{2-} = sulfate, NO_3^- = nitrate.

Figure 6-15 Distribution of associations for hospital admissions and emergency department visits for cardiovascular-related effects and short-term $PM_{2.5}$ and $PM_{2.5}$ components exposure in studies detailed in Figure 6-14.

6.1.15.1 Elemental and Black Carbon

In coronary artery disease patients in Boston, MA similar negative associations were observed between $PM_{2.5}$ and BC with rMSSD for 30-minute up to 5-day exposures (Zanobetti et al., 2010). Negative associations were also observed for HF, although associations were stronger for BC than $PM_{2.5}$ with averaging times from 2−5 days. No associations were observed in this panel for $PM_{2.5}$ exposures with SDNN, but BC exposures from 30-minutes up to 2-hours were reduced (Zanobetti et al., 2010). Associations were similar for BC and $PM_{2.5}$ in studies conducted with panels having pre-existing cardiovascular disease as Schneider et al. (2010) and Bartell et al. (2013) observed negative associations between BC and $PM_{2.5}$ with pNN50 and rMSSD, or HRV, respectively. Finally, Weichenthal et al. (2014a), in a quasi-experimental study that included women cycling on high and low traffic routes for 2-hours, found that associations between SDNN, LF, and LF/HF were similarly positive for both $PM_{2.5}$

and BC. However, negative associations observed between $PM_{2.5}$ and rMSSD and pNN50 were not observed for BC.

Several studies examined associations between measures of vascular function and ambient BC concentrations in addition to $PM_{2.5}$. While Madrigano et al. (2010) reported positive associations between VCAM-1 and BC that were not observed for $PM_{2.5}$, other studies did not find associations between BC and VCAM-1 or other biomarkers of vascular function including VEGF, ICAM-1, and ET-1 (Wilker et al., 2011; Liu et al., 2009). Ljungman et al. (2014) report evidence for associations between BC and pulse wave amplitude for 2 to 5-day averages in the Framingham Heart Study, which was consistent with results for $PM_{2.5}$.

In a quasi-experimental study conducted by Strak et al. (2013a), associations were null for fibrinogen and platelet counts with $PM_{2.5}$ and BC; however, positive associations were reported between $PM_{2.5}$ and vWF that were not observed for BC. Conversely, substantial reductions in lag time in FXII-mediated (intrinsic) thrombin generation were associated with BC exposures but not $PM_{2.5}$ exposures (Strak et al., 2013b). Croft et al. (2017) and Chen et al. (2017) also examined associations between BC and biomarkers related to coagulation in panels of adults with pre-existing cardiovascular conditions and observed positive associations between BC and fibrinogen and 12-hour up to 3-day lagged exposures; although associations with $PM_{2.5}$ were only observed by Croft et al. (2017) and 1−24 hour lags. Associations were not observed for D-dimer or vWF in these studies.

In a panel study including 31 young, healthy adults exposed to air pollution at five different sites with intermittent exercise, Steenhof et al. (2014) reported mixed results for associations between EC and WBC counts measured 2 and 18 hours post-exposure, though patterns in associations were very similar to those for $PM_{2.5}$. More specifically, positive associations were observed for WBC counts, neutrophils 2 hours post-exposure, and monocytes 18 hours post-exposure. In this same panel, positive associations were observed for both $PM_{2.5}$ and EC, but the magnitude of effect was smaller for EC (Strak et al., 2013a).

Liu et al. (2009) did not find evidence for associations between 24-hour outdoor BC or personal measurements of $PM_{2.5}$ and biomarkers for inflammation or oxidative stress (i.e., IL6, TNF-α, TBARS, 8-isoprostane) in a panel of older adults residing in retirement communities. Similar results were observed in studies conducted by Wittkopp et al. (2013) and Chen et al. (2017) in panels of adults with coronary artery disease or having risk factors for CVD as null associations were observed for CRP and up to 5-day averages of EC or 3-day lags for BC. In contrast, Croft et al. (2017) reported positive associations for CRP and 12 and 24-hour lags of BC, although negative associations were observed with myeloperoxidase, a marker for neutrophil activity.

6.1.15.2 Organic Carbon

In contrast with previous studies, recent studies generally support an association of OC with CVD-related hospital admissions, ED visits, cardiovascular function metrics (e.g., HRV), and biomarkers of inflammation (e.g., WBC, CRP). Due to the relatively few studies, it is difficult to judge the consistency of recent results for any one CVD endpoint. That said, the consistency and magnitude of CVD effect associations generally are similar for OC and $PM_{2.5}$ (Figure 6-14 and Figure 6-15), which are in line with the large contribution of OC to total $PM_{2.5}$ mass (Section 2.4.4).

Like $PM_{2.5}$, OC was associated with CVD-related ED visits and hospital admissions in locations across U.S. regions. One of the most informative studies is an extensive analysis of Medicare beneficiaries in 64 cities, which found CVD hospital admissions were associated with OC, particularly during the cold season at lag 0 (Ito et al., 2013). While these associations were strongest at lag 0 in the cold season, OC showed associations present at longer lag periods; however, no individual component had stronger associations than $PM_{2.5}$ mass. A study in Denver, CO reported that $PM_{2.5}$ concentrations of OC were associated with hospital admissions for IHD and aggregate CVD (Kim et al., 2012). On the other hand, in Denver, CO Kim et al. (2012) did not observe a positive association between OC and CBVD hospital admissions. Sarnat et al. (2015) observed a positive association between ED visits for heart failure and $PM_{2.5}$ OC content in the St. Louis, MO metropolitan area. A study of eight California counties found a small positive association with CVD hospital admissions and vehicle-related $PM_{2.5}$ and OC.

A recent study evaluated HRV metrics and exposure to OC in patients with IHD in Erfurt, Germany; an increase in 24-hour exposure to OC was associated with decreases in HF, rMSSD, and pNN50; similar associations were observed for $PM_{2.5}$ with the exception of the association with HF (Schneider et al., 2010). In addition, a number of studies observed positive associations between OC exposure and biomarkers of coagulation and inflammation. In a quasi-experimental study conducted in Utrecht, the Netherlands, OC was associated with fibrinogen, platelet counts, and vWF (Strak et al., 2013a), while associations were only observed between $PM_{2.5}$ and vWF in this study. Chen et al. (2017) did not observe associations between fibrinogen and OC or $PM_{2.5}$, but positive associations were reported for D-dimer and OC with 1 and 2-day lagged exposures. In a recent panel study, Steenhof et al. (2014) reported mixed results for associations between OC and WBC counts measured 2 and 18 hours post-exposure, though patterns in associations were generally similar to those for $PM_{2.5}$. More specifically, positive associations were observed for WBC counts and monocytes 18 hours post-exposure, though OC was associated with lymphocytes and not neutrophils in contrast to $PM_{2.5}$. In this same panel, positive associations were observed for both $PM_{2.5}$ and OC, but the magnitude of effect was larger for OC (Strak et al., 2013a). Wittkopp et al. (2013) and Chen et al. (2017) examined OC in a panel of older adults and those with risk factors for cardiovascular disease, respectively, and did not find evidence for associations with CRP, although Wittkopp et al. (2013) did find positive associations with soluble receptor for IL6 that were not observed for $PM_{2.5}$.

6.1.15.3 Secondary $PM_{2.5}$—Sulfate, Nitrate, Ammonium

Several recent studies add to the limited supporting evidence in the 2009 PM ISA for associations of sulfate (SO_4^{2-}), nitrate (NO_3^-), and ammonium (NH_4^+) with CVD ED visits and hospital admissions, though the evidence is not entirely consistent. Evidence for effects on other CVD outcomes is limited. In most locations, results are similar between $PM_{2.5}$ and sulfate and nitrate in direction and magnitude of association.

An analysis of Medicare data across 119 U.S. counties found that nitrates from $PM_{2.5}$ were associated with CVD hospital admissions (Levy et al., 2012), and Peng et al. (2009) observed a similar pattern in the same population over a slightly shorter time period. Similarly, Sarnat et al. (2015) observed that ED visits for IHD were positively associated with $PM_{2.5}$ nitrates in St. Louis, MO. In 4 cities in southern Europe, Basagaña et al. (2015) reported positive associations with sulfate from $PM_{2.5}$. In contrast, studies in Denver (Kim et al., 2012), Houston (Liu et al., 2016b) and California (Ostro et al., 2016) reported that $PM_{2.5}$ concentrations of sulfates and nitrates were not associated with aggregate CVD hospital admissions. Using data for transmural myocardial infarctions in the NJ MIDAS registry, Rich et al. (2010) observed the largest effects on the days with the highest tertile of sulfate, nitrate, and ammonium, and the lowest tertile of elemental carbon. The authors interpreted their findings as indicating that $PM_{2.5}$ on days with pollution mixtures that are formed through atmospheric chemistry and depleted in primary $PM_{2.5}$ pollutants were most strongly associated with transmural infarctions.

Evidence for associations between sulfate or nitrate and other CVD endpoints is more limited, but generally positive. Despite reporting a generally null association between $PM_{2.5}$ and ICD activations, Anderson et al. (2010) observed a positive association between SO_4^{2-} and atrial fibrillation in London, England. Strak et al. (2013a) examined associations between sulfate and nitrate with fibrinogen, platelet counts, and vWF. Positive associations were observed for both nitrate and sulfate with fibrinogen, though associations with $PM_{2.5}$ were null. In contrast, $PM_{2.5}$ and sulfate were positively associated with vWF, but associations with nitrate were null. In addition, the extrinsic coagulation pathway was positively associated with nitrate and sulfate, but null for $PM_{2.5}$ (Strak et al., 2013b).

6.1.15.4 Metals

Compared with $PM_{2.5}$ mass, short-term increases in ambient concentrations of metals are inconsistently associated with CVD ED visits and hospital admissions. In the expanded body of recent studies, none observed associations with a metal but not $PM_{2.5}$ mass (Figure 6-15). Most studies observed an association with some metal, and studies that examined numerous metals often observed an association with multiple metals. However, findings are inconsistent for any individual metal or the sum of metals.

Among Medicare beneficiaries in Connecticut and Massachusetts, Bell et al. (2014) found that $PM_{2.5}$ from Ca, Zn, and V were positively associated with CVD hospital admissions. In an additional

study of Medicare beneficiaries in 64 cities, CVD hospital admissions were associated with copper, iron, selenium, silicon, and zinc (Ito et al., 2013). No individual component had stronger associations than $PM_{2.5}$ mass. In separate analyses of hospital admissions (Liu et al., 2016b) and ED visits (Liu et al., 2016a) in Houston, TX authors reported positive associations between stroke and bromine, nickel (ED visits) and As (hospital admissions), but observed negative associations for zinc, calcium, iron, potassium, manganese, vanadium, (ED visits), and potassium, (hospital admissions). Sarnat et al. (2015) reported that ED visits for IHD were negatively associated with 24-hour concentrations of $PM_{2.5}$ Fe and Si concentrations in St. Louis, MO while CVD hospital admissions were negatively associated with Si concentrations. A study of eight California counties (Ostro et al., 2016) found a small positive association with potassium, and zinc, while Basagaña et al. (2015) reported positive associations with Zn, Fe, and Mn from $PM_{2.5}$ in 4 cities in southern Europe.

In Atlanta, GA Suh et al. (2011) observed that $PM_{2.5}$ transition metals were associated with CVD, and specifically IHD, hospital admissions. Similarly, in New York City, NY Ito et al. (2011) found that most of the $PM_{2.5}$ chemical components considered were associated with CVD hospital admissions, making it difficult to draw conclusions about specific components.

Ambient concentrations of metals can be spatiotemporally more heterogeneous than $PM_{2.5}$ total mass, and thus, exposure measurement error could contribute to inconsistent findings for metals. Another uncertainty not addressed in the evidence is whether metals are independently associated with CVD effects as gaseous pollutants were not examined and correlations with gases and other $PM_{2.5}$ components were generally not reported.

6.1.15.5 Other $PM_{2.5}$ components

New information links cardiovascular effects with cyclohexanes and hopanes, though information is available from few studies and locations for each. In a combined analysis from Atlanta, GA Birmingham, AL and Dallas, TX Kioumourtzoglou et al. (2013) observed that cyclohexane concentrations, a marker of gasoline exhaust, were associated with higher rates of IHD and heart failure. Sarnat et al. (2015) observed a positive association between ED visits for heart failure and hopanes in the St. Louis, MO metropolitan area, though Kioumourtzoglou et al. (2013) reported null associations with hopanes.

6.1.15.6 Sources of $PM_{2.5}$

Several recent studies apportioned $PM_{2.5}$ components into source factors and provide some evidence linking $PM_{2.5}$ from traffic to cardiovascular hospital admissions. Studies of CVD hospital admissions are note entirely consistent, but provide some evidence for an association with $PM_{2.5}$

concentration during wildfires. Evidence is generally sparse for $PM_{2.5}$ from dust or soil, oil, salt, and local industry.

Some studies have attempted to identify specific sources or components of $PM_{2.5}$ that may be most strongly associated with hospital admissions or ED visits for CVD. Cardiovascular hospital admissions were associated with $PM_{2.5}$ from motor vehicles or traffic in various U.S. regions. In New York City, NY Lall et al. (2011) found that IHD, heart failure, and cerebrovascular disease hospital admissions were associated with $PM_{2.5}$ from traffic, but not other $PM_{2.5}$ components. In a subsequent analysis in the same data set, Lall et al. (2011) found that $PM_{2.5}$ derived from traffic was associated with same-day rates of hospital admissions for CVD while $PM_{2.5}$ from soil was inversely related. A study of eight California counties found small, positive associations with hospital admissions for IHD, heart failure, and arrhythmia and vehicle- or soil-related $PM_{2.5}$ in addition to $PM_{2.5}$ mass (Ostro et al., 2016). In source-based analyses Ito et al. (2013) reported an association with the traffic category during the cold season and CVD hospital admissions. Another large, multicity Medicare study also found that CVD hospitalizations were strongly related to $PM_{2.5}$ components from traffic sources, as well as sea salt/street salt, industrial combustions, and soil and road sources (Zanobetti et al., 2009). A study of Medicare beneficiaries by Zanobetti et al. (2009) noted stronger associations with MI and $PM_{2.5}$ from traffic, industrial combustion sources, sea salt/street salt, industrial sources, and wood burning and soil. Ostro et al. (2016) also examined $PM_{2.5}$ in relation to MI, and though they reported no association with $PM_{2.5}$ mass, they did report small positive associations with vehicle and soil related $PM_{2.5}$.

Examination of wildfire-related $PM_{2.5}$ was available from different regions across the U.S. In the 2009 PM ISA Delfino et al. (2009a) reported positive associations of total CVD admissions, IHD, CHF, and CBVD with southern California wildfires during 2003. Smaller studies reported inconsistent evidence of associations across outcomes. A study during a month of Colorado wildfires in 2012 reported generally null associations for all CVD outcomes except IHD (Alman et al., 2016). Conversely, a small study in Albuquerque, NM reported positive associations with total CVD admissions, CBVD, and PVD during a 2011 wildfire (Resnick et al., 2015). Additionally, two small studies of rural North Carolina peat wildfire events reported positive associations with hypertension and all-cause cardiac outcomes (Tinling et al., 2016) and CHF (Rappold et al., 2012; Rappold et al., 2011). In a large study of 561 urban and rural counties in the western U.S. using Medicare data Liu et al. (2017) reported null associations between total CVD HA/ED visits on wildfire smoke days compared to nonsmoke days from 2004−2009. This study is notable for the ability to incorporate a large number of rural counties into the analysis by using modeled wildfire-specific $PM_{2.5}$ data; however, the use of dichotomous exposure to define smoke and nonsmoke days may be source of exposure misclassification, even in sensitivity analyses. Furthermore, though wildfires are generally regional events, the use of county level exposure assignment may contribute to exposure misclassification particularly among large, rural western counties. Overall, evidence is limited for any association between exposure to wildfire derived $PM_{2.5}$ and cardiovascular HA/ED visits. Variability in study results may be related to regional heterogeneity in wildfire characteristics that depend on fuel sources, ecology, and meteorological conditions.

6.1.15.7 Associations Between $PM_{2.5}$ Components and Sources and Effects in People with Diabetes

Associations of short-term exposure BC with increases in inflammatory markers and HOMA-IR (Brook et al., 2016; O'Neill et al., 2007), decreased HRV and BAD (Table 6-32). Sulfate was associated with circulating markers of inflammation but not with BAD, FMD or NMD. OC was negatively associated with BAD (Zanobetti et al., 2014b). The single study that considered copollutant confounding reported that the association between BC and HRV did not persist after adjustment for NO_2 or CO.

Table 6-32 Summary of studies evaluating short-term exposure to $PM_{2.5}$ components and sources in people with diabetes.

Study	Study Population	Exposure Assessment	Concentration	Outcome	Copollutants Examined
(O'Neill et al., 2007) Boston, MA 1998−2002	N = 92 RCT participants Type 2 diabetes	24-h avg 1 monitor within 1.5 km of clinic	BC Mean (SD): 1.1 (0.8) IQR 0.6	ICAM-1 VCAM-1 vWF	NR
†(Brook et al., 2016) Beijing, China BC	Adults with metabolic syndrome	24-h avg, lag 1−7 day, 3 monitors	BC Mean (SD) 6.5 (3.7) IQR 4.5	HOMA-IR	NR
†(Sun et al., 2015) Shanghai, China 2010	N = 53 Type 2 diabetes	4-h moving avg prior to clinic visit, monitor near residence (April, June, Sept)	BC Mean (SD): 4.09 (2.37)	SDNN	Correlations (*r*): PNC5−560 = 0.52 2-pollutant models decreased after adjustment for Ozone Increased/null after adjustment for NO_2 and CO
†(Zanobetti et al., 2014b) Boston, MA 2006−2010 Five follow-up exams 2 weeks apart	N = 64 49−54 yr Type 2 diabetes	24 h avg, 1 monitor, reside within 25 km 1 and 5-day avg concentrations	BC Mean 0.61 Median 0.54 IQR 0.35	BAD FMD NMD	Correlations (*r*): $PM_{2.5}$ = 0.65, OC = 0.50, PN = −0.05, SO_4 = 0.52
†(Zanobetti et al., 2014b) Boston, MA 2006−2010 Five follow-up exams 2 weeks apart	N = 64 49−54 yr Type 2 diabetes	24 h avg, 1 monitor, reside within 25 km 1 and 5-day avg concentrations	OC Mean 3.03 Median 2.85 IQR 1.75	BAD FMD NMD	Correlations (*r*): $PM_{2.5}$ = 0.54, BC = 0.50, PN = −0.15, SO_4 = 0.48

Table 6-32 (Continued): Summary of studies evaluating short-term exposure to $PM_{2.5}$ components and sources in people with diabetes.

†(Zanobetti et al., 2014b) Boston, MA 2006−2010 Five follow-up exams 2 weeks apart	N = 64 49−54 yr Type 2 diabetes	24 h avg, 1 monitor, reside within 25 km 1 and 5-day avg concentrations	Sulfate Mean 2.13 Median 1.61 IQR 1.47	BAD FMD NMD	Correlations (*r*): $PM_{2.5}$ = 0.76, BC = 0.52, PN = −0.27, OC = 0.43
†(O'Neill et al., 2007) Boston, MA 1998−2002	N = 92 RCT participants Type 2 diabetes	24-h avg 1 monitor within 1.5 km of clinic	Sulfate Mean (SD): 3.0 (2.0) IQR 2.2	ICAM-1 VCAM-1 vWF	NR

BAD = Brachial Artery Diameter; FMD = Flow Mediated Dilation; NR = Not Reported; NDM = Nitroglycerin Mediated Dilation; SDNN = Standard Deviation of NN intervals; rMSSD = Root Mean Square of the Successive Differences between adjacent NNs; ICAM-1 = intercellular adhesion molecule-1; VCAM-1 = vascular cell adhesion molecule-1; vWF = Von Willebrand factor; MPO = myeloperoxidase; hs CRP = high sensitivity c-reactive protein; IL-6 = interleukin 6

6.1.15.8 Toxicology Studies of Individual Components and Sources as Part of the PM Mixture

It is still not known whether particular sources or components of $PM_{2.5}$ are responsible for health effects or if certain sources and components can be ruled out as not contributing to adverse health effects. At the time of the last PM NAAQS review, the ISA concluded that "many constituents of PM can be linked with differing health effects and the evidence is not yet sufficient to allow differentiation of those constituents or sources that are more closely related to health outcomes" (U.S. EPA, 2009). The following section is organized by health endpoint and exposure duration and includes in vivo toxicology studies where animals were exposed via inhalation. Lippmann et al. (2013b) conducted a series of studies where $ApoE^{-/-}$ mice were exposed to $PM_{2.5}$ CAPs for six hours/day, five days/week for a total of six months (NPACT Study 1). Separate studies were conducted in Manhattan, NY, Tuxedo, NY, East Lansing, MI, Seattle, WA and Irvine, CA that began in 2007 with the last one concluding in 2011. At all locations, mice were exposed to CAPs at nominal 8−10 times ambient concentrations, resulting in mean exposure concentrations of 138 $\mu g/m^3$ at Irvine, 136 $\mu g/m^3$ at Tuxedo, 122.9 $\mu g/m^3$ at Manhattan, 67.8 $\mu g/m^3$ at East Lansing and 60.5 $\mu g/m^3$ at Seattle. Measured $PM_{2.5}$ components included for source apportionment were Al, Ba, Br, Ca, Cu, Fe, K, Mn, Ni, Pb, S, Se, Si, V, Zn, and EC. In addition, NO_2 data were used for the Manhattan analysis to aid in the identification and separation of a traffic source category. Acute CAPs exposure resulted in some changes in HR and HRV measurements. Generally, the most significant effects were observed for mice exposed to $PM_{2.5}$ from either site in NY, with decreases in HR and LF/HF and increases in SDNN and rMSSD at lag 0 and 1 (and to a lesser extent at lag 2) in animals exposed to Manhattan $PM_{2.5}$. For Tuxedo, the pattern was opposite, with significant increases in HR and LF/HF and significant decreases in SDNN and rMSSD at lag 0 (and to a lesser extent at lag 1 and 2). Very few significant changes in heart rate variability parameters were observed in animals exposed to $PM_{2.5}$ in East Lansing, Seattle or Irvine.

The number of significant changes in HR and HRV by site at Lag day 0 were analyzed for 16 individual components. Across all of the sites, the greatest number of HR/HRV changes were for Na (149), Br (144) and Si (138). As mentioned previously, Manhattan and Tuxedo had double the number of HR/HRV changes compared to East Lansing, Seattle or Irvine. For Manhattan, the greatest number of HR/HRV changes was for Ni and *P* (both with 68) followed by Na (65), V (59), S (54) and EC (50). The pattern was different for Tuxedo, as the greatest number of HR/HRV changes was associated with Br (49), *P* (46), S (43) and K (42). The fewest number of HR/HRV changes across all sites was for Cr (31), Pb (40), Cu (57) and Mn (59).

Embedded within the NPACT study, a subset of data and results were provided in in Chen et al. (2010). This subset focused on the Manhattan and Tuxedo (aka Sterling Forest) exposures and HR and HRV changes. ApoE$^{-/-}$ mice were exposed for 6 months to filtered air or $PM_{2.5}$ CAPs from May to September 2007. Mean CAPs concentrations in Manhattan were identical to those reported in Lippmann et al. (2013b) of 122.9 µg/m^3 and slightly higher than those reported in Lippmann et al. (2013b) of 133.3 µg/m^3 in Sterling Forest. As expected, the changes in HR and HRV parameters with CAPs concentration were similar to the NPACT study. Decreases in HR and LF/HF and increases in SDNN, rMSSD, LF and HF were observed with mice exposed to Manhattan CAPs at all time periods (9 AM−2 PM, 7 PM−10 PM, 1 AM−4 AM) for lags 0 and 1. At Sterling Forest, increases in HR and decreases in SDNN, rMSSD, LF, and HF were observed at lag 0 and select periods at lag 1. When examining 20 individual elements with HR and HRV responses, Br, EC, Na, Ni, *P*, S, and V consistently resulted in significant changes across all time periods (magnitude and directions not provided) on lags 0 and 1 at the Manhattan site. Al and Se were associated with significant changes at lag 1 only and Ni and *P* were associated with significant changes at lag 2. At the Sterling Forest site, only S was associated with significant changes at lag 0, with Br and Zn at lag 1, and only Si for lags 0 and 1.

Two pollutant regression models were also performed using CAPs, S or EC as one factor and individual components as the second factor. For animals exposed to Manhattan CAPs, the CAPs associations were more strongly associated with altered cardiac function compared to the majority of elements for lag 0 and 1. Ni and S demonstrated stronger associations with ECG changes compared to other elements at lag 0. For animals exposed to Sterling Forest CAPs, the CAPs association were also stronger than those for the other elements at lag 0. Individual elements Br, S, Si, and Zn were more strongly associated at lag 1 and lag 2 compared to other elements.

In a study conducted for 13 consecutive days (8 hr/day) in summer 2005 and winter 2006 in southwest Detroit, MI, ECG changes were assessed in male SH rats exposed to $PM_{2.5}$ CAPS (Rohr et al.). Mean concentration of CAPS during the summer exposure was 518 µg/m^3, with mean exposure concentrations in the winter being 357 µg/m^3. PM composition was much more variable in summer compared to winter. Over the entire 8-hour exposure period in summer, significant differences in HR, SDNN or rMSSD were not observed between air controls and CAPs-exposed animals. When 30-minute intervals were examined during summer exposures, reductions in SDNN were associated with EC, Fe, Sr,

Mg, As, Ca, Ti, Mn, Se, Ba, Sb, Pb, Ce and Zn. Over the entire 8-hour period in winter, only HR demonstrated significant responses. Increased HR was associated with Mg and decreased HR was associated with Fe, Ti, Cu, Pb, Sn, Co, EC, OC, Se and In. For 30-minute intervals in winter, both HR and rMSSD were significantly different between the air and CAPs exposed groups. Generally, HR was decreased in the PM-exposed animals and rMSSD was increased. Reductions in HR were associated with Ba, As, Tb, EC, Cd, Zn, S, Sr, Mn, Ca, Ti, Fe, Rb, Cr, Mg, Se, Sb, K and Cu; only La had an association with increased HR. Increases in rMSSD were associated with Ba, EC, Zn, As and Rb.

In a study with similar methods to (Rohr et al., 2011), male SH rats were exposed to $PM_{2.5}$ CAPs from Steubenville, OH for 13 consecutive days (8 hr/day) in August 2006 (Kamal et al., 2011). During exposure, winds originated from the southwest (SW) or northeast (NE). Mean CAPs concentration over the exposure period was 406 $\mu g/m^3$. Approximately 30 $PM_{2.5}$ components were identified and used in univariate regression to connect to ECG changes. Furthermore, PMF was used to determine the major emission sources contributing the $PM_{2.5}$ concentrations during the study period. Sulfate and OC made up over 50% of CAPs mass. Using 30-minute average data over the entire exposure period (regardless of wind direction), significant CAPs effects were observed for HR and SDNN, but not rMSSD. When separating out wind direction, HR and SDNN changes were significant for both the SW and NE wind directions, whereas rMSSD changes were only significant for the SW wind direction. Generally, decreases in HR were observed with wind originating from the NE and associated with S, Se, Pb, Rb, Mn, Zn, Sr, Fe, Cd. In contrast, increases in HR were observed with wind originating from the SW and associated with Mo, La, PM mass, Ce, V, Ti, As and Sb. For SDNN, the majority of changes were decreases with more components associated when winds were from the NE (Sb, Pb, Zn, Rb, As, Sn, K, V, Cd, Mo, Ti, Cr). Fewer components were associated with decreased SDNN with winds from the SE (Mo, As, Sb). Changes in rMSSD were only observed with wind from the SW direction, with both increases (Al, Mg) and decreases noted (Mo, V). To assess the contribution of $PM_{2.5}$ grouped components on resultant health effects in toxicological studies, we used the approach from (Stanek et al., 2011). This approach is consistent with the Review Panel of the NPACT initiative that states both source categories and component concentrations should be used directly in the health analyses (assuming the study design permits) with a focus on examining consistencies and differences between the two approaches (Lippmann et al., 2013b). Four criteria were applied to the studies that were identified during the literature search. Each study needed to meet all of the criteria in order to be included:

- exposures conducted using $PM_{2.5}$ from U.S. airsheds or those representative of the U.S. (e.g., Europe, Canada);
- inclusion of at least five PM components;
- grouping of PM components using statistical methods, for which the groups were not predefined based on common physical or chemical properties (e.g., water soluble vs. nonsoluble); and
- formal statistical analysis investigating the relationship between groups of PM components or PM sources and health effects.

Studies of that examined $PM_{2.5}$ using individual components or individual source emissions are not included, as this is a limited approach that does not consider the combined contribution of the $PM_{2.5}$ mixture to health effects.

In the NPACT Study 1 (Lippmann et al., 2013b), a source characterization statistical model was used to determine associations between identified source categories and the HR and HRV changes.

Table 6-33 shows general HR and HRV results over the exposure period for each location and identified source category. This is a semi-quantitative evaluation of the number of significant associations, given that there were 6 cardiac measures (HR, SDNN, rMSSD, LF, HF, and LF/HF) analyzed over 4 different time periods (9 AM−2 PM, 7 PM−10 PM, 10 PM−1 AM, 1 AM−3 AM) and 3 different lags (0, 1 and 2).

Table 6-33 NPACT study results for identified source categories and occurrence of heart rate (HR) and heart rate variability (HRV) changes.

Location	Identified Source Categories	General HR and HRV Results
Manhattan, NY	Incineration (Pb, Zn); Steel (Fe, Mn); Soil (Al, Si, Ca); Residual oil combustion (Ni, V); Sulfur-coal (S, Se); Fireworks (K, Ba, Cr); Salt (Na, Mg, Cl); Traffic (EC, NO_2); Secondary aerosols (S, OC)	Residual oil combustion had the largest number of HR/HRV changes (54); combining sulfur-coal and secondary aerosol source categories to represent regionally transported $PM_{2.5}$ had even greater number of responses (59); salt and traffic demonstrated changes (48 and 44, respectively); changes associated with soil were less frequent (13); for steel and incineration, the strongest associations were on lag 0 with little response on lag 1 or 2
Tuxedo, NY	Sulfur-coal (Se, S, *P*, Br); Soil (Si, Ti, Al, Ca); Salt (Na, Cl); Ni refinery (Fe, Ni, Zn, Ca, Mn, V)	Sulfur-coal had the most number of HR/HRV changes (27), with soil having the second most (24); soil had most number of responses on lag 1 (18); almost all salt significant associations were on lag 0 (13 of 14)
East Lansing, MI	Soil (Si, Ca, Al, Fe); Sulfur-coal (S); Residual oil combustion (V, Ni); Zn-Cl (Zn, Cl); EC-OC (EC, OC)	Overall much fewer instances of significant HR/HRV associations compared to other sites (20 total across all source categories); soil and Zn-Cl had the most number of HR/HRV changes (6 each), although greatest soil associations were observed with lag 2; the most number of sulfur-coal associations were observed at lag 0 (4); little associations with OC-EC and residual oil combustion (2 and 1, respectively)

Table 6-33 (Continued): NPACT study results for identified source categories and occurrence of heart rate (HR) and heart rate variability (HRV) changes.

Location	Identified Source Categories	General HR and HRV Results
Seattle, WA	Salt (Na, Mg, Cl); Soil (Al, Si, Ca, Fe); Traffic and road dust (Ca, Mn, Cu, Fe, Zn, EC); Biomass combustion (K, Cu, EC); Residual oil combustion (V, Ni); Sulfates (S, Br)	Soil had the most HR/HRV changes (31) across all lags; residual oil combustion and salt had second and third most responses (13 and 8, respectively) with both demonstrating more changes at lag 2; biomass combustion was only associated with HR/HRV changes on lag 0 (6) and sulfates only associated with HR/HRV changes on lag 2 (5)
Irvine, CA	Residual oil combustion (V, Ni); Soil (Si, Al); Traffic (Mn, Cu, Ca, EC); Biomass combustion (K, EC); Salt (Cl, K); Metals (Pb, Zn)	Soil had the most number of significant HR/HRV changes (20), with most observed on lag 2 (14); a similar temporal relationship was demonstrated with biomass combustion (11 total, with 6 on lag 2); residual oil combustion was third (10) distributed evenly across the lags; soil, metals and traffic had much fewer significant associations with HR/HRV changes (5, 4, and 3, respectively)

As expected, those locations with greater $PM_{2.5}$ responses, also demonstrated more counts of significant associations between source categories and HR and HRV measurements, albeit all locations had at least one source category strongly associated with a change in cardiac function.

Looking across locations and source categories, soil was associated with HR/HRV changes in mice exposed to $PM_{2.5}$ at any location, with the greatest frequencies occurring on lag 1 or 2. Residual oil combustion was most frequently associated with HR/HRV changes in Manhattan across all lags and was also frequently observed in Seattle and Irvine, albeit to a greater extent on lags 1 and 2 in Seattle. There was a much greater frequency of HR/HRV changes related to traffic in Manhattan compared to Seattle and Irvine, which is likely explained by the fact that the laboratory in Manhattan is located in close proximity to busy roads. The source categories of secondary aerosols in Manhattan, sulfur-coal in Tuxedo and East Lansing, and sulfates in Seattle were all associated with HR/HRV changes. However, the frequency of these changes were less than other source categories, with the exception of Tuxedo (where concentrations were much higher than Seattle or East Lansing). In Manhattan, Tuxedo, Seattle and Irvine, salt was also associated with HR/HRV changes, with frequency of occurrence being in the middle of the range of all source categories at each location; the timing of the associations (i.e., lag) varied by location. Biomass combustion was associated with HR/HRV changes only in Seattle and Irvine, with the association only being observed at lag 0 in Seattle.

6.1.16 Summary and Causality Determination

A large body of recent evidence confirms and extends the evidence from the 2009 PM ISA (U.S. EPA, 2009) indicating that there is a causal relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects. The strongest evidence in the 2009 PM ISA was from epidemiologic studies of ED visits and hospital admissions for IHD and HF, with supporting evidence from epidemiologic studies of cardiovascular mortality. Changes in various measures of cardiovascular function in CHE studies provided some biological plausibility for these associations. In addition, animal toxicological studies reporting some evidence of reduced myocardial blood flow during ischemia, altered vascular reactivity, and ST segment depression provided additional biological plausibility. In the current review, evidence supporting the causal determination includes generally positive associations reported from epidemiologic studies of hospital admissions and ED visits for cardiovascular-related effects, and in particular, for IHD and HF. Results from these observational studies are supported by experimental evidence from CHE and animal toxicological studies of endothelial dysfunction, as well as endpoints indicating impaired cardiac function, increased risk of arrhythmia, changes in HRV, increases in BP, and increases in indicators of systemic inflammation, oxidative stress, and coagulation. Additional results from observational panel studies, though not entirely consistent, provide at least some evidence of increased risk of arrhythmia, decreases in HRV, increases in BP, and ST segment depression. Thus, epidemiologic panel studies also provide some support to the causal determination and to biological plausibility. Finally, epidemiologic studies of CVD-related mortality provide additional evidence that demonstrates a continuum of effects from biomarkers of inflammation and coagulation, subclinical endpoints (e.g., HRV, BP, endothelial dysfunction), ED visits and hospital admissions, and eventually death. The current body of evidence also reduces uncertainties from the previous review related to potential copollutant confounding and limited biological plausibility for CVD effects following short-term $PM_{2.5}$ exposure. Evidence supporting the causal determination for short-term $PM_{2.5}$ exposure and cardiovascular effects reached in this ISA is discussed below and summarized in Table 6-34, using the framework for causal determination described in the Preamble to the ISAs (U.S. EPA, 2015).

The generally consistent, positive associations observed in numerous epidemiologic studies of ED visits and hospital admissions for IHD, HF and combined cardiovascular-related endpoints contribute to the evidence supporting a causal relationship between short-term $PM_{2.5}$ exposure and CVD. Among this body of evidence, nationwide studies of older adults using Medicare reported positive associations between $PM_{2.5}$ concentrations and HF hospital admissions (Section 6.1.3.1). Consistent with the results of these large Medicare studies, additional multicity studies conducted in the northeast reported positive associations between short-term $PM_{2.5}$ concentrations and ED visits or hospital admissions for IHD (Sections 6.1.2.1), while studies conducted in the U.S. and Canada reported positive associations between short-term $PM_{2.5}$ concentrations and ED visits for HF. Results from epidemiologic studies conducted in single cities contribute additional support to the causal determination, but are less consistent, showing both positive and null associations between $PM_{2.5}$ concentrations and these endpoints (Section 6.1.2 and Section 6.1.3). When considered as a whole, the recent body of IHD and HF epidemiologic evidence is in

agreement with evidence from previous ISAs reporting mainly positive associations between short-term $PM_{2.5}$ concentrations and ED visits and hospital admissions. In addition, a number of more recent CHE, animal toxicological, and epidemiologic panel studies provide evidence that $PM_{2.5}$ exposure could plausibly result in IHD or HF through pathways that include endothelial dysfunction, arterial thrombosis, and arrhythmia (Section 6.1.1). Also supporting the plausibility for IHD and HF endpoints are more recent epidemiologic panel studies reporting some evidence of ST segment depression (Section 6.1.2.2) and a recent CHE study and animal toxicological study showing decreased cardiac function following short-term $PM_{2.5}$ exposure (Section 6.1.3.2 and Section 6.1.3.3).

Results from additional CHE studies published since the last review also support a causal relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects. The most consistent evidence from these studies is for endothelial dysfunction as measured by changes in BAD or FMD. More specifically, in contrast to the last review where a single study did not find changes in endothelial function, all but one of the studies in the current review examining the potential for endothelial dysfunction reported an effect of $PM_{2.5}$ on measures of blood flow (Section 6.1.13.2) relative to FA exposure. That being said, all studies were not in agreement with respect to the timing of the effect or the mechanism by which reduced blood flow was occurring (i.e., endothelial independent vs. endothelial dependent mechanisms). In addition to endothelial dysfunction, CHE studies using CAPs, but not filtered DE generally reported evidence for small increases in blood pressure, although there were inconsistencies across studies with respect to changes in SBP and DBP. It is notable however, that in CAPs studies where increases in one measure of BP (e.g., SBP), but not the other (e.g., DBP) was found to be statistically significant, that other measure of BP usually changed as well, but the change was not found to be statistically significant (Section 6.1.6.3). In addition, although not entirely consistent, there is also some evidence across CHE studies for conduction abnormalities/arrhythmia (Section 6.1.4.3), changes in HRV (Section 6.1.10.2), changes in hemostasis that could promote clot formation (Section 6.1.12.2), and increases in inflammatory cells and markers (Section 6.1.11.2). Thus, when taken as a whole, CHE studies are in coherence with epidemiologic studies by demonstrating that short-term exposure to $PM_{2.5}$ may result in the types of cardiovascular endpoints that could lead to ED visits and hospital admissions.

Animal toxicological studies published since the 2009 PM ISA also support a causal relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects. A recent study demonstrating decreased cardiac contractility and left ventricular pressure in mice is coherent with the results of epidemiologic studies reporting associations between short-term $PM_{2.5}$ exposure and HF (Section 6.1.3.3). In addition, similar to CHE studies, there is generally consistent evidence in animal toxicological studies for indicators of endothelial dysfunction (Section 6.1.13.3). Studies in animals also provide evidence for changes in a number of other cardiovascular endpoints following short-term $PM_{2.5}$ exposure. Although not entirely consistent, these studies provide at least some evidence of conduction abnormalities and arrhythmia (Section 6.1.4.4), changes in HRV (Section 6.1.10.3), changes in BP (Section 6.1.6.4), and evidence for systemic inflammation and oxidative stress (Section 6.1.11.3). Finally, these toxicological

studies also suggest that genetic background, diet, and PM composition may influence the effect of short-term $PM_{2.5}$ exposure on some of these health endpoints.

As outlined above, across the scientific disciplines there is evidence for a continuum of cardiovascular-related health effects following short-term exposure to $PM_{2.5}$. These effects range from relatively modest increases in biomarkers related to inflammation and coagulation, to subclinical CVD endpoints such as endothelial dysfunction, to ED visits and hospital admissions for outcomes such as IHD and HF. In coherence with this continuum of effects is a body of epidemiologic studies reporting a relatively consistent relationship between short-term $PM_{2.5}$ exposure and CVD-related mortality. These epidemiologic studies also reduce a key uncertainty from the last review by providing evidence that gaseous pollutants are not likely to confound the $PM_{2.5}$-cardiovascular mortality relationship.

Taken together, the recent evidence described throughout Section 6.1 extends the consistency and coherence of the evidence base reported in the 2009 PM ISA and 2004 AQCD. Direct evidence for $PM_{2.5}$ exposure-related cardiovascular effects can be found in a number of CHE and animal toxicological studies. In coherence with these results are epidemiologic panel studies also finding that $PM_{2.5}$ exposure is associated with some of the same cardiovascular endpoints reported in CHE and animal toxicological studies. There is a limited number of studies evaluating some of these endpoints, and there are some inconsistencies in results across some of these animal toxicological, CHE and epidemiologic panel studies, though this may be due to substantial differences in study design, study populations, or differences in PM composition across air sheds. That being said, the results from these epidemiologic panel, CHE, and animal toxicological studies, in particular those related to endothelial dysfunction, impaired cardiac function, ST segment depression, thrombosis, conduction abnormalities, and BP provide coherence and biological plausibility for the consistent results from epidemiologic studies observing positive associations between short-term $PM_{2.5}$ concentrations and IHD and HF, and ultimately cardiovascular mortality. Overall, considering the entire evidence base, there continues to be sufficient evidence to conclude that **a causal relationship exists between short-term $PM_{2.5}$ exposure and cardiovascular effects.**

Table 6-34 Summary of evidence for a causal relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{2.5}$ concentrations	Increases in ED visits and hospital admissions for IHD and CHF in multicity studies conducted in the U.S., Canada, Europe, and Asia Increases in cardiovascular mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia.	Section 6.1.2.1 Section 6.1.3.1 Section 6.1.9	5.8−18.6 μg/m^3 5.8−18.0 μg/m^3
Consistent evidence from controlled human exposure studies at relevant $PM_{2.5}$ concentrations	Consistent changes in measures of endothelial dysfunction Generally consistent evidence for small increases in measures of blood pressure following CAPs exposure Additional evidence of conduction abnormalities, heart rate variability, impaired heart function, systemic inflammation/oxidative stress	Section 6.1.13.2 Section 6.1.6.3 Section 6.1.4.3 Section 6.1.3.2 Section 6.1.10.2 Section 6.1.11.2	24−325 μg/m^3 See Tables in identified sections
Consistent evidence from animal toxicological studies at relevant $PM_{2.5}$ concentrations	Consistent changes in indicators of endothelial dysfunction. Additional evidence of changes in impaired heart function, conduction abnormalities/arrhythmia, heart rate variability, blood pressure, systemic inflammation/oxidative stress	Section 6.1.13.3 Section 6.1.6.4 Section 6.1.4.4 Section 6.1.3.3 Section 6.1.10.3 Section 6.1.11.3	168.7−510 μg/m^3 See Tables in identified sections
Epidemiologic evidence from copollutant models provides some support for an independent $PM_{2.5}$ association	The magnitude of $PM_{2.5}$ associations remain positive, but in some cases are reduced with larger confidence intervals in copollutant models with gaseous pollutants. Further support from copollutant analyses indicating positive associations for cardiovascular mortality. Recent studies that examined potential copollutant confounding are limited to studies conducted in Europe and Asia. When reported, correlations with gaseous copollutants were primarily in the low to moderate range ($r < 0.7$).	Section 6.1.14.1	
Consistent positive epidemiologic evidence for associations between $PM_{2.5}$ exposure and CVD ED visits and hospital admissions across exposure measurement metrics	Positive associations consistently observed across studies that used ground-based (i.e., monitors), model (e.g., CMAQ, dispersion models) and remote sensing (e.g., AOD measurements from satellites) methods, including hybrid methods that combine two or more of these methods.	Kloog et al. (2014)	

Table 6-34 (Continued): Summary of evidence indicating that a causal relationship exists between short-term $PM_{2.5}$ exposure and cardiovascular effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Generally consistent evidence for biological plausibility of cardiovascular effects	Strong evidence for coherence of effects across scientific disciplines and biological plausibility for a range of cardiovascular effects in response to short-term $PM_{2.5}$ exposure. Includes evidence for reduced myocardial blood flow, altered vascular reactivity, and ST segment depression.	Section 6.1.1 Figure 6-1	
Uncertainty regarding geographic heterogeneity in $PM_{2.5}$ associations	Multicity U.S. studies demonstrate city-to-city and regional heterogeneity in $PM_{2.5}$-CVD ED visit and hospital admission associations. Evidence supports that a combination of factors including composition and exposure factors may contribute to the observed heterogeneity.	Section 6.1.2.1 Section 6.1.3.1	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

6.2 Long-Term $PM_{2.5}$ Exposure and Cardiovascular Effects

The scientific evidence pertaining to the cardiovascular health effects of $PM_{2.5}$ reviewed in the 2009 PM ISA was "sufficient to infer a causal relationship between long-term $PM_{2.5}$ exposure and cardiovascular effects" (U.S. EPA, 2009). The strongest line of evidence comprised findings from several large U.S. cohort studies that consistently showed positive associations between $PM_{2.5}$ exposure and cardiovascular mortality (Krewski et al., 2009; Miller et al., 2007; Laden et al., 2006; Pope III et al., 2004). While several studies included in the 2009 ISA for PM reported associations of long-term PM_{10} exposure with morbidity outcomes such as post-MI congestive heart failure (CHF) (Zanobetti and Schwartz, 2007) and deep vein thrombosis (DVT) (Baccarelli et al., 2008), epidemiologic evidence relating to $PM_{2.5}$ was limited to a study of postmenopausal women (Miller et al., 2007) and cross-sectional analyses of self-reported cardiovascular effects among participants in the German Heinz Nixdorf Recall (HNR) study (Hoffmann et al., 2009; Hoffmann et al., 2006). These studies reported associations with coronary heart disease (CHD) and stroke. Biological plausibility and coherence with the epidemiologic findings were provided by studies using genetic mouse models of atherosclerosis demonstrating enhanced atherosclerotic plaque development and inflammation following 4 to 6-month exposures to $PM_{2.5}$ CAPs (U.S. EPA, 2009). Evidence from a limited number of toxicological studies in

mice reporting CAPs-induced effects on coagulation factors, hypertension and vascular reactivity was also drawn upon to support the causal conclusion. Recent epidemiologic studies add to the already strong evidence base supporting the association of long-term exposure to $PM_{2.5}$ with cardiovascular mortality (Section 6.2.10). Associations between long-term exposure to $PM_{2.5}$ and cardiovascular morbidity outcomes (i.e., IHD, stroke) were observed in some studies with the most consistent results in people with preexisting diseases (CHAPTER 12). Additional experimental studies of long-term exposure to $PM_{2.5}$ CAPs add to the collective evidence available to support a direct effect of $PM_{2.5}$ on the cardiovascular system, and provide biological plausibility for associations observed in epidemiologic studies.

Some uncertainties remained to be addressed at the completion of the 2009 PM ISA despite the strong evidence supporting a causal relationship between long-term exposure to $PM_{2.5}$ and cardiovascular effects. The following sections provide an evaluation of the most policy relevant scientific evidence, focusing on the extent to which recently available studies further characterize the relationship between long-term exposure to $PM_{2.5}$ and cardiovascular effects. Specifically, the current section focuses on studies where long-term average $PM_{2.5}$ concentrations are less than 20 $\mu g/m^3$ whereas the epidemiologic studies supporting the causal conclusion in the 2009 ISA were generally conducted in urban areas where mean $PM_{2.5}$ concentrations ranged up to 29.0 $\mu g/m^3$. In addition, an expanded set of longitudinal epidemiologic analyses that is currently available to assess the effect of long-term exposure to $PM_{2.5}$ on the incidence of cardiovascular disease and to examine temporal changes in specific endpoints such as coronary artery calcium (CAC), markers of systemic inflammation and coagulation. A more extensive literature on CAPs exposure reduces uncertainties related to inclusion of diesel and other mixture studies in the 2009 PM ISA. These studies, in combination with a limited number of recently available epidemiologic analyses that examine copollutant confounding, strengthen the evidence for a direct effect of long-term $PM_{2.5}$ on the cardiovascular system. Finally, an expanded set of studies describing the shape of the C-*R* function across the range of $PM_{2.5}$ concentrations is available and studies that use spatiotemporal exposure models to characterize exposure to populations that may be at greater distance from air monitors add to the collective evidence in the current review.

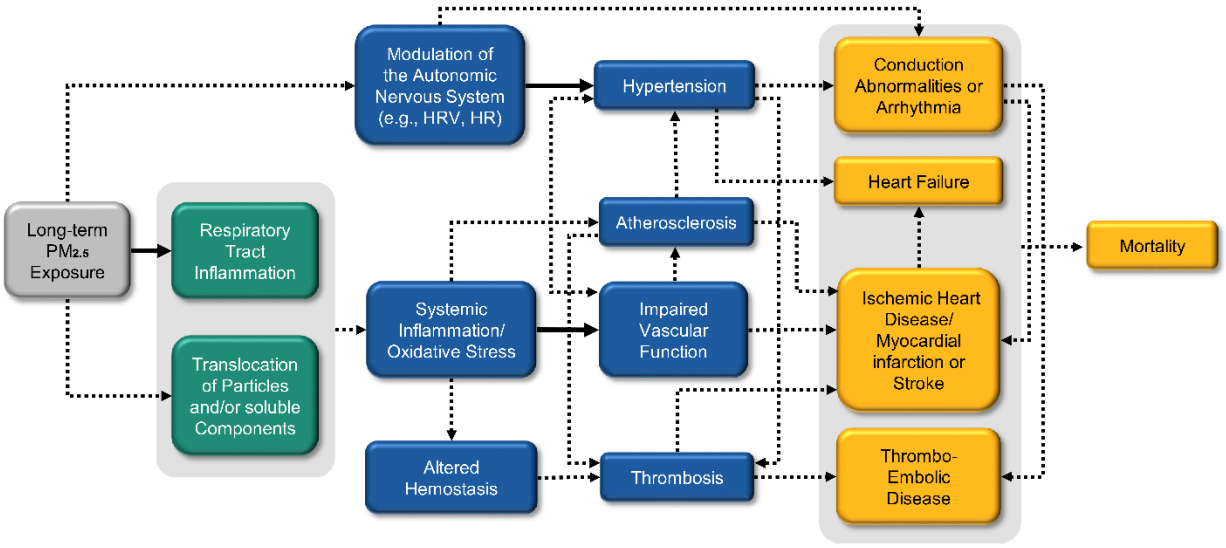
The subsections below provide an evaluation of the most policy relevant scientific evidence relating-long-tern $PM_{2.5}$ exposure to cardiovascular health effects. To clearly characterize and put this evidence into context, there is first a discussion of the biological plausibility of cardiovascular effects following long-tern $PM_{2.5}$ exposure (Section 6.2.1). Following this discussion, the health evidence relating long-tern $PM_{2.5}$ exposure and specific cardiovascular health outcomes is discussed in detail: ischemic heart disease and myocardial infarction (Section 6.2.2), cerebrovascular disease and stroke (Section 6.2.3), atherosclerosis (Section 6.2.4) heart failure and impaired heart function (Section 6.2.5) cardiac electrophysiology and arrhythmia (Section 6.2.6), blood pressure and hypertension (Section 6.2.7), peripheral vascular disease (PVD), venous thromboembolism and pulmonary embolisms (Section 6.2.8), aggregated cardiovascular outcomes (Section 6.2.9), and cardiovascular-related mortality (Section 6.2.10). The evidence for an effect of $PM_{2.5}$ exposures on endpoints such as changes in heart rate variability (HRV) and endothelial function are discussed (Section 6.2.11, Section 6.2.12, Section 6.2.13,

and, Section 6.2.14), as are copollutant confounding (Section 0), shape of the concentration response function (Section 6.2.16), and the relationship between health effects and exposure to specific $PM_{2.5}$ components (Section 6.2.17). Finally, the collective body of evidence is integrated across and within scientific disciplines[62], and the rationale for the causality determination is outlined in Section 6.2.18.

6.2.1 Biological Plausibility

This subsection describes the biological pathways that potentially underlie cardiovascular health effects resulting from long-term inhalation exposure to $PM_{2.5}$. Figure 6-16 graphically depicts these proposed pathways as a continuum of pathophysiological responses—connected by arrows—that may ultimately lead to the apical cardiovascular events observed in long-term epidemiologic studies. This discussion of "how" long-term exposure to $PM_{2.5}$ may lead to these cardiovascular events also provides biological plausibility for the epidemiologic results reported later in Section 6.2. In addition, most studies cited in this subsection are discussed in greater detail throughout Section 6.2.

[62] As detailed in the Preface, risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations unless otherwise noted.



Note: the boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below

Figure 6-16 Potential biological pathways for cardiovascular effects following long-term exposure to $PM_{2.5}$.

When considering the available health evidence, plausible pathways connecting long-term exposure to $PM_{2.5}$ to the apical events reported in epidemiologic studies are proposed in Figure 6-16. The first proposed pathway begins as respiratory tract inflammation leading to systemic inflammation[63]. The second proposed pathway involves modulation of the autonomic nervous system. Once these pathways are initiated, there is evidence from experimental and observational studies that long-term exposure to $PM_{2.5}$ may result in a series of pathophysiological responses that could lead to cardiovascular events such as IHD and HF.

Long-term inhalation exposure to $PM_{2.5}$ may result in respiratory tract inflammation and oxidative stress (Section 5.2). Inflammatory mediators such as cytokines produced in the respiratory tract have the potential to enter into the circulatory system where they may cause distal pathophysiological responses that could lead to overt cardiovascular disease. For example, following long-term exposure to $PM_{2.5}$, Kampfrath et al. (2011) reported that vascular dysfunction occurred via NADPH oxidase and inflammatory pathways that required toll like receptor 4 (TLR4). In addition, release of inflammatory

[63] It is also possible that particles ~200 nm or less, or soluble particle components can translocate directly into the circulatory system (Chapter 4) and lead to systemic inflammation, although the extent to which particle translocation occurs remains unclear.

mediators into the circulation such as monocyte chemoattractant protein 1 (MCP-1) can result in the recruitment of additional inflammatory cells, and thus amplify the initial inflammatory response (Carr et al., 1994). Thus, it is important to note that there is evidence from long-term experimental studies in animals (Tanwar et al., 2017; Aztatzi-Aguilar et al., 2015; Gorr et al., 2014; Lippmann et al., 2013a; Ying et al., 2013; Deiuliis et al., 2012; Wold et al., 2012; Kampfrath et al., 2011) demonstrating an increase in inflammatory cells, cytokines, or oxidative stress markers in the circulatory system following long-term $PM_{2.5}$ exposure. The release of cytokines such as IL-6 into the circulation can stimulate the liver to release inflammatory proteins and coagulation factors that can alter hemostasis and increase the potential for thrombosis (Lucking et al., 2011; van Eeden et al., 2005). Evidence from several $PM_{2.5}$ epidemiologic studies identified an association between long-term exposure to $PM_{2.5}$ and coagulation factor and/or liver derived inflammatory markers (e.g., CRP) in the blood (Hajat et al., 2015; Viehmann et al., 2015; Hennig et al., 2014; Ostro et al., 2014). These observed effects may alter the balance between pro and anticoagulation proteins and therefore, increase the potential for thrombosis, which may then promote IHD, stroke, or thromboembolic disease elsewhere in the body. Systemic inflammation has also been shown to induce impaired vascular function (Kampfrath et al., 2011)—a systemic pathological condition characterized by the altered production of vasoconstrictors and vasodilators—that over time promotes plaque formation leading to atherosclerosis. Specifically, vascular dysfunction is often accompanied by endothelial cell expression of adhesion molecules and release of chemo attractants for inflammatory cells. Macrophages may then internalize circulating lipids leading to the formation of foam cells: a hallmark of atherosclerotic lesions that may increase in size with $PM_{2.5}$ exposure, particularly in the presence of genetic and dietary risk factors (Rao et al.; Lippmann et al., 2013a). Over time, these atherosclerotic lesions may become calcified as evidenced in a longitudinal epidemiologic study of $PM_{2.5}$ (Kaufman et al., 2016), and this often leads to arteriole stiffening and promotion of IHD or stroke. Importantly, evidence for impaired vascular function in response to long-term exposure to $PM_{2.5}$ is found in animal experimental studies (Ying et al., 2015; Kampfrath et al., 2011; Sun et al.).

In addition to long-term $PM_{2.5}$ exposure leading to cardiovascular disease through inflammatory pathways, there is also evidence that exposure to $PM_{2.5}$ could lead to cardiovascular disease through modulation of the autonomic nervous system. That being said, the mechanism by which long-term exposure to $PM_{2.5}$ results in autonomic nervous system modulation remains unclear. Nonetheless, there is evidence from studies in animals demonstrating modulation of autonomic function (as evidenced by changes in HRV and/or HR) following long-term $PM_{2.5}$ exposure (Ying et al.; Lippmann et al., 2013a; Wold et al., 2012). Moreover, there is also evidence for an increase in BP (Aztatzi-Aguilar et al., 2016; Ying et al., 2015; Wold et al., 2012) in animals following long-term $PM_{2.5}$ exposure. These results are consistent with associations reported in epidemiologic studies between long-term exposure to $PM_{2.5}$ and increases in BP and hypertension (Zhang et al., 2016; Chen et al., 2014a). This is important given that hypertension can lead to HF through cardiac remodeling that results in reduced pumping efficiency (Santos et al, 2014). Similarly, hypertension can contribute to impaired vascular function and atherosclerosis (Brook et al., 2010a), which as noted above, may lead to IHD. Hypertension may also result in arrhythmia through cardiac remodeling (Cascio, 2016; Brook et al., 2010a). Thus, it is

noteworthy that there is epidemiologic evidence of associations between long-term exposure to $PM_{2.5}$ and indicators of potential arrhythmia (Van Hee et al., 2011). Arrhythmia can also contribute to IHD and stroke. For example, atrial fibrillation (a type of arrhythmia) is characterized by blood pooling and potentially clotting in the upper chamber (atria) of the heart. These clots can ultimately be pumped out of the heart and lodged in arteries supplying the brain with oxygen, thereby resulting in a stroke. Studies of hypertension and arrhythmia therefore provide additional plausibility for epidemiologic studies finding associations between long-term exposure to $PM_{2.5}$ and IHD, HF, stroke, and ultimately mortality.

When considering the available evidence, there are plausible pathways connecting long-term exposure to $PM_{2.5}$ to cardiovascular health effects. The first proposed pathway begins with respiratory tract injury and inflammation that may enter into the circulatory system potentially inducing a series of pathophysiological responses that could ultimately result in IHD, stroke, HF, or thromboembolic disease elsewhere in the body (Figure 6-16). The second proposed pathway involves changes in the autonomic nervous system that may result in hypertension, arrhythmia, and potentially the same apical events (Figure 6-16). Taken together, these proposed pathways provide biological plausibility for epidemiologic results of cardiovascular health effects and will be used to inform a causal determination, which is discussed later in the chapter (Section 0).

6.2.2 Ischemic Heart Disease and Myocardial Infarction

The terms ischemic heart disease (IHD) coronary artery disease (CAD) or coronary heart disease (CHD) are generally interchangeable as they appear in the epidemiologic literature on the effects of air pollution. The majority of IHD is caused by atherosclerosis (Section 6.2.4), which can result in the blockage of the coronary arteries and restriction of blood flow to the heart muscle. A myocardial infarction (MI) or heart attack is an acute event that results in heart muscle tissue death secondary to coronary artery occlusion. Studies that examine the ability of short-term exposure to $PM_{2.5}$ to trigger an MI are discussed in Section 6.1.2 whereas the studies examining the effect of long-term exposure on the incidence of MI or IHD are discussed here (Section 6.2.2).

The literature examining the association of long-term exposure to $PM_{2.5}$ with IHDs has expanded substantially from the few studies available for inclusion in the 2009 PM ISA. Overall, findings from recent epidemiologic studies do not provide entirely consistent evidence of an association between long-term exposure to $PM_{2.5}$ and IHD in the populations studied. The strongest evidence of an association with IHD, however, is found in populations with pre-existing diseases (CHAPTER 12).

6.2.2.1 Epidemiologic Studies

This section evaluates the epidemiologic studies reporting associations of long-term exposure to $PM_{2.5}$ with the development, prevalence or recurrence of IHDs including MI (Table 6-35).

Table 6-35 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and ischemic heart disease.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
Miller et al. (2007) 36 metro areas, U.S. Prospective cohort $PM_{2.5}$: 2000 Follow-up: 1994−1998	WHI observational cohort N = 65,893 Median follow-up: 6 yr	Annual avg of closest monitor (2000) Most women within 10 km of monitor	Median 13.4 IQR 11.6−18.3	MI and CHD Medical record review by physician adjudicators	Copollutant model: NR Copollutant correlations: NR
†Hart et al. (2015b) U.S. (contiguous states) Prospective cohort $PM_{2.5}$: 1989−2006 Follow-up: 1988−2006	NHS N = 114,537 Follow-up: ~16 yr	Annual avg at residential address, spatiotemporal model with monthly surface $PM_{2.5}$ measurements; (C-V R2 0.76 and 0.77 pre- (limited $PM_{2.5}$ data) and post-1999, respectively) See Yanosky et al. (2009) for details	Mean (1989−2006): 13.4 (SD:3.3) Mean: 2000−2006: 12 (SD: 2.8)	Self-reported physician diagnosed IHD with medical record review	Copollutant models: NR Copollutant Correlations: $PM_{10-2.5}$: r = 0.2; PM_{10}: r = 0.67
†Lipsett et al. (2011) California, U.S. Prospective cohort $PM_{2.5}$: 1999−2005 Follow-up: 1995−2000	CTS N = 124,614 Avg follow-up: 5.6 yr	Multi-yr avg using IDW interpolation of monitors within 20 km (250 by 250 m grid) residential address	Mean:15.64 (SD: 4.48) IQR: 8.02 Range: 3.11−28.35	Incident MI (hospital records)	Copollutant model: NR Copollutant Correlations: PM_{10}: r = 0.91, NO_2: r = 0.81, CO: r = 0.53, SO_2: r = 0.02
†Puett et al. (2011) NE and MW, U.S. (13 contiguous states) Prospective cohort $PM_{2.5}$: 1988−2002 Follow-up: 1989−Jan 2003	HPFU n = 51,529 males	Annual avg at residential address, spatiotemporal model with monthly surface $PM_{2.5}$ measurements; (C-V R^2 = 0.77, and 0.69; precision = 2.2 and 2.7 µg/m^3, (post-1999 and pre-1999, respectively) see Yanosky et al. (2009) for details	Mean: 17.8 (SD: 3.4) IQR: 4.3	Nonfatal MI (medical record review)	Copollutant model: $PM_{10-2.5}$ Copollutant correlations: NR

Table 6-35 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and ischemic heart disease.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Madrigano et al. (2013) Worcester, MA Incident case control Exposure: 2000 Cases: 1995−2003	Worcester Heart Attack Study n = 4,467 Acute MI cases; n = 9,072 controls	Annual avg at residential address, spatiotemporal model with monthly surface $PM_{2.5}$ measurements; Observations of AOD calibrated to LUR (78 monitors); exposure (10 by 10 km grid) Mean out-of-sample R^2 = 0.85 (Kloog et al., 2011)	Mean (area $PM_{2.5}$): 9.43 (SD: 44); Mean (local $PM_{2.5}$) 1.07 (SD: 1.56); Mean (total $PM_{2.5}$): 10.5 (SD: 1.55)	Confirmed AMI	Copollutant model: regional $PM_{2.5}$ adjusted for local $PM_{2.5}$ from traffic Copollutant correlations: NR
†Hartiala et al. (2016) Ohio, U.S. Prospective $PM_{2.5}$: 1998−2010 Outcome 2001/07−2010	N = 6,575 Ohio residents undergoing elective cardiac evaluation	3-yr avg IDW interpolation at zip code centroid	Mean: 15.5 SD 1.1	Confirmed MI (adjudicated diagnosis)	NO_2 r = 0.15 Copollutant model: NR
†Cesaroni et al. (2014) 11 Cohorts in Finland, Sweden, Italy, Denmark and Germany Prospective cohort $PM_{2.5}$: 2008−2011 Follow-up: 1992−2007, depending on cohort	ESCAPE N = 100,166 Avg follow-up: 11.5 yr	Annual avg $PM_{2.5}$ estimated by LUR with input from measurements from 20 locations per study area Model performance R^2 ≥0.61	Mean ranged from 7.3 (SD = 1.3) to 31 (1.7)	IHD (hospital records)	Copollutant models: NR Correlations available for each cohort reported
†Hoffmann et al. (2015) Prospective cohort $PM_{2.5}$: Aug 2008−Sep 2009 Outcome: 2000/03 (baseline)	HNR study N = 4,433 Avg follow-up: 7.9 yr	Annual avg $PM_{2.5}$ at residential address estimated by LUR with input from 20 locations	Mean: 18.4	MI, sudden cardiac death and fatal CHD Medical record review by committee	Copollutant models: NR Copollutant correlations: NR
†Atkinson et al. (2013) 205 medical practices, U.K. Prospective cohort $PM_{2.5}$: 2002 Follow-up:2003−2007	General Practice database N = 836,557 patients (40−89 yr)	Annual avg (2002) estimated using dispersion model (1 by 1 km grid) linked to residential postal code $PM_{2.5}$ model validation: R^2 = 0.5 (correlation with national air quality network)	Mean 12.9 (SD 1.4) Range 7.2−20.2 IQR: 1.9	MI (medical records)	Copollutant models: NR PM10 r = 0.99, SO_2 r = 0.53; NO_2 r = 0.87; O_3 r = −0.43

Table 6-35 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and ischemic heart disease.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
†Tonne et al. (2015) Greater, London Prospective cohort $PM_{2.5}$: 2003−2010 Follow-up: 2003/07−2010	MINAP (MI Survivors) N = 18,138 Avg follow-up 4 yr	Annual avg estimated using dispersion models (20 by 20 m grid) time-varying exposure assigned within 100 m of patients' residential postal code centroid	Mean: 14.6 (SD: 1.3); IQR: 1.5	Readmission for STEMI or non-STEMI and death combined	Copollutant models: NR Copollutant correlations: PM_{10} r = 0.96; O_3 r = −0.82, NO_X r = 0.73; NO_2 r = 0.71
†Koton et al. (2013) 8 Medical Centers, Israel $PM_{2.5}$: 2003−2005 Follow-up: 1992/93–2005	Post-MI patients (≥65 yrs) admitted to medical centers Avg follow-up 13.2 yr N = 341	Multi-yr avg at residence, kriging interpolation (12 monitors); Imputed values uncertainty lower than 7 µg/m^3 (C-V error 1.6−6% overall)	Median: 23.9 (Range: 17.0−26.6)	Recurrent MI, heart failure, stroke or TIA	Copollutant models: NR Copollutant correlations: NR

AOD = Aerosol optical depth, Avg = average, CHD = coronary heart disease, C-V = cross-validation, CTS = California Teacher Study, ESCAPE = European Study of Cohorts for Air Pollution, HPFU = Health Professionals Follow-up, IQR = interquartile range, LUR = land use regression, MINAP = Myocardial Ischemia National Audit Project; MI = myocardial infarction, N, n = number of subjects, NHS = Nurses' Health Study, NR = not reported; STEMI = ST elevation myocardial infarction; TIA = transient ischemic attack; WHI = Women's Health Initiative, Yr = years

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

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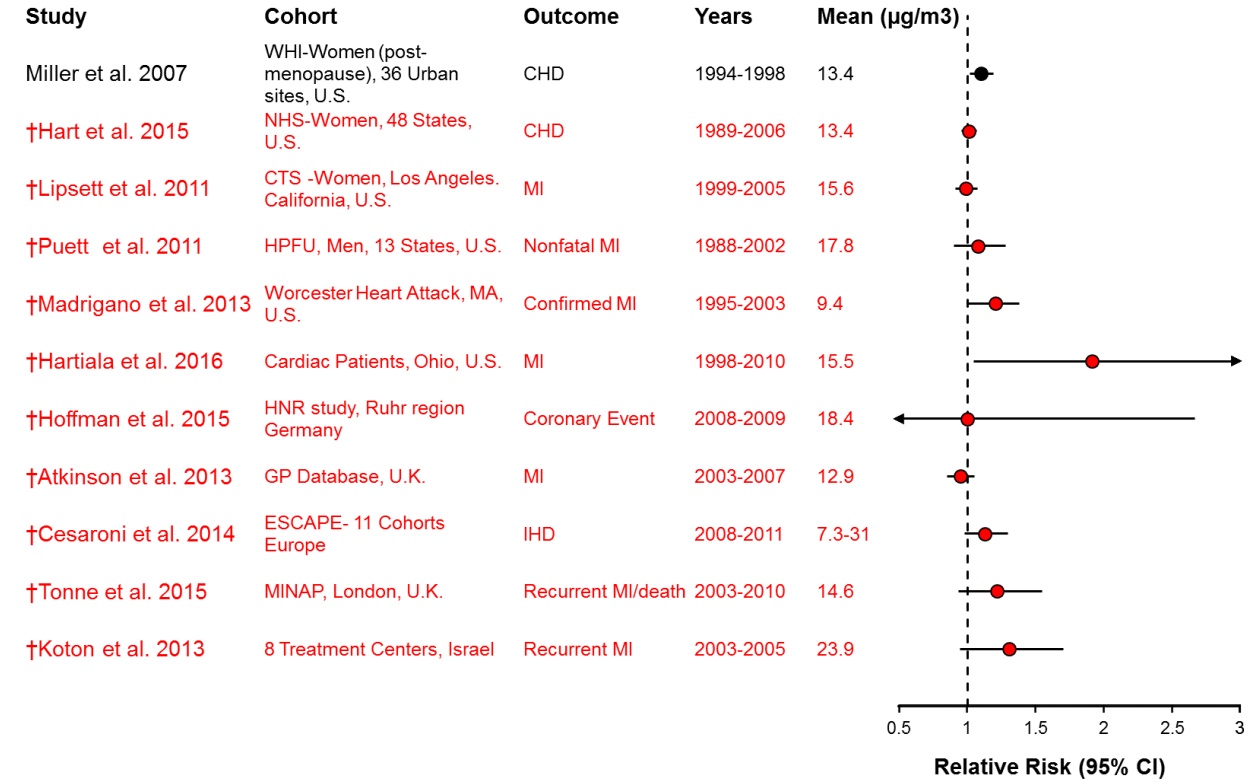
Associations in prospective cohort studies are presented in Figure 6-17. In a large, prospective study reviewed in the 2009 PM ISA, Miller et al. (2007) reported a hazard ratio (HR) for incident CHD morbidity and mortality of 1.10 (95%CI: 1.02, 1.19) among post-menopausal women. Several recent studies have followed up on this finding by examining the effect of long-term exposure to $PM_{2.5}$ in women. Hart et al. (2015b) observed no association between long-term exposure to $PM_{2.5}$ and incident CHD among women enrolled in the Nurses' Health Study (NHS) [HR: 1.01 95%CI: 0.96,1.07] although increased CHD risk was observed among women with diabetes [HR: 1.10 95%CI: 0.99,1.21]. The women in NHS were younger (38% premenopausal) than the women in the WHI, potentially explaining the discrepancy in the findings between these studies. In an analysis of women enrolled in the California Teachers' Study (CTS), Lipsett et al. (2011) reported no association with incident MI (hospitalizations and deaths combined) [HR: 0.99 (95%CI: 0.91, 1.08)], although increased risks of fatal IHD (see Section 6.2.10) and stroke were observed (see Section 6.2.3). Results from a CTS sensitivity analysis that was restricted to post-menopausal women did not indicate a positive association (Lipsett et al., 2011).

The remaining North American studies, which examined populations of men, or both men and women, generally report positive associations between long-term $PM_{2.5}$ exposure and MI, although the width of the confidence intervals varies between studies. Puett et al. (2011) conducted a prospective analysis of the Health Professionals Follow-up Study (HPFS), which consists of male medical professionals reporting an association of 1.08 (95%CI: 0.90, 1.28). This association was largely unchanged after adjustment for $PM_{10-2.5}$ (Puett et al., 2011). In an incident case control analysis of confirmed acute MI Madrigano et al. (2013) reported a stronger association [OR: 1.21 (95%CI: 1.00, 1.38)] between long-term exposure to $PM_{2.5}$ and acute MI. This study derived exposure metrics to distinguish regional $PM_{2.5}$ from local traffic-related $PM_{2.5}$ sources of exposure, and found the association with regional $PM_{2.5}$ was not attenuated in a copollutant model containing local traffic-related $PM_{2.5}$. A limitation of this study was its lack of adjustment for smoking. In another study, Hartiala et al. (2016) reported an association of long-term exposure to $PM_{2.5}$ with confirmed MI among those undergoing cardiac evaluation at a clinic in Ohio. Notably, Madrigano et al. (2013) and Hartiala et al. (2016) confirmed potential cases of MI.



†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Mean concentrations in µg/m^3. Hazard Ratios are standardized to a 5 µg/m^3 increase in $PM_{2.5}$ concentrations. Corresponding quantitative results are reported in Supplemental Table 6S-16 (U.S. EPA, 2018). WHI = Women's Health Initiative; CHD = Coronary Heart Disease; MI = Myocardial Infarction; IHD = Ischemic Heart Disease; NHS = Nurses Health Study; CTS = California Teachers Study; HPFU = Health Professionals Follow-up Study; ESCAPE = European Study of Cohorts for Air Pollution; HNR = Heinz Nixdorf Recall study; MINAP = Myocardial Ischemia National Audit Project.

Figure 6-17 Associations between long-term exposure to $PM_{2.5}$ and Ischemic Heart Disease or Myocardial Infarction. Associations are presented per 5 µg/m^3 increase in pollutant concentration.

Several European studies examined the association of long-term $PM_{2.5}$ and IHD or MI reporting somewhat inconsistent across cohorts. A study from the European ESCAPE project, which includes 11 cohorts in five European countries (Finland, Sweden, Denmark, Germany, and Italy) (Cesaroni et al., 2014) is available for review. Average annual exposure to $PM_{2.5}$ was assigned using the area-specific land use regression models. Cohort specific hazard ratios were variable and the meta-analytically combined effect estimate for $PM_{2.5}$ was [HR: 1.13 (95%CI: 0.98, 1.30)]. In sensitivity analyses the authors considered exposures below various thresholds of average $PM_{2.5}$ concentrations. For the seven cohorts with participants exposed to <15 µg/m^3 average annual $PM_{2.5}$, the meta-analyzed hazard ratio was 1.19 (1.00, 1.42). The outcome determination in the ESCAPE project was cohort-specific, but most cohorts

used ICD codes linked with hospital and death records and defined incidence based on outcome dates. Although most of the cohorts did not include physician review and adjudication for case identification, a separate analysis of data from the HNR study (Hoffmann et al., 2015), with case review by an independent committee, reported no association between coronary events (MI, fatal CHD and sudden death) and long-term $PM_{2.5}$ exposures, after adjustment for noise and other covariates [HR: 1.00 (95%CI: 0.38, 2.67)], although an association with stroke was observed (Section 6.2.3). The confidence intervals from the HNR study were wide due to the small number of cases (n = 135 for coronary events). In another European study, Atkinson et al. (2013) reported a negative association between long-term $PM_{2.5}$ exposure and MI ascertained from a database of information from general practitioners in the U.K. Studies of recurrent MI among MI survivors yielded positive associations (Tonne et al., 2015; Koton et al., 2013). Koton et al. (2013) treated several important confounders (e.g., smoking) as time-varying and both Koton et al. (2013).

Several cross-sectional analyses, including analyses of U.S. national survey data, are available to consider the association of long-term $PM_{2.5}$ exposure with prevalent IHD or hospital admissions (To et al., 2015; Beckerman et al., 2012; Feng and Yang, 2012; Gan et al., 2011). Overall, results from these studies do not provide consistent evidence of an association and only Gan et al. (2011) considered the temporality of the association.

In summary, some well-conducted prospective studies indicate an association between long-term exposure to $PM_{2.5}$ and IHD outcomes in post-menopausal women (Miller et al., 2007) and in a meta-analysis of European cohorts (Cesaroni et al., 2014). Studies also indicate the potential for those with pre-existing disease to be at elevated risk of IHD morbidity [e.g., diabetics in the NHS (Hart et al., 2015b), cardiac patients (Hartiala et al., 2016) or those who experienced a previous MI (Tonne et al., 2015; Koton et al., 2013)]. Most studies considered important covariates such as menopausal status, hormone replacement therapy, smoking and SES. Although the WHI analysis of Miller et al. (2007) did not adjust for SES, Chi et al. (2016a) considered both individual and neighborhood level SES in a subsequent WHI analysis of combined coronary events (see Section 6.2.9), reporting that the association remained unchanged after adjustment for these factors. Lipsett et al. (2011) reported no association between $PM_{2.5}$ exposure and incidence of MI in the CTS, including in a sensitivity restricted to post-menopausal women; however, it is notable that an association with cardiovascular-related mortality was observed in this study. Similarly, no association with coronary events was observed in the HNR study but an association with stroke was reported (Hoffmann et al., 2015). The risk estimate reported by Miller et al. (2007) was for coronary events (i.e., morbidity and mortality combined) providing coherence for the evidence of consistent positive associations between long-term $PM_{2.5}$ exposure and mortality from cardiovascular causes. Several exposure assessment methods including spatiotemporal models and LUR were applied but not studies examined the influence of the choice of exposure model within a study. Consideration of confounding by copollutants was limited while correlations reported between pollutants varied by cohort but were generally moderate to high (Table 6-35).

6.2.3 Cerebrovascular Disease and Stroke

Cerebrovascular disease typically includes conditions hemorrhagic stroke, cerebral infarction (i.e., ischemic stroke) and occlusion of the precerebral and cerebral arteries (see Section 6.1.5). The 2009 PM ISA identified one study that indicated a positive association between $PM_{2.5}$ and cerebrovascular morbidity and mortality in post-menopausal women (Miller et al., 2007). Although the results are not entirely consistent across studies or stroke subtype, some recent well-conducted studies also support a positive association between long term exposure to $PM_{2.5}$ and stroke.

6.2.3.1 Epidemiologic Studies

Studies of the association between long-term exposure to $PM_{2.5}$ and cerebrovascular diseases are summarized in Table 6-36.

Table 6-36 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and cerebrovascular disease.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
Miller et al. (2007) 36 metro areas, U.S. Prospective cohort $PM_{2.5}$: 2000 Follow-up: 1994−1998	WHI observational cohort N = 65,893 Median follow-up: 6 yr	Annual avg of closest monitor (2000), most women within 10 km of monitor	Median 13.4 IQR 11.6−18.3	CBVD Stroke Medical record review by physician adjudicators	Copollutant model: NR Copollutant correlations (*r*): NR
†Hart et al. (2015b) U.S. (contiguous states) Prospective cohort $PM_{2.5}$: 1989−2006 Follow-up: 1988−2006	NHS N = 114,537 Follow-up: ~16 yr	Annual avg at residential address, spatiotemporal model with monthly surface $PM_{2.5}$ measurements; (C-V R^2 0.76 and 0.77 pre- (limited $PM_{2.5}$ data) and post-1999, respectively) See Yanosky et al. (2009)	Mean (1989−2006): 13.4 (SD:3.3) Mean: 2000−2006: 12 (SD: 2.8)	Self-reported physician diagnosed Stroke	Copollutant model: NR Copollutant correlations (*r*): $PM_{10-2.5}$: *r* = 0.2; PM_{10}: *r* = 0.67
†Lipsett et al. (2011) California, U.S. Prospective cohort $PM_{2.5}$: 1999−2005 Follow-up: 1995−2000	CTS N = 124,614 Avg follow-up: 5.6 yr	Multi-year avg using IDW interpolation of monitors within 20 km (250 by 250 m grid) residential address	Mean:15.64 (SD: 4.48) IQR: 8.02 Range: 3.11−28.35	Incident Stroke (hospital records)	Copollutant model: NR Copollutant correlations(*r*): PM_{10}: *r* = 0.91, NO_2: *r* = 0.81, CO: *r* = 0.53, SO_2: *r* = 0.02
†Puett et al. (2011) Northeast and Midwest, US (13 contiguous states) Prospective cohort $PM_{10-2.5}$: 1988−2002 Follow-up: 1989−Jan 2003	Health Professionals Follow-up Study N = 51,529 Avg follow-up NR	Annual avg at residential address, spatiotemporal model with monthly surface $PM^{2.5}$ measurements; C-V R^2 = 0.77, and 0.69; precision = 2.2 and 2.7 µg/m^3, (post-1999 and pre-1999, respectively) see Yanosky et al. (2009)	Mean: 17.8 (SD: 3.4) IQR: 4.3	IS, HS (medical record review)	Copollutant model: $PM_{10-2.5}$ Copollutant correlations(*r*): NR

Table 6-36 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and cerebrovascular disease.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
†Hartiala et al. (2016) Ohio, U.S. $PM_{2.5}$: 1998−2010 Outcome 2001/07−2010	N = 6,575 Cardiac evaluation patients Ohio residents	3-yr avg IDW interpolation at zip code centroid	Mean: 15.5 SD 1.1	stroke	Copollutant correlations(*r*): NO_2 = 0.15 Copollutant model: NR
†Stafoggia et al. (2014) 11 Cohorts in Finland, Sweden, Italy, Denmark and Germany Prospective cohort $PM_{2.5}$: 2008−2011 Follow-up: 1992−2007, depending on cohort	ESCAPE 99,446	Annual avg $PM_{2.5}$ estimated by LUR with input from measurements from 20 locations per study area Model performance: R^2 ≥0.61	Mean ranged from 7.3 (SD = 1.3) to 31 (1.7)	CBVD (medical and death record review)	Copollutant model: NR Copollutant correlations (*r*): NR
†Hoffmann et al. (2015) Ruhr region, Germany Follow-up: 2000/03−2012 $PM_{2.5}$: Aug 2008−Jul 2009	HNR study N = 4,433	Annual avg $PM_{2.5}$ estimated by LUR with input from measurements from 20 locations per study area Model performance: R^2 ≥0.61 see Cesaroni et al. (2014)	Mean 18.4 (SD 1.06); 5−95th: 3.51	Self-reported stroke with medical record review	Copollutant model: NR Copollutant correlations (*r*): NR
†Atkinson et al. (2013) U.K. Prospective cohort $PM_{2.5}$: 2002 Follow-up:2003−2007	General Practice database N = 205 practices N = 836,557 patients (40−89 yrs)	Annual avg (2002), dispersion model (1 by 1 km grid) at residential postal code $PM_{2.5}$ model validation: R^2 = 0.5 (correlation with national air quality network)	Mean 12.9 (SD 1.4) Range 7.2−20.2 IQR: 1.9	Stroke (medical records ICD10 I61)	Copollutant model: NR Copollutant correlations (*r*): PM_{10} *r* = 0.99, SO_2 *r* = 0.53; NO_2 *r* = 0.87; O_3 *r* = −0.43

Table 6-36 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and cerebrovascular disease.

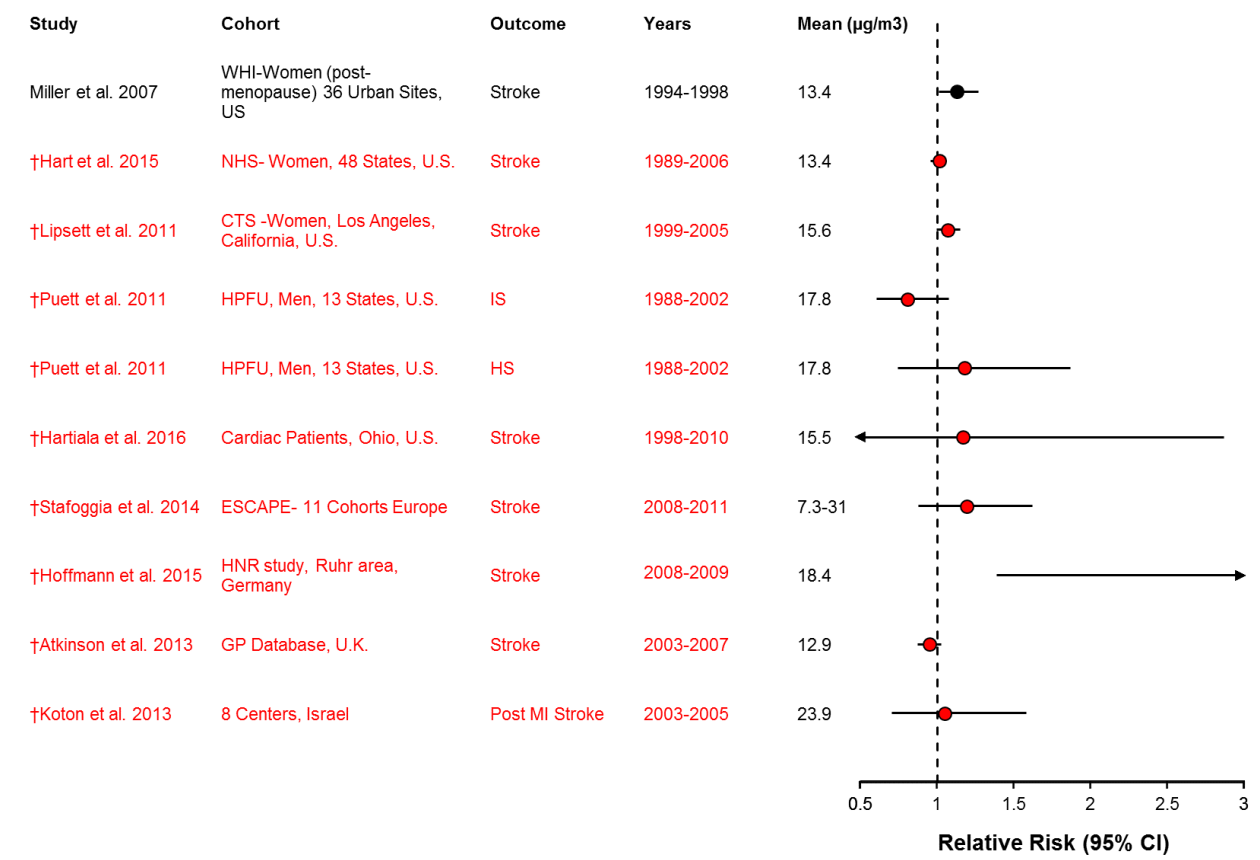
Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
†Koton et al. (2013) 8 Medical Centers, Israel $PM_{2.5}$: 2003−2005 Follow-up: 1992/93–2005	Post-MI patients (≥65 yrs) admitted to medical centers Avg follow-up 13.2 yrs N = 160 cases	Multi-yr avg at geocoded residential address, kriging interpolation (12 monitors) Imputed values with kriging uncertainty lower than 7 µg/m^3 (C-V error 1.6−6% overall)	Median: 23.9 (Range: 17.0−26.6)	Recurrent stroke or TIA	Copollutant model: NR Copollutant correlations (*r*): NR

Avg = average, AOD = Aerosol optical depth, CBVD = cerebrovascular disease, CTS = California Teacher Study, C-V = cross-validation, ESCAPE = European Study of Cohorts for Air Pollution; FSA Forward Sortation Area; HS = Hemorrhagic Stroke; HNR = Heinz Nixdorf Recall study; ICD = International Classification of Disease, IQR = interquartile range, IS = Ischemic Stroke, MINAP = Myocardial Ischemia National Audit Project, NHS = Nurses' Health Study, N (n) = number of subjects, NR = not reported, SD = standard deviation, TIA = transient ischemic attack, yrs = years

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Prospective studies of the association between long-term $PM_{2.5}$ exposure and the incidence of stroke are presented in Figure 6-18. In a study reviewed in the 2009 PM ISA Miller et al. (2007) reported associations of both CBVD and stroke with long-term exposure to $PM_{2.5}$ among post-menopausal women enrolled in WHI who were free of the conditions at baseline [HR: CBVD: 1.16 (95%CI: 1.04, 1.30) and HR stroke: 1.13 (95%CI: 1.04, 1.30)]. Several recent studies conducted in cohorts of women are available for comparison to the WHI findings. The CTS reported associations of $PM_{2.5}$ on incident stroke [HR: 1.07 (95%CI: 0.99, 1.15)] (Lipsett et al., 2011). The association with incident stroke did not include the null value when the sample was restricted to postmenopausal women [HR: 1.09 (95%CI: 1.01, 1.17)]. A prospective analysis of the relatively younger women enrolled in the NHS, reported an increased risk among women with diabetes [HR: 1.29 (95%CI: 1.14, 1.45)] but not in the population, overall [HR: 1.01 (95%CI: 0.96, 1.05)] (Hart et al., 2015b).

Several U.S. studies of men or men and women combined were also available for review. In a cohort of men enrolled in the HPFU study, Puett et al. (2011) examined the effect of long-term exposure to $PM_{2.5}$ on hemorrhagic stroke (HS) and ischemic stroke (IS), classified using National Survey of Stroke criteria and reviewed by physicians. The number of case was small (n = 230 for IS and n = 70 for HS), resulting in estimates with wide CIs [HR: 0.80 (95%CI: 0.61, 1.08)] for IS and HR: 1.18 (95%CI: 0.74, 1.85) HS]. In a study of cardiac patients in Ohio, Hartiala et al. (2016) reported an imprecise association (i.e., wide confidence intervals) between long-term exposure to $PM_{2.5}$ and stroke [HR: 1.17 (95%CI: 0.49, 2.87)] that was attenuated in fully adjusted models that considered a large array of cardiovascular risk factors (i.e., obesity smoking, physical activity and land use development).



†Studies published since the 2009 Integrated Science Assessment for Particulate Matter. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Mean concentrations in $\mu g/m^3$. Hazard Ratios are standardized to a 5- $\mu g/m^3$ increase in $PM_{2.5}$ concentrations. Corresponding quantitative results are reported in Supplemental Table 6S-17 (U.S. EPA, 2018). MI = Myocardial Infarction; IS = ischemic stroke; HS = hemorrhagic stroke; WHI = Women's Health Initiative; NHS = Nurses' Health Study; HPFU = Health Professional's Follow-up; ESCAPE = European Study of Cohorts for Air Pollution; HNR = Heinz Nixdorf Recall; GP = General Practitioner.

Figure 6-18 Associations between long-term exposure to $PM_{2.5}$ and the incidence of stroke. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration.

Within the European ESCAPE study, long-term exposure to $PM_{2.5}$ was positively associated with incident stroke [HR: 1.19 (95%CI: 0.88, 1.62)] in the fully adjusted model, which included variables to control for SES (Stafoggia et al., 2014). Researchers observed a more precise result when restricting to the six cohorts for which the LUR model performed the best (R^2>0.6) [HR 1.75 (1.30, 2.35)]. Additionally, stratified analyses indicated that effects may be larger in magnitude in older age groups and among never-smokers. The authors restricted the analysis to individuals exposed to <15 $\mu g/m^3$ concentrations of $PM_{2.5}$ and observed a HR of 1.33 (95%CI: 1.01, 1.77). As mentioned previously, most ESCAPE cohorts did not have physician review and adjudication of cases. A separate analysis of data

from the HNR study, one of the ESCAPE cohorts, with case review by an independent committee, reported a relatively large association between long-term $PM_{2.5}$ exposure and stroke that persisted after adjustment for noise [HR: 5.24 (95%CI: 1.39, 19.65).] In contrast to these studies indicating an association between $PM_{2.5}$ and stroke, the previously described English general practice database found no association; however, cases were not validated by physician review and the $PM_{2.5}$ prediction model performance was relatively low ($R^2 = 0.5$) (Atkinson et al., 2013). A final study examined the effect of $PM_{2.5}$ on first stroke and recurrent stroke in a cohort of Israeli first MI patients (Koton et al., 2013). Numbers of events were small and exposures higher than some areas in the US (median $PM_{2.5}$: 23.9 $\mu g/m^3$); however, cases were validated by physician review and analyses included time-varying confounders. The study reported an imprecise relationship between $PM_{2.5}$ and the first stroke after MI [HR: 1.05 (95%CI: 0.71, 1.58)] but a larger magnitude association for recurrent strokes [HR: 1.22 (95%CI: 0.95, 1.55)].

Several cross sectional or ecological analyses of prevalent stroke or first hospital admission for stroke that provide some support for the associations observed in prospective studies were also conducted (To et al., 2015; Feng and Yang, 2012; Johnson et al., 2010).

In summary, studies of women enrolled in the WHI study and in the CTS support a positive association between long term exposure to $PM_{2.5}$ and stroke (Lipsett et al., 2011; Miller et al., 2007). Hart et al. (2015b) reported an association in women with diabetes but not in the NHS population, overall. Evidence was inconsistent across other populations studied and confidence intervals around effect estimates were generally wide (Figure 6-18). Several studies are limited by lack of physician adjudication of stroke and outcomes and small sample sizes for stroke subtype analyses. The exposure assessment methods that were applied varied by study but included spatiotemporal models and LUR. There was no evaluation of the influence of the exposure model choice within a study and analysis of copollutant confounding was limited.

6.2.3.1.1 Subclinical Cerebrovascular Disease

Various diagnostic tools can be used to examine risk of cerebrovascular disease. Cerebrovascular hemodynamics, measured through transcranial Doppler ultrasound, is an important component of assessing cerebrovascular blood flow. White matter hyperintensity, detected through magnetic resonance imaging (MRI), is thought to be caused in part by ischemia in the brain and has been shown to predict stroke, dementia, and death (Debette and Markus, 2010). Covert or silent brain infarcts can also be detected with MRI. Both white matter hyperintensity and covert brain infarcts can appear in persons with no history of clinical cerebrovascular event history, and can therefore be used as markers of subclinical disease in asymptomatic individuals. Recent epidemiologic studies have examined subclinical measures of cerebrovascular disease. No studies of this type were available for the 2009 PM ISA (U.S. EPA, 2009). There is a paucity of laboratory animal studies on stroke and cerebrovascular disease with long-term particle exposure. There were no studies on this endpoint in the 2009 PM ISA, and no new studies have

been published since. The nervous system chapter in this ISA reviews studies of brain morphology that are relevant to cerebrovascular disease.

Wellenius et al. (2013) assessed cerebrovascular hemodynamics within the NAS, a cohort of older adults in Boston, by calculating cerebrovascular resistance (i.e., mean arterial blood pressure/middle cerebral artery blood flow velocity) at rest as well as in response to a CO_2 challenge (i.e., induces cerebral vasodilation and increased blood flow) and a sit-to-stand maneuver (i.e., cerebral autoregulation). While no effects of $PM_{2.5}$ were observed on cerebral vasoreactivity or autoregulation, there was an effect of 28-day average $PM_{2.5}$ on increasing resting cerebrovascular resistance [14.33% (95%CI: 6.17, 23.00) due to a decreasing resting middle cerebral artery blood flow [-12.50% (95%CI: -17, 7.0,) (Wellenius et al., 2013). Wilker et al. (2015) examined the effect of $PM_{2.5}$ on white matter hyperintensity and presence of covert brain infarcts (binary) among participants with no history of dementia, stroke, or transient ischemic attack. While there was little evidence of a $PM_{2.5}$ association with white matter hyperintensity, a predictor of stroke, there was a relationship with the presence of cerebral brain infarcts [OR: 2.20 (95%CI: 1.05, 4.66)]. Although studies are limited in number, they provide some evidence to support an effect of $PM_{2.5}$ on cerebrovascular conditions in participants exposed to average $PM_{2.5}$ exposures 12.6-12.1 $\mu g/m^3$ [(Wellenius et al., 2013) and (Wilker et al., 2015), respectively].

6.2.4 Atherosclerosis

Atherosclerosis is the process of plaque buildup into lesions on the walls of the coronary arteries that can lead to narrowing of the vessel, reduced blood flow to the heart and IHD. The development of atherosclerosis is dependent on the interplay between plasma lipoproteins, inflammation, endothelial activation, and neutrophil attraction to the endothelium, extravasation, and lipid uptake. Risk factors for atherosclerosis include high LDL/low HDL cholesterol, high blood pressure, diabetes, obesity, smoking and increasing age. The 2009 PM ISA reviewed a series of cross-sectional studies examining measures that assessed atherosclerosis within large arterial vascular beds in distinct regions of the body [i.e., carotid intima-media thickness (CIMT), coronary artery calcium (CAC), and ankle-brachial index (ABI).] Overall, findings from these studies were inconsistent, with studies reporting null or positive imprecise associations with CIMT, CAC, and ABI (U.S. EPA, 2009). Exposure measurement error, variation in baseline measures of atherosclerosis as well as statistical power were noted as possible explanations for the lack of association observed in these studies. Although findings from more recent studies are not entirely consistent across populations and measures of atherosclerosis, an extended MESA analysis reported a longitudinal increase in coronary artery calcification (CAC) (Kaufman et al., 2016) At the time the 2009 ISA was completed, the biological plausibility for $PM_{2.5}$ induced atherosclerotic plaque development was provided by a small number of experimental animal studies, with several of the experiments conducted in the same laboratory (U.S. EPA, 2009). An additional experimental study is currently available for review.

6.2.4.1 Epidemiologic Studies

Studies that examine the relationship between long-term exposure to $PM_{2.5}$ and measures of atherosclerosis are characterized in Table 6-37.

Table 6-37 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and atherosclerosis.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Kaufman et al. (2016) 6 urban sites, U.S. Prospective cohort $PM_{2.5}$: 2005-2009 Follow-up:2000-2010/12	MESA 45-84 yrs (baseline) N = 3,459 Follow-up: 10 yrs	Annual avg derived from individual-weighted indoor and outdoor ambient $PM_{2.5}$ spatio-temporal model with residential history, Model fit R^2 = 0.90-0.97 C-V R^2 = 0.72 (0.54-0.85 depending on site)	Mean: 14.2 (range: 9.2-22.6) IQR range: 12.9-15.7	cIMT CAC	Copollutant model: NR Copollutant correlations (*r*): NR
†Chi et al. (2016b) 4 urban sites, U.S Cross-sectional Follow-up:2000-2010/12	MESA N = 1,207 ≥55 yrs	Annual avg prior to blood draw, at residence using spatiotemporal model see (Keller et al., 2015)	10.7 IQR: 2.2	DNA methylation in circulating monocytes	Copollutant model: NR Copollutant correlations (*r*): NR
†Dorans et al. (2016) $PM_{2.5}$: 2003-2009 Outcome: 2002-2005 and 2008-2011	Framingham Heart Study Offspring N = 3,399	Annual avg at grid of residence (1 x 1 km), spatiotemporal model, C-V R^2 = 0.88)	Median (IQR) = 10.7 (1.4) for 2003 Median (IQR) = 9.8 (1.1) for 2003-2009	CAC	Copollutant model: NR Copollutant correlations (*r*): NR
†Hartiala et al. (2016) Ohio residents Prospective cohort $PM_{2.5}$: 1998-2010 Outcome: 2001-2007-2010	CAD patients N = 6,575 Follow-up = 3 yr	3-year avg using IDW interpolation at zip code level (within 50 km of monitor)	Mean = 15.5 (SD = 1.1)	Severity of atherosclerosis (vessels with ≥50% stenosis)	Copollutant model: NR Copollutant correlations (*r*): NR

Table 6-37 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and atherosclerosis.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Künzli et al. (2010) Los Angeles, CA Prospective analysis of 5 RCTs $PM_{2.5}$: 2000	Healthy Adults N = 1,483 40-82 yrs (baseline) VEAPS: 1996-2000 BVAIT: 2001-2006, EPAT: 1994-1998 TART: 1997-2000 WELLHART: 1995-2000 Avg follow-up: 2-3 yrs	Annual mean at residence, Kriging interpolation (25 x 25 m grid), 23 monitors Model performance: NR	Mean: 20.8 (SD2.4) IQR: 20.5-22.1	Change in cIMT	Copollutant model: Adjusted for proximity to traffic Copollutant correlations (*r*): NR
†Gan et al. (2014) Vancouver, Canada Prospective cohort $PM_{2.5}$: 2003 Follow-up: 2004/5 – 2009/11	M-CHAT N = 509 30-65 (baseline) Follow-up: ~5 yr	Annual mean at residence, LUR Model fit R^2 = 0.52; mean error-1.50 µg/m³	Mean 4.1 (SD: 1.45) IQR 1.4	Change in cIMT	Copollutant model: NR Copollutant Correlations: BC *r* = 0.13; NO_2 *r* = 0.45, NO *r* = 0.43; Noise *r* = 0.19
†Aguilera et al. (2016) 4 Cities, Switzerland Cross-sectional $PM_{2.5}$: 2001/02-2010/11 Outcome: 2010/2011	SAPALDIA 50 yrs (or older, baseline) N = 1,503	Multi yr avg at residential address (2001-2011) estimated using Gaussian dispersion models (200 by 200 m grid)	Mean 17 (SD: 2.0) (2001-2011) Annual avg: 15.2 (SD: 1.6)	cIMT	Copollutant model: NR Copollutant correlations (*r*): $PM_{2.5}$ last yr and 2001-2011 *r* = 0.96; $PM_{2.5}$ vehicular *r* = 0.80; $PM_{2.5}$ crustal 0.75; PNC 0.86, LDSA 0.94
Young Adults					
†Lenters et al. (2010) Utrecht, Netherlands Cross-sectional $PM_{2.5}$: 2000 Outcome: 1999-2000	ARYA N = 745	Annual avg (2000) at childhood home address using regional concentrations and LUR see (Beelen et al., 2008)	Mean 20.7 (SD: 1.2) 5th−90th: 16.5-19.9	cIMT (Pulse wave velocity discussed under arterial stiffness)	Copollutant model: NR Copollutant correlations (*r*): NO_2 *r*>0.5

Table 6-37 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and atherosclerosis.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Breton et al. (2016) Retrospective cohort $PM_{2.5}$: 1980-2009 Outcome: 2007/2009	College Students TROY N = 768	Monthly avg to estimate prenatal exposure using IDW spatial interpolation at residential history (interpolation range 50 km unless data available within 5 km) Leave one out cross-validation: R^2 0.53	Mean 19.5 (SD: 6.1)	Carotid artery arterial stiffness and cIMT	Copollutant model: NR Copollutant correlations (*r*): 1st Trimester: O_3 *r* = -0.01, NO_2 *r* = 0.71, PM_{10} *r* = 0.89 (Note: generally consistent across trimesters)
†Breton et al. (2012) Retrospective cohort $PM_{2.5}$: 1980-2009 Outcome: 2007/2009	College Students TROY N = 768	Monthly avg to estimate childhood exposure (0-5 yrs, 6-12 yrs) and lifetime avg using IDW spatial interpolation at residential address (interpolation range 50 km unless data available within 5 km)	0-5 yrs: 18.2 (SD: 5.3) 6-12 yrs: 15.7 (SD 5.0) Lifetime: 15.7 (SD: 5.0)	cIMT	Copollutant model: NR Copollutant correlations (*r*): Age 0-5: NO_2 *r* = 0.77, O_3 *r* = 0.9, PM_{10} *r* = 0.89 Age 6-12: NO_2 *r* = 0.8, O_3 *r* = -0.15, PM_{10} *r* = 0.85 Lifetime: NO_2 *r* = 0.82, O_3 *r* = -0.04, PM_{10} *r* = 0.87

Avg = average, ARYA = Atherosclerosis Risk in Young Adults, BVAIT = B-Vitamin Atherosclerosis Intervention Trial, CTM = chemistry transport model, EPAT = Estrogen in the Prevention of Atherosclerosis Trial, IMPROVE = Stockholm, Sweden, KORA = Augsburg, Germany, LDSA = Lung deposited surface area, M-CHAT = Multicultural Community Health Assessment Trial, MESA = Multi-Ethnic Study of Atherosclerosis, RCTs = Randomized Controlled Trials, REGICOR = Girona area, Spain, SAPALDIA = Swiss cohort study on Air Pollution and Lung and Heart Diseases, TROY = Testing Responses on Youth, VEAPS = Vitamin E Atherosclerosis Progression Study, WELLHART = Women's Estrogen-Progestin Lipid-Lowering Regression Trial

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Several analyses from the MESA Air cohort, which comprises a large ethnically diverse study population recruited between 2000 and 2002 from six U.S. communities thus allowing within-city contrasts. Recent analyses of this cohort contribute to the evidence describing the relationship between long-term exposure to $PM_{2.5}$ and atherosclerosis. In general, cross-sectional analyses that included control for study site reported no association regardless of $PM_{2.5}$ exposure assessment method (Adar et al., 2013; Sun et al., 2013). Results from an interim longitudinal analysis (Adar et al., 2013) showing a $PM_{2.5}$ associated increase in cIMT were not retained when additional years of follow-up were available (Kaufman et al., 2016). Kaufman et al. (2016) observed no association with cIMT [-0.9 mm (95%CI: -3.0, 5.0)] while reporting a 4.1 agatston unit increase per year (95%CI: 1.4, 6.8) for CAC. CAC is a stronger predictor of subsequent CHD than cIMT, which typically indicates earlier vascular injury than CAC, in MESA study participants (Gepner et al., 2015). The effect of $PM_{2.5}$ on CAC progression was stronger in people with hypertension, those who are not obese and older adults. Modification of this association by race was not observed. Also in the MESA cohort, Chi et al. (2016b) observed associations of long-term $PM_{2.5}$ exposure with DNA methylation in circulating monocytes. By contrast, Dorans et al. (2016) reported an imprecise (i.e., wide CIs) association between exposure to long-term $PM_{2.5}$ and CAC progression using defined thresholds based on the variability of within-person repeated CAC measurements in the Framingham Heart Study [OR: 1.23 (95%CI: 0.77, 1.92)]. The change in CAC in association with long-term exposure to $PM_{2.5}$ was also reported [-2.86 (95%CI: -8.57, 2.86)]. The shape of the concentration-response functions for these studies are discussed in Section 6.2.16.

Several other studies examined the longitudinal changes in atherosclerosis indicated by the presence of lesions or cIMT, but studies of CAC were not available for comparison to results reported in the MESA and Framingham Health Studies. Long-term exposure to $PM_{2.5}$ was associated with both mild and severe atherosclerosis, defined as ≥50 stenosis in 1-2 and >3 vessels, respectively among coronary artery disease patients in Ohio (Hartiala et al., 2016). Künzli et al. (2010) examined the relationship between long-term exposure to $PM_{2.5}$ and the rate of atherosclerosis progression reporting a small positive association of $PM_{2.5}$ with cIMT progression rate [1.27 µm/yr (95%CI: -0.16, 2.69)]. The association of $PM_{2.5}$ with cIMT in was more than twofold larger among those living within 100 meters of a highway, however. By contrast, Gan et al. (2014) observed no association with change in cIMT in a smaller sample (N = 509) in Vancouver Canada where the mean $PM_{2.5}$ concentration is relatively low (4 $\mu g/m^3$).

Several cross-sectional analyses examined atherosclerotic lesions and cIMT reported results that were not entirely consistent (Aguilera et al., 2016; Newman et al., 2015; Perez et al., 2015; Bauer et al., 2010). Studies of the effect of exposure during prenatal and childhood lifestages and atherosclerosis as young adults were also conducted. Among young adults in their twenties, neither Lenters et al. (2010) nor (Breton et al., 2012) observed large (relative the width of the confidence interval) increases in cIMT in association with $PM_{2.5}$ exposure, regardless of childhood exposure window [0.69 µm (95% CI: -4.41, 5.79) and -1.51 (95%CI: -5.19, 2.17)]. In an analysis focusing on prenatal exposure Breton et al. (2016) reported an imprecise (i.e., wide CIs) small magnitude association with $PM_{2.5}$ [1.48% increase in cIMT (95% CI: -1.77, 4.74)].

In summary, several epidemiologic studies have continued to examine the relationship between long-term $PM_{2.5}$ exposure and atherosclerosis among adults since the completion of the 2009 PM ISA. These studies were conducted within North America and Europe with some extending analyses of the same populations discussed in the 2009 PM ISA (i.e., MESA, HNR). A strength of the expanded body of literature is that it includes analyses of the longitudinal change in measures of atherosclerosis in relation to long-term exposure to $PM_{2.5}$ (Hartiala et al., 2016; Kaufman et al., 2016; Gan et al., 2014; Künzli et al., 2010). MESA analyses supported a $PM_{2.5}$ effect on CAC among middle to older aged adults, while the Dorans et al. (2016) analysis of Framingham Heart Study offspring did not provide support for an association with CAC progression or longitudinal change in CAC. Associations of long-term exposure to $PM_{2.5}$ with cIMT were not consistently observed across cohorts or when variable methods (e.g., exposure assessment methods) were applied within the same cohort. Relationships between $PM_{2.5}$ and CIMT at younger ages were generally not supported in the limited number of studies. Consideration of copollutant confounding was limited across the evidence base.

6.2.4.2 Toxicological Studies of Atherosclerosis

Atherosclerosis and related pathways have been studied primarily in the Apolipoprotein E (ApoE) knockout mouse (Piedrahita et al., 1992; Zhang et al., 1992), The ApoE molecule is involved in the clearance of fats and cholesterol. When ApoE (or the low- density lipoprotein (LDL) receptor) is deleted from the genome, mice develop severely elevated lipid and cholesterol profiles. As a result, the lipid uptake into the vasculature is increased and the atherosclerotic process is dramatically hastened. Furthermore, the LDLs in $ApoE^{-/-}$ mice are highly susceptible to oxidation (Hayek et al., 1994), These mice exhibit cholesterol levels exceeding 1,000 mgdL (normal is ~150 mgdL) (Moore et al., 2005; Huber et al., 1999). which may be a crucial event in the air pollution-mediated vascular changes. However, it should be noted that this model is primarily one of peripheral vascular disease rather than coronary artery disease.

In the 2009 PM ISA, studies found increased atherosclerotic plaque area in aortas of $ApoE^{-/-}$ mice exposed to $PM_{2.5}$ CAPs for 4-6 months from an exurban site located in Tuxedo NY or an urban site located in Manhattan, NY. Since the publication of the 2009 PM ISA, Lippmann et al. (2013a) have conducted additional plaque progression analyses in Irvine, CA; Lansing, MI; and Seattle, WA, as well as in Tuxedo and Manhattan, NY. The authors reported that plaque progression in $ApoE^{-/-}$ mice varied by site. Specifically, increased ($p < 0.05$) plaque areas relative to control animals were identified in the brachiocephalic artery of mice exposed to $PM_{2.5}$ from Manhattan, NY (6 mo after exposure), Tuxedo, NY (3 and 6 mo after exposure), and ($p < 0.05$) in East Lansing, MI. Increased (6 mo after exposure, $p < 0.05$) plaque progression relative to control animals was also identified in the left common carotid artery of mice exposed to $PM_{2.5}$ from Tuxedo (6 mo after exposure) and Irvine (2 mo after exposure). Animals exposed to $PM_{2.5}$ from Seattle did not have increased plaque progression relative to controls in either the brachiocephalic or the carotid arteries. However, it is important to note that the mice were older

in the studies performed in Seattle and Irvine. Therefore, the Seattle and Irvine mice were older at the onset of PM exposures than animals used in studies at the other sites and this could have affected the results of these studies. Nonetheless, the results in other locations provide evidence for $PM_{2.5}$-mediated effects on atherosclerotic plaque progression in a genetically susceptible mouse model. More information on this study can be found in Table 6-38 below.

Table 6-38 Study specific details from toxicological studies of long-term $PM_{2.5}$ exposure and atherosclerosis.

Study	Study Population	Exposure Details	Endpoints Examined
(Lippmann et al., 2013a) NPACT Study 1	$ApoE^{-/-}$ mice, M, n = 4−8 per treatment group	CAPs from Irvine, CA; Tuxedo, NY; Manhattan, NY, Lansing, MI; or Seattle, WA (138, 136, 123, 68, or 60 ug/m^3, respectively) for 6 h/day, 5 days/week for 6 mo	Atherosclerotic plaque progression by ultrasound 2 mo, 4 mo, and 6 mo post

$APOE^{-/-}$ = apolipoprotein E null mice, n = number d = day, h = hour, mo = month, CAPs = concentrated ambient particles, post = after exposure,

6.2.5 Heart Failure and Impaired Heart Function

Heart failure (HF) refers to a set of conditions including congestive heart failure (CHF) in which the heart's pumping action is weakened. With CHF the blood flow from the heart slows, failing to meet the oxygen demands of the body, and returning blood can back up, causing swelling or edema in the lungs or other tissues (typically in the legs and ankles). Risk factors for HF include IHD, high blood pressure, atrial fibrillation, and diabetes. Right sided HF, is typically a consequence of left-sided HF but can also result from damage to the pulmonary vasculature, which can result in increased right ventricular (RV) mass, reduced flow to the left ventricle and reduced left ventricular (LV) mass. In chronic HF, the heart typically enlarges and develops more muscle mass. LV mass is known to predict the development of HF and can be assessed with magnetic resonance imaging (MRI) (Drazner et al., 2004). Ejection fraction (EF), which is the percent of blood that is pumped from the ventricle during each contraction, is another measure of how well the heart pumps that can be assessed through echocardiography. Although depressed EF provides evidence of HF, EF may be normal in a large proportion of HF patients. There were no studies examining the association between long-term exposure to $PM_{2.5}$ and CHF reviewed in the 2009 PM ISA. The evidence has expanded substantially with the recent epidemiologic and toxicological studies providing support for an effect of long-term exposure to $PM_{2.5}$ on CHF and impaired cardiac function.

6.2.5.1 Epidemiologic Studies

There were no epidemiologic studies examining the association between long-term exposure to $PM_{2.5}$ and CHF reviewed in the 2009 PM ISA (U.S. EPA, 2009). A small number of recent studies have examined the effects of $PM_{2.5}$ on heart failure or related indices (Table 6-39) generally reporting positive associations. The U.K. general practice cohort described in Section 6.2.2, which included nearly 13,000 cases of incident heart failure identified by ICD codes with physician review, reported a positive association with long-term exposure to $PM_{2.5}$ [HR 1.17 (95%CI: 1.03, 1.17)] (Atkinson et al., 2013). A relatively small Israeli cohort was exposed to higher $PM_{2.5}$ concentrations than most areas of the U.S. (median [range]: 23.9 [17.0-26.6]), and benefitted from physician review of medical records for case ascertainment and reported a HR for heart failure and recurrent heart failure after first MI with increasing $PM_{2.5}$ of 1.22 (95%CI: 0.89, 1.67) (Koton et al., 2013). A cross-sectional analysis of women reported a positive association between $PM_{2.5}$ and the prevalence of heart failure [OR: 1.14 (95%CI: 1.06, 1.23)] (To et al., 2015).

Table 6-39 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and heart failure.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
†(Atkinson et al., 2013) U.K. Prospective cohort $PM_{2.5}$: 2002 Follow-up:2003-2007	General Practice database N = 205 practices N = 836,557 patients (40-89)	Annual avg (2002) dispersion model (1 by 1 km grid) at residential postal code $PM_{2.5}$ model validation: R^2 = 0.5 (correlation with national air quality network)	Mean 12.9 (SD 1.4) Range 7.2-20.2 IQR: 1.9	Heart Failure ICD10 I50)	Copollutant model: NR Copollutant correlations (*r*): PM_{10} *r* = 0.99, SO_2 *r* = 0.53; NO_2 *r* = 0.87; O_3 *r* = -0.43
†Koton et al. (2013) 8 Medical Centers, Israel $PM_{2.5}$: 2003-2005 Follow-up: 1992/93 – 2005	Post-MI patients (≥65 yrs) admitted to medical centers Avg follow-up 13.2 yrs N = 258	Multi-yr avg estimated using kriging interpolation (12 monitors); exposure assigned based on geocoded residential address Imputed values with kriging uncertainty lower than 7 µg/m^3 (cross-validation error 1.6-6% overall)	Median: 23.9 (Range: 17.0-26.6)	Heart failure re-admission	Copollutant model: NR Copollutant correlations (*r*): NR
†(Van Hee et al., 2009) 6 Communities, U.S. Cross-sectional $PM_{2.5}$: 2000 Baseline exam: 2000-02	MESA N = 6,814	Annual avg kriging interpolation at residential address	Range of annual mean ~ 12-22	LVMI (cardiac MRI)	Copollutant model: NR Copollutant correlations (*r*): NR

Table 6-39 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and heart failure.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†(Aaron et al., 2016) $PM_{2.5}$ 1999-2001 MRI: 2000-2002	MESA N = 4,204 45-84 yrs	Spatiotemporal Model to estimate annual average concentration at residence. Secondary model to estimate individually weighted $PM_{2.5}$ concentration using infiltration fraction	Mean: 16.4 SD: 3.4 (ambient) Mean 11 SD: 3.7	RV mass, volume, EF	Copollutant model with $PM_{10-2.5}$, NO_2 (D'Souza et al., 2017) Copollutant correlations (*r*): NR
†(Ohlwein et al., 2016) Cross-sectional $PM_{2.5}$: 2008-2009 Baseline: 2007/10	SALIA N = 402 Women, 69-79 yrs	LUR at residence Model fit R_2 = 0.88, cross-validation R_2 = 0.79	Median: 17.4 (IQR: 16.9-18.8)	E/E" ratio LAVI (Tissue Doppler)	Copollutant model: NR Copollutant correlations (*r*): *r* = 0.85 for NO_X, *r* = 0.86 for NO_2

Avg = average, CHF = congestive heart failure, E/"E ratio = peak Early diastolic filling velocity/peak Early diastolic mitral annulus velocity, LAVI = left atrial volume index, LVMI = Left ventricular mass index, MESA = Multi Ethnic Study of Atherosclerosis, MRI = magnetic resonance imaging, NR = not reported, RVM = right ventricular mass, RVV = right ventricular volume, SALIA = Study on the Influence of Air Pollution on the Lung.

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

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No association of long-term exposure to $PM_{2.5}$ with left ventricular mass index LVMI or depressed EF was observed in a cross-sectional analysis of the MESA cohort after adjustment for study center (Van Hee et al., 2009). An increase in RV mass [0.11 g (95%CI: -0.05, 0.27)] was observed in the MESA cohort, in association with long term exposure to $PM_{2.}$ after controlling for site and other covariates, however. Associations with RV end diastolic volume and RV mass/end-diastolic volume ratio were also observed but were attenuated after adjustment for site. A sensitivity analysis showed that the increase in RV mass persisted after adjustment for LV mass, indicating that the findings may be explained by pulmonary vascular damage. D'Souza et al. (2017) found that this increase in RV mass was slightly reduced but remained after adjustment for $PM_{10-2.5}$ and NO_2.

Ohlwein et al. (2016) conducted a cross-sectional analysis of the SALIA cohort to determine the association, using an adjusted means ratio (MR) of long-term $PM_{2.5}$ exposure with diastolic function. Two metrics, E/E' ratio and left atrial volume index (LAVI) were determined. The E/E ratio is the ratio of peak early diastolic filling velocity to peak early diastolic mitral annulus velocity and a value less than eight indicates normal diastolic function. LAVI is an indicator of diastolic function severity and a known predictor for cardiovascular disease. The authors observed that LAVI was increased in association with long-term exposure to $PM_{2.5}$.

In summary, the small number of studies provide evidence supporting a possible relationship between heart failure and $PM_{2.5}$ with the epidemiologic studies of long-term exposure to $PM_{2.5}$ reporting positive associations with HF. An association with RV mass was observed, but no association was with LVM or EF, among MESA participants. A cross-sectional association between $PM_{2.5}$ and increased LAVI was observed in the SALIA cohort.

6.2.5.2 Toxicology Studies of Impaired Heart Function

There were no animal studies in the 2009 PM ISA examining heart failure in response to long-term $PM_{2.5}$ exposure. Since the publication of the 2009 PM ISA, (Aztatzi-Aguilar et al., 2015) reported increased ($p < 0.05$) coronary artery wall thickness and a statistically significant ($p < 0.05$) increase in two genes typically associated with responding to cardiac damage: Acta 1 and Col3a1-. Similarly, Ying et al. (2015) reported that long-term exposure to $PM_{2.5}$ increased ($p < 0.05$) heart weight, and ($p < 0.05$) contractility of aortic rings in response to phenylephrine, while decreasing ($p < 0.05$) stroke volume, and ($p < 0.05$) cardiac output in SH rats. Importantly, these effects were reversible after stopping $PM_{2.5}$ exposure and allowing 5 weeks of recovery time. These authors also found an increase in the cardiac hypertrophic markers Acta1 and Myh7 ($p < 0.05$), but not in Serca2. In an additional study, Wold et al. (2012) reported that relative to controls, mice exposed long-term to $PM_{2.5}$ had a statistically significant increase in heart weight ($p < 0.05$), displayed cardiac remodeling as evidenced by increased diastolic dimensions, and had a statistically significant decrease ($p < 0.05$) in contractility in response to dobutamine, but preserved coronary flow. Cardiac remodeling results were consistent with additional

experiments indicating a statistically significant decrease in ($p < 0.05$) Serca-2 protein levels, increased ($p < 0.05$) myosin heavy chain β protein levels, and increased ($p < 0.05$) collagen expression in whole heart homogenates (Wold et al., 2012). However, in contrast to these studies, Lippmann et al. (2013a) did not find changes in cardiac function measurement following long-term exposure of $APOE^{-/-}$ mice to $PM_{2.5}$ from Manhattan or Tuxedo, NY. Nonetheless, there is evidence across multiple animal toxicological studies demonstrating that long-term exposure to $PM_{2.5}$ may lead to impaired heart function.

Recent studies also highlight that exposure to $PM_{2.5}$ during gestation may result in cardiac dysfunction later in life. Gorr et al. (2014) exposed female mice to $PM_{2.5}$ during pregnancy and while nursing and then assessed cardiac function in offspring. The authors reported that at adulthood, offspring had reduced left ventricular fractioning with greater ventricular systolic diameter ($p < 0.05$), reduced ejection fraction ($p = 0.0005$), and other indicators of cardiac dysfunction when compared to FA control mice. In a follow-up study using a similar exposure scenario, Tanwar et al. (2017) confirmed earlier findings of ventricular dysfunction and also reported collagen deposition, as well as prolonged increased ($p > 0.05$) action potentials in isolated cardiomyocytes. They also measured decreased levels of calcium homeostasis proteins (Serca-2A, NCX, *p*-PLN). Furthermore, work from the same lab, Tanwar et al. (2017) demonstrated that prenatal exposure alone was sufficient to produce heart failure in adulthood, looking at similar outcomes as Gorr et al. (2014). More information on studies published since the 2009 ISA can be found in Table 6-40 below.

Table 6-40 Study-specific details from toxicological studies of long-term $PM_{2.5}$ exposure and impaired heart function.

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult Sprague-Dawley rats, M, n = 4 per treatment group	Inhalation of 178 μg/m^3 $PM_{2.5}$ from a high traffic and industrial area north of Mexico City in early summer for 5 h/day for 8 weeks (4 days/week).	Coronary artery wall thickness measured in myocardial slices collected 24 h post-exposure Gene expression consistent with cardiac damage in heart tissue collected 24 h post-exposure
(Gorr et al., 2014)	Pregnant (In utero) and neonatal FVB mice offspring	Inhalation of 51.69 μg/m^3 $PM_{2.5}$ CAPS from Columbus, OH, exposures of dams for 6 h/day, 7 days/week, from the day after vaginal plug discovery until weaning of pups. After weaning, mice were exposed to room air until 3 mo old	Birth weight, body and heart weights, end-systolic and end-diastolic ventricular dimensions, fractional shortening and posterior wall thickness. Contraction length and calcium reuptake during relaxation, cardiac collagen content.

Table 6-40 (Continued): Study-specific details from toxicological studies of long-term $PM_{2.5}$ exposure and impaired heart function.

Study	Study Population	Exposure Details	Endpoints Examined
(Tanwar et al., 2017)	FVB mice, pregnant (in utero) and offspring	In utero inhalation of 73.61 ug/m^3 $PM_{2.5}$ CAPs for 6h/day, 7 days/week throughout pregnancy.	Pressure-volume loop, fractional shortening, left ventricular end-systolic and -diastolic diameter, left ventricular posterior wall thickness, end-systolic elastance, contractile reserve, contractility, collagen deposition, inflammatory response, epigenetic markers 12 week after birth
(Wold et al., 2012)	8 week old C57BL/6 mice, M	Inhalation of 85 µg/m^3 (16.9-266.4 µg/m^3) $PM_{2.5}$, for 6 h/day, 5 days/week, for 9 mo from Columbus, OH	Heart weight, contractility, cardiac remodeling, hypertrophic markers, cardiac fibrosis post exposure
(Ying et al., 2015)	4 week old SH rats, M, n = 6/treatment group	Inhalation of 128.3 ± 60.4 µg/m^3 $PM_{2.5}$ CAPs Exposed 6 h/day, 5 days/week for 15 week from Columbus, OH	Heart weight, contractility of aortic rings, stroke volume and cardiac output post 15 week exposure other exposed rats were not sacrificed in order for stroke volume and cardiac output analysis to be repeated after removal of $PM_{2.5}$ exposure. Hypertrophic markers 15 week post
(Lippmann et al., 2013a) NPACT Study 1	$ApoE^{-/-}$ mice, M, n = 4-8 per treatment group,	CAPs from Tuxedo, NY, Manhattan, NY (136, 123, ug/m^3, respectively) for 6 h/day, 5 days/week for 6 mo	Ejection fraction, fractional shortening, cardiac wall thickness
(Tanwar et al., 2017)		Pregnant FVB mice and their offspring	Exposure to filtered air or Ohio State $PM_{2.5}$ CAPs at an average concentration of 73.61 µg/m^3 for 6 h/day, 7 days/week throughout pregnancy (prenatal only).
			At 12 weeks of age in offspring, echocardiographic assessment of pressure and volume changes in the heart including left ventricular (LV) systolic and diastolic internal dimensions (LVESd and LVEDd) and systolic and diastolic posterior wall thickness (PWTs and PWTd). Percent fractional shortening (%FS). Ca++ flux. Collagen deposition in the heart. Epigenetic modification (Sirt 1 and 2, Dnmt1, 3a and 3b).

$APOE^{-/-}$ = apolipoprotein E null mice, CAPs = concentrated ambient particles, d = day, h = hour, m = male, n = number, SH = spontaneously hypertensive, week = week.

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6.2.6 Cardiac Electrophysiology and Arrhythmia

2 Electrical activity in the heart is typically measured using surface electrocardiography (ECG).
3 ECGs measure electrical activity in the heart due to depolarization and repolarization of the atria and

ventricles (see Section 6.1.4). Atrial fibrillation (AF) is the most common type of arrhythmia. Despite being common, clinical and subclinical forms of AF are associated with reduced functional status, quality of life and is associated with downstream consequences such as ischemic stroke (Prystowsky et al., 1996; Laupacis et al., 1994) and CHF (Roy et al., 2009), contributing to both cardiovascular disease (CVD) and all-cause mortality (Kannel et al., 1983). Ventricular fibrillation is a well-known cause of sudden cardiac death and commonly associated with myocardial infarction, heart failure, cardiomyopathy, and other forms of structural (e.g., valvular) heart disease. Pathophysiologic mechanisms underlying arrhythmia include electrolyte abnormalities, modulation of the ANS, membrane channels, gap junctions, oxidant stress, myocardial stretch and ischemia. Ventricular conduction and repolarization abnormalities such as QRS and QT interval prolongation, their subclinical correlates including left ventricular hypertrophy, and clinical antecedents including hypertension are also associated with cardiac arrest (Rautaharju et al., 1994).

In a study reviewed in the 2009 PM ISA Liao et al. (2009) reported that neither 30- nor 365-day $PM_{2.5}$ concentrations were associated with supraventricular or ventricular ectopy, which are the most frequent forms of arrhythmia in the general population, among women enrolled in the WHI clinical trials. The association between long-term exposure to $PM_{2.5}$ and ventricular repolarization abnormalities was not studied at the time the 2009 PM ISA was published. There are no experimental animal studies and such studies continue to be lacking.

6.2.6.1 Epidemiologic Studies

Several recent studies have examined the association between long-term exposure to $PM_{2.5}$ and arrhythmogenic effects in additional populations (Table 6-41). Atkinson et al. (2013) found that ICD-coded arrhythmias and cardiac arrest were not associated with annual mean $PM_{2.5}$ concentrations. In the REGARDS cohort, O'Neal et al. (2016) examined the cross-sectional association with premature atrial contractions (PACs) and long-term $PM_{2.5}$ exposure reporting [OR: 1.19 (95%CI: 1.05, 1.34)]. Van Hee et al. (2011) examined associations between ventricular conduction, repolarization, and spatiotemporally modeled annual mean $PM_{2.5}$ concentrations of 4,783 MESA participants in six U.S. centers. Consistent with O'Neal et al. (2016), Van Hee et al. (2011) found strong, positive, and ORs for associations between prolonged QRS, prolonged QT, and long-term $PM_{2.5}$ concentrations. The study also found increasing ORs when controlling for study center that were robust to additional control for subclinical atherosclerosis, findings that were presented to support the importance of the study's within-city $PM_{2.5}$ gradients and their atherosclerosis-independent mechanism of ECG effects (Van Hee et al., 2011).

Table 6-41 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and arrhythmia and ventricular conduction.

Study	Study Population	Exposure Assessment	Concentration ($\mu g/m^3$)	Outcome	Copollutants Examined
†Atkinson et al. (2013) U.K. Prospective cohort $PM_{2.5}$: 2002 Follow-up:2003-2007	General Practice database N = 205 practices N = 836,557 patients (40-89)	Annual avg (2002) estimated using dispersion model (1 by 1 km grid) linked to residential postal code $PM_{2.5}$ model validation: R^2 = 0.5 (correlation with national air quality network)	Mean 12.9 (SD 1.4) Range 7.2-20.2 IQR: 1.9	Arrhythmia and cardiac arrest	Copollutant model: NR Copollutant correlations (*r*): PM_{10} *r* = 0.99, SO_2 *r* = 0.53; NO_2 *r* = 0.87; O_3 *r* = -0.43
(Liao et al., 2009) 24 States, U.S.	WHI N = 57,422	30-day and annual avg estimated using log-normal kriging interpolation at geocoded residential address	NR	VE and SVE detected on ECG	Copollutant model: NR Copollutant correlations (*r*): NR
†(O'Neal et al., 2016) Southern states, U.S. Cross-sectional 2003-2007	REGARDS N = 26,609	1-yr avg, MODIS plus ground measurements, 10 x 10 km grid	Mean 13.5 (SD = 1.9)	Premature atrial contraction	Copollutant model: NR Copollutant correlations (*r*): NR
(Van Hee et al., 2009) 6 Communities, U.S. Cross-sectional $PM_{2.5}$: 2000 Baseline exam: 2000-02	MESA N = 6,814	Annual avg $PM_{2.5}$ predictions using hierarchical spatio-temporal model (see (Szpiro et al., 2010)) Root mean square error 0.34-0.94 $\mu g/m^3$	Range in annual avg (1 y prior to outcome) ~12-22	QT prolongation Intraventricular conduction decay (12 lead ECG)	Copollutant model: NR Copollutant correlations (*r*): NR

Avg = average, ICD = International Classification of Disease, MESA = Multiethnic Study of Atherosclerosis, NR = not reported, REGARDS = REasons for Geographic and Racial Differences in Stroke, VE = ventricular ectopy, SVE = supraventricular ectopy, WHI = Women's Health Initiative.

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

6.2.7 Blood Pressure and Hypertension

High blood pressure is typically defined as a systolic blood pressure above 140 mm hg or a diastolic blood pressure above 90 mm Hg. Hypertension, the clinically relevant consequence of chronically high blood pressure, typically develops over years. Small population-level changes in blood pressure, even in the absence of clinical hypertension, can have large effects on clinical outcome prevalence (Rose, 1985). Pulse pressure (PP) or the difference between SBP and DBP, as well as mean arterial pressure (MAP), which is a function of cardiac output, systemic vascular resistance and central venous pressure, are additional outcome metrics used in studies of air pollution on blood pressure. Because high blood pressure increases the force on the artery walls the condition can damage the blood vessels and increase risk for cardiovascular disease and stroke. Ventricular remodeling that occurs with hypertension leads to the repolarization abnormalities (see Section 6.2.6) often accompany hypertension and chronic conditions such diabetes and renal disease. Further, hypertension is one of the array of conditions including high blood sugar, excess body fat around waste and abnormal triglycerides that comprise metabolic syndrome (see CHAPTER 7), which is a risk factor for heart disease, stroke and diabetes.

The 2009 PM ISA reviewed a limited number of long-term PM exposure and blood pressure reporting small magnitude effects. The body of literature has grown substantially, and currently includes longitudinal analyses generally showing small magnitude increases in SBP, PP, and MAP in association with long term exposure to $PM_{2.5}$. Recent studies of children did not support an association between long-term $PM_{2.5}$ exposure and blood pressure.

6.2.7.1 Epidemiologic Studies

6.2.7.1.1 Blood Pressure

Several analyses of data from established cohorts, that generally report associations between increasing long-term $PM_{2.5}$ concentration and increasing blood pressure, are available for review (Table 6-42). Hicken et al. (2013) completed blood pressure measurements among 5,570 MESA participants with $PM_{2.5}$ exposure assigned using 30- day averages from all monitors within their MESA site. Chan et al. (2015) examined 43,629 participants from across the United States enrolled in the Sister Study. Both studies showed elevated SBP, PP, and MAP with $PM_{2.5}$ exposures but no effect on DBP. A sensitivity analysis in MESA study using 60-day average $PM_{2.5}$ exposure yielded similar results. Effect sizes reported in these studies were typically small (e.g., SBP: 1.4 (0.4, 1.7) mm hg (Chan et al., 2015); SBP: 0.95 (0.5, 1.4) mm hg (Hicken et al., 2013)). No evidence of modification by race was observed, while associations with blood pressure were higher in the higher income group in MESA (Hicken et al.,

2013). Wellenius et al. (2012b), examined blood pressure changes during an orthostatic challenge of older adult participants in the MOBILIZE study (changes between supine blood pressure and 1- and 3-minute standing blood pressure). Although effects of $PM_{2.5}$ were observed on static supine and standing diastolic blood pressures, no evidence was found to indicate that $PM_{2.5}$ exposure over the previous 28 days influences the change in blood pressure that occurs between supine and standing states. By contrast, the pooled analysis of 12 European cohorts from ESCAPE, reported null effects of $PM_{2.5}$ for both systolic and diastolic blood pressure (Fuks et al., 2014). Study-specific estimates were variable in magnitude and direction (Fuks et al., 2014). Meta-analyzed associations reported in the ESCAPE study were strengthened after adjustment for NO_2.

Table 6-42 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and blood pressure in adults.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome(s)	Copollutants Examined
†(Hicken et al., 2013) Cross-sectional $PM_{2.5}$: 2002 Outcome: 2000-2002	MESA N = 6,814 45-85 yrs	1 mo avg prior to exam estimated from daily monitor avg	NR	Mean difference in SBP, DBP, PP and MAP	Copollutant models: NR Copollutant correlations (*r*): NR
†(Chan et al., 2015) Cross-sectional $PM_{2.5}$: 2006 Outcome: 2003/09	Sister Study N = 43,629 35-76 yrs	Annual avg at residential address estimated kriging interpolation incorporating satellite observations of AOD, see (Sampson et al., 2013)C-V R^2 = 0.88	Nationwide IQR: 8.8-12.4 (regional distribution in Fig 2)	SBP, DBP, PP, MAP	Copollutant models: NR Copollutant correlations (*r*): NR
†(Wellenius et al., 2012b) $PM_{2.5}$: 2005-2008 Outcome: 2005-2008	MOBILIZE Boston N = 747 ≥70 yrs	28 d avg of daily measurements within 10 km of clinic and 20 km of participants' residence	Mean: 8.6 IQR: 4.9	Change in SBP, DBP, supine SBP, supine DBP	Copollutant models: NR Copollutant correlations (*r*): NR

Table 6-42 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and blood pressure in adults.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome(s)	Copollutants Examined
†(Fuks et al., 2014) 15 Cohorts, 9 Countries, Europe Outcome: 1990-2000 $PM_{2.5}$: 2008-2011 (Fuks et al., 2011)	ESCAPE N = 164,484	Annual avg estimated using LUR residential address See (Eeftens et al., 2012) Mean model fit R^2 = 0.71	Mean: 12 (range of means: 6.6-18.4)	Blood pressure Hypertension Intake of BP lowering medication	Copollutant correlations (*r*): $PM_{2.5}$ absorbance *r* = 0.47-0.99 $PM_{10-2.5}$ *r* = .02-0.77 BI2 *r* = 0.19-0.75 (range depends on study area) Copollutant models adjusted for NO_2, traffic noise

Avg = average, AOD = Aerosol Optical Density, BP = blood pressure, C-V = cross validated, DBP = Diastolic Blood Pressure, ESCAPE = European Study of Cohorts for Air Pollution Exposure, LUR = land use regression, MAP = Mean Arterial Pressure, MESA = Multi-ethnic study of Atherosclerosis, MOBILIZE = Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston, N, n = number of subjects, NR = not reported, PP = Pulse Pressure, SBP = Systolic Blood Pressure

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Children

Studies (Table 6-43) examining long term $PM_{2.5}$ exposure and blood pressure among children (Bilenko et al., 2015a; Bilenko et al., 2015b; Liu et al., 2014a) were completed in the United States and Europe. A study of newborns in Massachusetts found elevated SBP with higher $PM_{2.5}$ averages over the 30-, but not 60- or 90-day periods before birth (van Rossem et al., 2015) while trimester specific associations between $PM_{2.5}$ and increased SBP increased but confidence intervals were wide [β = 0.66 (95%CI: -1.31, 2.62)]. The three studies of annual $PM_{2.5}$ exposure conducted in European countries among 10- and 12-year olds (Bilenko et al., 2015a; Bilenko et al., 2015b; Liu et al., 2014a) did not provide evidence supporting an association between long-term $PM_{2.5}$ exposure and increased blood pressure in children. Both small increases and small decreases were observed in these studies.

Table 6-43 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and blood pressure in children.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome(s)	Copollutants Examined
†van Rossem et al. (2015) 1999-2002 1st prenatal visit $PM_{2.5}$ 2000-2008	Project Viva N = 1,131 mother-infant pairs	Spatiotemporal models including satellite observations of AOD, 10 x 10 km grid linked to residence, out of sample R^2 0.87 Temporal model using a fixed-site monitor, reside within 40 km	90 day median 11.8; IQR = 2.3 (spatiotemporal) 90 day median 10.9; IQR = 2 (temporal)	Newborn blood pressure	Copollutant model: NR Copollutant Correlations (*r*): 0.5 BC 0.41 NO_2 0.20 NO_X 0.20 03 0.29 CO
†Liu et al. (2014a) Munich, Leipzig, Wesel, Germany $PM_{2.5}$: 2008-2009	GINIplus LISAplus N = 2,368 10 yrs old	Annual avg estimated at residence using LUR See (Eeftens et al., 2012)	Mean 14.88 (IQR: 4.07)	SBP DBP	Copollutant model: NR Copollutant Correlations (*r*): NR
†Bilenko et al. (2015a) $PM_{2.5}$: Feb 2009-Feb 2010 Outcome: concurrent (12 yr after recruitment 1996/97)	PIAMA N = 1,147 Children 12 yrs	Annual avg estimated at residence (birth and concurrently with exam) using LUR	Mean 16.3 (IQR: 1.2)	SPB DBP	Copollutant model: NR Copollutant Correlations (*r*): NR
†Bilenko et al. (2015b) Cross-sectional $PM_{2.5}$: Feb 2009-Feb 2010 Outcome: concurrent (12 yr after recruitment 1996/97)	PIAMA N = 1,432 12 yrs old	Annual avg estimated at residence (birth and concurrently with exam) using LUR See (de Hoogh et al., 2013)	Median: 16.5 (IQR: 1.2)	SPB DBP	Copollutant model: NR Copollutant Correlations (*r*): 0.67 noise, 0.82 $PM_{2.5}$ abs

Avg = average, AOD = aerosol optical density, DBP = diastolic blood pressure, GINIplus: German Infant Nutritional Intervention plus environmental and genetic influences on allergy development, LISAplus: lifestyle related factors on the Immune System and Development of Allergies in Childhood Study, LUR = land use regression, MOBILIZE = Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston, NR = not reported, N, n = number of subjects, PIAMA = Prevention and Incidence of Asthma and Mite Allergy study, SBP = systolic blood pressure

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

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6.2.7.1.2 Hypertension

Prospective studies of the association between long-term exposure to PM2.5 and hypertension are described in Table 6-44. Zhang et al. (2016) conducted a prospective analysis of long-term exposure to $PM_{2.5}$ and self-reported hypertension among women enrolled in the NHS. A positive association of incident hypertension with annual average $PM_{2.5}$ exposure was reported [HR: 1.02 (95%CI: 1.00, 1.03)]. By contrast Coogan et al. (2016) reported no association between long-term $PM_{2.5}$ exposure and hypertension in the Black Women's Health Study (BWHS) [HR: 0.98 (95%CI: 0.88, 1.11)]. This finding, which was based on a refined spatiotemporal exposure model and included additional years of follow-up, supersedes the earlier report indicating a large but imprecise association with hypertension in this cohort [HR: 1.22 (95%CI: 0.97, 1.52)] (Coogan et al., 2012). The largest study of incident hypertension, conducted within a population-based sample of Ontario, Canada residents, reported a fully adjusted HR of 1.07 (95% CI: 1.03, 1.11) (Chen et al., 2014a). This study used the Ontario hypertension database to classify hypertension, including those with at least one hospital admission with a diagnosis of hypertension or two physician claims for hypertension within a two-year period. Larger magnitude associations were reported among participants with diabetes [HR: 1.23 (95%CI: 1.04, 1.46) vs. 1.05 (95%CI: 1.01, 1.10) among those without diabetes]. There was no statistical evidence of modification by other factors (i.e., age, sex, BMI, education, smoking and COPD). Results of Chen et al. (2014a) that pertain to the shape of the C-*R* function are discussed in Section 6.2.16.

Several additional studies examine the cross-sectional association between long-term $PM_{2.5}$ exposure and hypertension (To et al., 2015; Babisch et al., 2014; Fuks et al., 2014; Johnson and Parker, 2009). These cross-sectional studies generally provide support for an association between long-term exposure to $PM_{2.5}$ and the prevalence of hypertension.

Table 6-44 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and hypertension.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome(s)	Copollutants Examined
†(Zhang et al., 2016) Prospective cohort $PM_{2.5}$: 1998-2007 Outcome: 1988-2008	NHS N = 74,880	Time varying annual avg estimated to compute 24-mo and cumulative avg using spatiotemporal models (1 x 1 km grid) C-V R^2 = 0.58 See (Yanosky et al., 2014)	Mean: 15.61	Hypertension SBP/DBP≥140/90 mm hg	$PM_{10-2.5}$ *r* = 0.37 Copollutant model adjusted for $PM_{10-2.5}$
†(Coogan et al., 2016) Prospective cohort $PM_{2.5}$: 1995-2009 Follow-up: 1995-2011	BWHS N = 9,579 black women free of hypertension at baseline (21-69 yrs)	LUR and BME in spatiotemporal model, exposure assigned at residence	Mean 13.9 IQR: 2.9	Self-report of doctor diagnosed Hypertension and concurrent use of antihypertensive medication	Copollutant model: NR Copollutant Correlations (*r*): NR
†(Chen et al., 2014a) Ontario, Canada Prospective cohort $PM_{2.5}$: 2001-2006 Outcome: 1996/2005 – Dec 2010	Ontario Hypertension Database N = 79,942 ≥35 yrs (baseline)	Annual avg at postal code estimated using satellite observations of AOD	Mean 10.7 (range 2.9-19.2)	Hypertension registry (ICD diagnostic codes 401-405, ICD10 I10-I13/15)	Copollutant model: NR Copollutant Correlations (*r*): NR

Avg = average, AOD = aerosol optical density, BME=Bayesian maximum entropy, BWHS = Black Women's Health Study, C-V=cross-validation, ICD=international classification of disease, IDW = inverse distance weighted, km=kilometer, LUR = land use regression, NHS = Nurses' Health Study.

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

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In summary, this expanded body of literature provides evidence of association between long-term $PM_{2.5}$ exposure, blood pressure, and hypertension, although consistency of associations varied with the specific outcome and averaging times examined. Limited evidence from studies of adult blood pressure indicated increases in systolic and diastolic blood pressure (SBP, DBP) as well as pulse pressure (PP) and mean arterial pressure (MAP) 28 to 60-day average exposures. Studies of children did not consistently report associations of between long-term exposures of months to years and increased blood pressure.

6.2.7.1.3 Gestational Hypertension and Preeclampsia

Epidemiologic studies examining increases in $PM_{2.5}$ concentrations and hypertensive disorders of pregnancy, including preeclampsia, are discussed in detail in Section 9.2.1. Overall, these do not observe consistent results. The methods by which exposure was assigned in these studies may contribute to the heterogeneity in associations observed across these studies. For example, the association between a composite outcome of gestational hypertensive disorders and $PM_{2.5}$ changed based on how concentrations were determined in a study conducted in California (Wu et al., 2011; Wu et al., 2009). However, two meta-analyses have estimated positive odds ratios (ORs 1.15-1.47) for $PM_{2.5}$ and preeclampsia, however both had large heterogeneity scores, and therefore a combined effect may be inappropriate (Hu et al., 2014; Pedersen et al., 2014).

6.2.7.1.4 Renal Function

Observed effects of long-term $PM_{2.5}$ exposure on renal function may be secondary to hypertension because chronic increases in vascular pressure can contribute to glomerular and renal vasculature injury, which can lead to progressive renal dysfunction. The relationship between BP and renal function is complicated, however, because hypertension contributes to renal dysfunction but damage to the kidneys can also cause increased BP. The 2009 PM ISA did not review studies of the association between long-term exposure to $PM_{2.5}$ and renal function. The literature remains limited but an epidemiologic study of older adult males in the NAS, Mehta et al. (2016) reported an association between annual average $PM_{2.5}$ exposure and lower estimated glomerular filtration rate (eGFR) (-4.45 mL/min/1.73 m^2 [95%CI: -7.12, -1.81]). A longitudinal decrease was also observed as a per year reduction in eGFR in this study.

6.2.7.2 Toxicology Studies of Changes in Blood Pressure (BP)

In the current ISA, studies using rats have demonstrated increased ($p < 0.05$) blood pressure in response to long-term $PM_{2.5}$ exposure. Aztatzi-Aguilar et al. (2016) exposed adult male Sprague–Dawley rats to Mexico City fine CAPS and measured BP on the 4th day of each weekly exposure for 8 weeks.

The mean arterial pressure (MAP) was calculated and found to be increased ($p < 0.05$) at weeks 1, 5, and 8. In an additional study, Ying et al. (2015) identified that long-term CAPs exposure increased ($p < 0.05$) BP in SH rats compared to filtered air controls. This increase in BP persisted throughout the 15-week exposure, but returned to baseline two weeks after $PM_{2.5}$ was withdrawn. Furthermore, Wold et al. (2012) found that relative to controls, mice exposed long-term to $PM_{2.5}$ had a statistically significant increase in SBP, DBP, and MAP, while pulse pressure decreased relative to controls ($p > 0.05$). In summary, these studies individually and collectively support that long term $PM_{2.5}$ exposure can increase BP. More information on studies published since the 2009 ISA can be found in Table 6-45 below.

6.2.7.2.1 Renin-Angiotensin System

As noted above (see Section 6.1.6.4.1), the renin-angiotensin system can have direct effects on changes in blood pressure. Since the publication of the 2009 PM ISA, additional studies have evaluated the effects of PM on this system. Long-term $PM_{2.5}$ exposure resulted in a statistically significant increase ($p < 0.05$) in At1r and B1r mRNA levels in rat heart tissue, whereas At2r, and ACE were not appreciably changed (Aztatzi-Aguilar et al., 2015). In a follow-up study, Aztatzi-Aguilar et al. (2016) found that in rat kidney tissue, although mRNA levels of Ace and At1r statistically significantly decreased at 8 weeks post exposure ($p > 0.05$), protein levels statistically significantly increased ($p < 0.05$) relative to controls. In addition, the authors also reported that B1r mRNA and protein was statistically significantly ($p < 0.05$) higher following long-term $PM_{2.5}$ exposure. Thus, there is evidence that long-term $PM_{2.5}$ exposure can result in the types of changes in the renin-angiotensin system that could lead to changes in blood pressure.

Table 6-45 Study-specific details from toxicological studies of long-term $PM_{2.5}$ exposure and blood pressure (BP).

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult Sprague-Dawley rats, M, n = 4 per treatment group	Inhalation of 178 µg/m^3 $PM_{2.5}$ from a high traffic and industrial area north of Mexico City in early summer for 5 h/day for 8 weeks (4 days/week).	Angiotensin and bradykinin system gene and protein expression in heart tissue post exposure
(Aztatzi-Aguilar et al., 2016)	Sprague Dawley rats, M, n = 12/group	Inhalation of 375 µg/m^3 $PM_{2.5}$ CAPs, 5 h/day, 4 day/week, for 8 week from Mexico City	Mean blood pressure on the 4th day of each weekly exposure for 8 weeks Angiotensin and bradykinin system gene and protein expression in kidney tissue post exposure
(Ying et al., 2015)	4 week old male SH rats, n = 6/group	Inhalation of 128.3 ± 60.4 µg/m^3 $PM_{2.5}$ CAPs for 6 h/day, 5 days/week for 15 weeks from Columbus, OH	SBP measured weekly during exposure
(Wold et al., 2012)	8 week old C57BL/6 mice, M	Inhalation of 85 µg/m^3 (16.9-266.4 µg/m^3) $PM_{2.5}$, for 6 h/day, 5 days/week, for 9 mo from Columbus, OH	SBP, DBP, and MAP recorded daily for 3 days post exposure

BP = blood pressure, CAP = concentrated ambient particle, d = day, h = hour, m = male, n = number, SBP = systolic blood pressure, week = week

6.2.8 Peripheral Vascular Disease (PVD), Venous Thromboembolism, Pulmonary Embolism

Thrombosis refers to intravascular formation of a blood clot inside the blood vessel. The clot can form an embolism that moves from its point of origin to a distant vessel where it can become lodged and occlude blood flow. Thrombi typically form in the deep (i.e., popliteal, femoral, iliac) veins of the lower extremities and can give rise to emboli that lodge in the pulmonary arteries. Deep vein thromboses (DVTs) and pulmonary emboli (PE) are the most common subtypes of venous thromboembolism (VTE). Although no studies of $PM_{2.5}$ were in the 2009 PM ISA, a case-control study reported an association between PM_{10} exposure and risk of deep vein thrombosis (DVT) (Baccarelli et al., 2008). Recent longitudinal analyses of report inconsistent results regarding the association of long-term exposure to $PM_{2.5}$ and VTE.

6.2.8.1 Epidemiologic Studies

Following the DVT study of Baccarelli et al. (2008), longitudinal analyses of the WHI (Shih et al., 2011) and the NHS (Pun et al., 2015) examined other $PM_{2.5}$ in relation to VTE. Shih et al. (2011) found no evidence of association with VTE [HR: 0.96 (95%CI: 0.73, 1.26)], nor did they find evidence of an interaction with hormone therapy as did Baccarelli et al. (2008). By contrast, Pun et al. (2015) reported a positive association [HR: 1.11 (95%CI: 1.00, 1.24)] among women in the NHS. VTE events are uncommon, especially in women with and without established risk factors for VTE and its subtypes. Overall, the evidence remains limited (Table 6-46).

Table 6-46 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and thromboembolism.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
†Shih et al. (2011) 40 Centers, U.S. Prospective cohort $PM_{2.5}$: 1999-2004 Follow-up: 1993/98 -2004	WHI Post-menopausal women with no history of DVT N = 26,450 Mean follow-up 7.7 yrs	Annual avg estimated using kriging interpolation at geocoded residential address	Mean: 13.4	Physician adjudicated DVT	Copollutant model: NR Copollutant Correlations (*r*): NR
†Pun et al. (2015) 11 States, U.S. $PM_{2.5}$: 1988-2007 Follow-up 1992-2008	NHS	Annual avg estimated using spatiotemporal model at residential address C-V regression slope = 0.87, error 1.81 µg/m^3	Mean: 12.6 IQR: 4.1	Self-reported diagnosis of PE confirmed by physician medical record review	Copollutant model: NR Copollutant Correlations (*r*): NR

Avg = average, C-V = cross validation, DVT = deep vein thrombosis, NHS = Nurses' Health Study, PE = Pulmonary Embolism, WHI = Women's Health Initiative.

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

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6.2.9 Aggregated Clinical Cardiovascular Outcomes

Several studies define outcome categories that aggregate across specific types of cardiovascular and cerebrovascular disease (CVD and CBVD) (Table 6-47). The outcomes, variously defined and combined, include MI, angina, atherosclerosis, aneurysm, chronic and acute ischemic heart disease, stroke or other cerebrovascular disease, coronary heart disease, heart failure, cardiac arrest, arterial embolism and thrombosis, and peripheral vascular disease, as well as relevant procedures such as revascularization, angioplasty, bypass, or cardiac device implants. Associations of long-term exposure to $PM_{2.5}$ with such aggregated clinical outcomes are presented here with an emphasis on studies that leverage large sample sizes and numbers of events within aggregated outcome groupings to conduct stratified analyses.

The analysis of post-menopausal women enrolled in WHI Miller et al. (2007) was described in the 2009 PM ISA and reported an association of long-term exposure to $PM_{2.5}$ and coronary events, including MI, revascularization and death from CHD, of 1.11 (95%CI: 1.04, 1.19). Recent studies continue to strengthen the evidence supporting an effect of long-term exposure $PM_{2.5}$ on aggregated cardiovascular outcomes. In a follow-up WHI analysis Chi et al. (2016a) examined modification by individual and neighborhood-level socioeconomic status (SES) to determine if these factors could explain the findings of Miller et al. (2007). Authors found that the association was not attenuated after adjustment for SES indicators [HR: 1.14 (95% CI: 1.02, 1.27)]. Although individual SES did not modify the association between long-term exposure to $PM_{2.5}$ and CVD, there was statistical evidence of modification by neighborhood SES. The strongest association was found in most disadvantaged neighborhood SES group [HR: 1.39 (95% CI: 1.21, 1.61)] with a null association in the least disadvantaged neighborhood SES group [HR: 0.90 (95%CI: 0.72, 1.07)].

In an analysis of data from Medicare recipients across the U.S. Makar et al. (2017) examined the association of 2-year $PM_{2.5}$ concentrations with hospital admissions for diseases of the circulatory system among those with annual average concentrations less than 12 $\mu g/m^3$. Authors found an increase in circulatory system hospital admissions [HR: 1.06 (95%CI: 1.02, 1.09), cutpoint of 12 $\mu g/m^3$ and [HR: 1.18 (95% CI 1.10, 1.27) cutpoint of 8 $\mu g/m^3$]. Positive associations between long-term exposure to $PM_{2.5}$ and cardiovascular disease were reported in cross-sectional studies (Feng and Yang, 2012; Johnson and Parker, 2009).

In summary, these studies generally support an effect of long-term exposure $PM_{2.5}$ on a variety of pooled cardiovascular outcomes. These studies are generally large, allowing stratified analyses. Findings of Feng and Yang (2012) and Hart et al. (2015b) related to regional differences in the association between long-term exposure to $PM_{2.5}$ and CVDs are discussed in Section 6.2.17.

Table 6-47 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and cardiovascular diseases.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
Miller et al. (2007) 36 metro areas, U.S. Prospective cohort $PM_{2.5}$: 2000 Follow-up: 1994/98-2002	WHI observational cohort N = 65,893 Median follow-up: 6 yrs	Annual avg of closest monitor (2000) within 10 km of monitor	Median 13.4 IQR 11.6-18.3	CVD event (MI, revascularization, stroke, death from CHD, CBVD) Medical record review by physician adjudicators	Copollutant model: NR Copollutant correlations: NR
†(Chi et al., 2016a) 36 metro areas, U.S. Prospective cohort $PM_{2.5}$: 2000 Follow-up: 1994/98-2005	WHI observational cohort Post-menopausal women 50-79 yrs N = 51,754 Mean follow-up 7.6 yrs	Annual avg (2000) kriging interpolation to estimate concentration at residential address C-V R^2 = 0.88 (Sampson et al., 2013)	Mean: 12.7 (SD: 2.9) IQR: 4.1	CVD Event (MI, stroke, death from CHD or CBVD)	Copollutant model: NR Copollutant correlations: NR
†Makar et al. (2017) Prospective cohort $PM_{2.5}$: 2000-2010 Outcome: 2002-2010	Medicare N = 32,119 MCBS survey participants 65+yrs	Spatiotemporal model incorporating satellite observations of AOD over a 1 x 1 km grid for entire US C-V R^2 = 0.84	Full Cohort Mean: 12 IQR: 3.41 Low pollution cohort Mean: 10.18 IQR: 2.46	Circulatory system HA ICD9: 390-459	Copollutant model: NR Copollutant correlations: NR

Avg = average, CVD = cardiovascular disease, CHD = coronary heart disease, CBVD = cerebrovascular disease, C-V = cross validation, hospital admissions = hospital admission, ICD = International Classification of Disease, MCBS = Medicare current beneficiary survey, MI = myocardial infarction, N, n = number of subjects, NR = not reported, WHI = Women's Health Initiative.

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

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6.2.10 Long-Term $PM_{2.5}$ Exposure and Cardiovascular Mortality

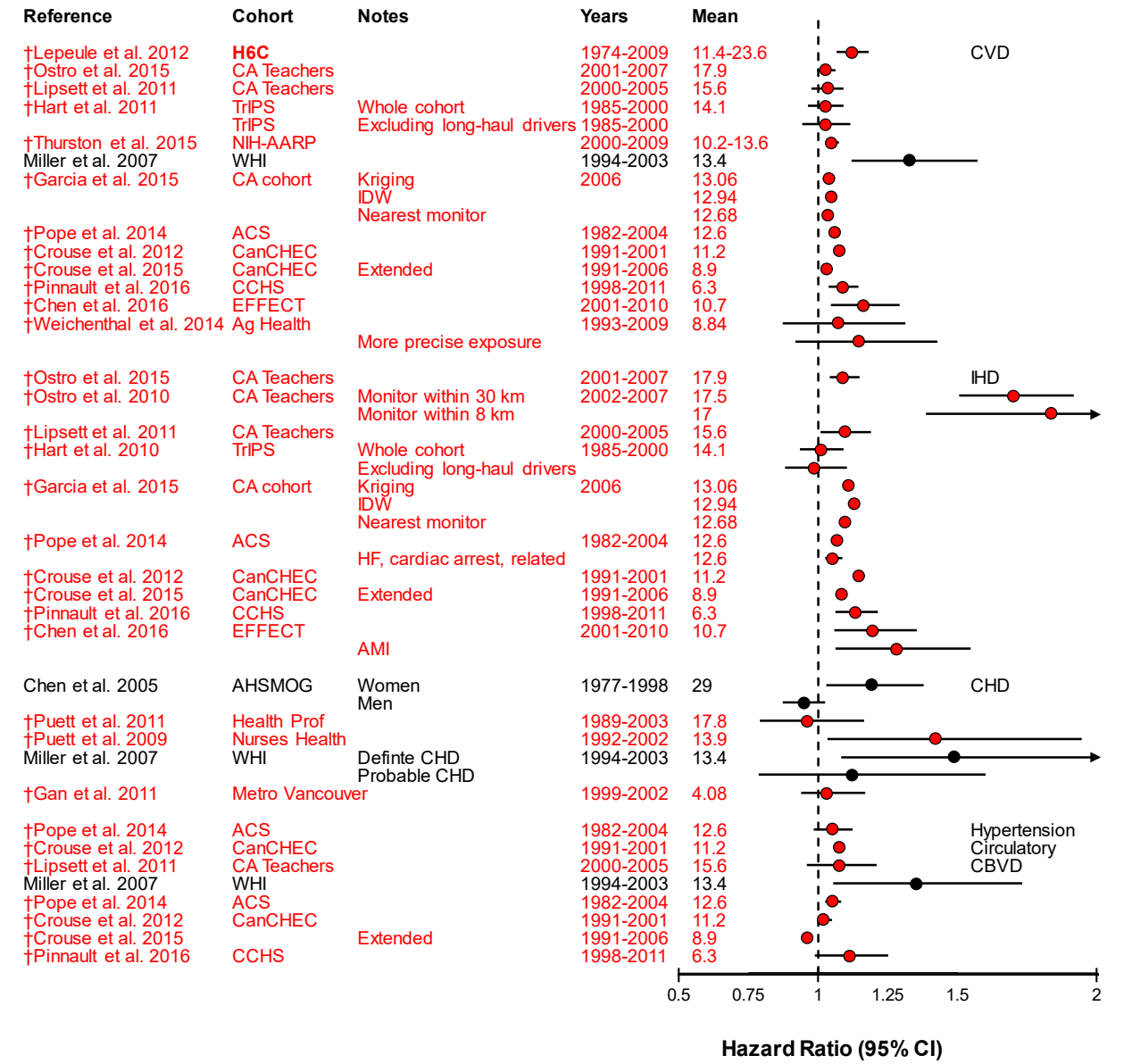
Studies that examine the association between long-term $PM_{2.5}$ exposure and cause-specific mortality outcomes, such as cardiovascular mortality, provide additional evidence for $PM_{2.5}$-related cardiovascular effects, specifically whether there is evidence of an overall continuum of effects. Evidence from studies of long-term $PM_{2.5}$ exposure and mortality are presented in detail in Section 6.2.10 evidence from studies investigating cardiovascular mortality provided some of the strongest evidence for a cardiovascular effect related to long-term $PM_{2.5}$ exposure in the 2009 PM ISA (U.S. EPA, 2009) and are summarized here to inform the effect of long-term $PM_{2.5}$ exposure on the continuum of cardiovascular health effects. The 2009 PM ISA (U.S. EPA, 2009) included evidence from a number multicity U.S. studies, including the American Cancer Society (ACS) cohort (Pope III et al., 2004), the Harvard six cities cohort (Laden et al., 2006), the Women's Health Initiative (WHI) (Miller et al., 2007), and the Seventh-Day Adventist (AHSMOG) cohort (Chen et al., 2005). These studies continue to provide strong support for the relationship between long-term exposure to $PM_{2.5}$ and cardiovascular mortality. In addition, extended analyses of the ACS and Harvard Six Cities studies, as well as results from recent cohort studies contribute to the body of evidence for this relationship (Figure 6-19).

Pope et al. (2014) and Turner et al. (2016) used the extended follow-up period of the ACS to examine the associations between long-term $PM_{2.5}$ exposure and cardiovascular, ischemic heart disease, heart failure and cardiac arrest, cerebrovascular disease, and hypertensive disease. The results of these extended analyses were consistent with previous results from the ACS cohort for cardiovascular and ischemic heart disease. In addition, these extended analyses provide associations for causes of death that had previously not been evaluated among the ACS cohort. Positive associations were observed with heart failure and cardiac arrest, cerebrovascular disease, and hypertensive disorder. Lepeule et al. (2012) reported the results of an extended analysis of the Harvard Six Cities cohort, extending the follow-up period to include deaths between 1974 and 2009, and the strong association with cardiovascular mortality persisted.

A recent series of studies conducted in Canada linked census data with data from the Canadian Mortality Database to create the Canadian Census Health Environment Cohort (CanCHEC) and evaluated the relationship between long-term $PM_{2.5}$ exposure and CVD (including IHD, CBVD, and circulatory) mortality. The authors observed positive associations between CVD mortality and long-term $PM_{2.5}$ exposure, with similar estimates for satellite-derived estimates and ground monitor estimates. The strongest association was for IHD mortality and the weakest was for cerebrovascular mortality (Figure 6-19). (Chen et al., 2016) limited their analyses to CanCHEC cohort participants residing in Ontario who had experienced an acute myocardial infarction, and observed positive associations with CVD, and IHD deaths, as well as deaths due to subsequent acute myocardial infarctions. Crouse et al. (2015) extended the follow-up period of the CanCHEC cohort to include five additional years (1991-2006) and observed positive associations for cardiovascular mortality, with the strongest association

observed between long-term exposure to $PM_{2.5}$ and mortality due to diabetes, followed by IHD. The association for cerebrovascular mortality was just below the null value. The general pattern and magnitude of these associations were generally unchanged in cumulative risk models that include O_3 and/or NO_2. Weichenthal et al. (2016a) evaluated the subset of the CanCHEC cohort living within 5 km of a ground monitor (n = 193,300) and observed associations with IHD mortality that were close to the null value.

Several recent U.S. cohort studies examined the association between long-term $PM_{2.5}$ exposure and cardiovascular mortality. The California Teachers Study (Lipsett et al., 2011; Ostro et al., 2010) observed positive associations between long-term $PM_{2.5}$ exposure and IHD and cerebrovascular mortality, with the strongest association observed with IHD (HR: 1.70; 95% CI: 1.51, 1.91 per 5.0 $\mu g/m^3$ increase in long-term $PM_{2.5}$ concentration). Analyses restricted to post-menopausal women yielded results similar to those for all subjects. Puett et al. (2009) examined the association between long-term $PM_{2.5}$ exposure and all-cause mortality among a cohort of female nurses in the Nurses' Health Study. The authors observed positive associations with CHD mortality (HR: 1.42, 95% CI: 1.03-1.94). Using a design like that of the Nurses' Health Study, Puett et al. (2011) investigated the effect of long-term $PM_{2.5}$ exposure and mortality among men enrolled in the Health Professionals Follow-up Study cohort. Near null associations were observed for CHD mortality in this cohort. Hart et al. (2011) examined the association between residential exposure to $PM_{2.5}$ and mortality among men in the U.S. trucking industry in the Trucking Industry Particle Study (TrIPS) and observed a modest positive association with cardiovascular mortality.



Associations are presented per 5 μg/m^3 increase in pollutant concentration. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Study results from Lepeule et al. (2012) are representative of results from the Harvard Six Cities Cohort; Study results from Pope et al. (2014) are representative of the results from the American Cancer Society Cohort. For complete results from these two cohorts, see Figures 1 and 2. IQR: interquartile range; CVD: cardiovascular disease; IHD: ischemic heart disease; CHD: coronary heart disease; CBVD: cerebrovascular disease; H6C: Harvard Six Cities cohort; TrIPS: Trucking Industry Particle Study; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet & Health Cohort; WHI: Women's Health Initiative; ACS: American Cancer Society Cohort; IDW: inverse distance weighting; HF: heart failure; CCHS: Canadian Community Health Survey; EFFECT: Enhanced Feedback For Effective Cardiac Treatment; AMI: acute myocardial infarction. †Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Figure 6-19 Associations between long-term exposure to $PM_{2.5}$ and cardiovascular mortality in recent North American cohorts.

The magnitude of the associations for long-term $PM_{2.5}$ exposure and cardiovascular mortality among women (Hart et al., 2015a; Lipsett et al., 2011; Ostro et al., 2010; Puett et al., 2009) was higher than those observed in many of the other North American cohorts of men or men and women combined, but similar to that observed by Miller et al. (2007), who also evaluated fatal CHD events among a cohort of post-menopausal women. Several studies that included cohorts of both men and women conducted stratified analyses to see if there was a difference in the association based on sex. Thurston et al. (2015) observed no difference between men and women when examining cardiovascular mortality. Weichenthal et al. (2014b) and (Pinault et al., 2016) reported slightly higher associations with men compared to women, while Beelen et al. (2014) observed higher associations compared among women compared to men. It is unclear why cohort studies that include only women tend to observe higher associations between long-term exposure to $PM_{2.5}$ and cardiovascular mortality compared to other cohorts, and that when cohorts that include both men and women are stratified by sex, the higher association among women is much less consistent.

Overall, the results of these recent U.S. and Canadian cohort studies demonstrate a consistent, positive association between long-term $PM_{2.5}$ exposure and cardiovascular mortality across various spatial extents, exposure assessment techniques, and statistical techniques, and locations, where mean annual average concentrations are ≤12 $\mu g/m^3$ (see CHAPTER 11 for study details related to exposure assessment and statistical methods). Additional cohort studies conducted in Europe observed similarly consistent, positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality (see Table 11-6 in Section 11.2.2.2), and support the evidence from the U.S. and Canada. Particularly noteworthy is a study conducted in Europe that combined data from 22 existing cohort studies and evaluated the association between long-term $PM_{2.5}$ exposure and cardiovascular (Beelen et al., 2014) mortality. Generally, the associations for cardiovascular mortality were near the null value, except for the subset of cardiovascular deaths attributable to cerebrovascular disease (HR: 1.21, 95% CI: 0.87, 1.69 per 5 $\mu g/m^3$ increase in $PM_{2.5}$) (Beelen et al., 2014).

6.2.11 Heart Rate (HR) and Heart Rate Variability (HRV)

Heart rate variability (HRV) represents the degree of difference in the inter-beat intervals of successive heartbeats, and is an indicator of the balance between the sympathetic and parasympathetic arms of the autonomic nervous system. Heart rate (HR) is modulated at the sinoatrial node by both parasympathetic and sympathetic branches of the autonomic nervous system (see Section 6.1.10).

6.2.11.1 Epidemiologic Studies of Heart Rate Variability (HRV)

Most studies have focused on the association between short-term PM exposure and HRV (see Section 6.1.10). There were no studies of the association between long-term PM exposure and HRV

in the 2009 PM ISA (U.S. EPA, 2009). In a recent study, Park et al. (2010) examined the long-term $PM_{2.5}$-HRV association. Thirty- to 60-day mean $PM_{2.5}$ concentrations from the closest monitor with available data were assigned to geocoded addresses of MESA cohort participants at the baseline cohort exam (2000-2002). Although some inverse HRV-$PM_{2.5}$ associations were observed in the population, overall, the evidence of decreased HRV (i.e., rMSSD, SDNN) was stronger among MESA participants with metabolic syndrome than without metabolic syndrome. Such $PM_{2.5}$-associated decreases in HRV are thought to be harmful given that reduced HRV is a risk factor for cardiovascular disease. This finding in MESA is consistent with that of Whitsel et al. (2009) who reported an inverse association between long-term PM_{10} exposure and HRV that was stronger among those with impaired glucose metabolism (IGM) enrolled in the WHI clinical trial studies.

6.2.11.2 Toxicological Studies of Heart Rate (HR) and Heart Rate Variability (HRV)

In the 2009 PM ISA, long term effects of $PM_{2.5}$ exposure on HRV and HR were not reported. Since the publication of the last review, the HEI NPACT study (Lippmann et al., 2013a) examined the effects of long-term $PM_{2.5}$ exposure from five airsheds (Tuxedo, NY; Manhattan, NY; E Lansing, MI; Seattle, WA and Irvine, CA) on measures of HRV in $APOE^{-/-}$ mice. These authors estimated by fitted curve a statistically significant increases in HR in Manhattan, NY for the first 50 days of the experiment that gradually decreased over the rest of the study. In contrast, using the same methodology, the authors estimated a statistically significant decrease in HR in Tuxedo, NY after 75 days. There were no statistically significant chronic changes in HR at other locations. In an additional study, Wold et al. (2012) reported that long term $PM_{2.5}$ exposure increased HR in SH rats. With respect to HRV, no changes were associated with chronic $PM_{2.5}$ exposure at any location in the NPACT study (Lippmann et al., 2013a). Thus, there is some evidence from animal toxicological studies for changes in HR, but not HRV following long-term exposure to $PM_{2.5}$. More information on studies published since the 2009 ISA can be found in Table 6-48 below.

Table 6-48 Study-specific details from toxicological studies of long-term $PM_{2.5}$ exposure and heart rate (HR) and heart rate variability (HRV).

Study	Study Population	Exposure Details	Endpoints Examined
(Lippmann et al., 2013a) NPACT Study 1	$ApoE^{-/-}$ mice, M, n = 4-8 per treatment group,	CAPs from Irvine, CA; Tuxedo, NY; Manhattan, NY, Lansing, MI; or Seattle, WA (138, 136, 123, 68, or 60 $\mu g/m^3$, respectively) for 6 h/day, 5 days/week for 6 mo	HR HRV time and frequency domains
(Wold et al., 2012)	8 week old C57BL/6 mice, M	Inhalation of 85 $\mu g/m^3$ (16.9-266.4 $\mu g/m^3$) $PM_{2.5}$, for 6 h/day, 5 days/week, for 9 mo from Columbus, OH	HR post exposure

$APOE^{-/-}$ = apolipoprotein E null mice n = number, h = hour, CAP = concentrated ambient particle, HR = heart rate, HRV = heart rate variability.

6.2.12 Systemic Inflammation and Oxidative Stress

Chronic systemic inflammation is known to affect the vascular system, potentially leading to thrombosis, plaque rupture, MI and stroke, metabolic effects, as well as effects in other organ systems (e.g., central nervous and reproductive systems). Systemic inflammation is associated with changes in the acute phase response, circulating white blood cells, pro-coagulation effects, and endothelial dysfunction. The epidemiologic studies that were reviewed in the 2009 ISA were limited to a cross-sectional study of the association of long-term exposure to PM_{10} with inflammation and coagulation and ecological studies of hematologic measures that could potentially provide insight into oxygen carrying capacity, viscosity and pro-coagulant potential of the blood (U.S. EPA, 2009). Recent longitudinal analyses that consider the time-dependent nature of pulmonary and systemic inflammatory responses have been conducted, and generally show effects on markers of inflammation. Recent experimental studies also add to the evidence reviewed in the 2009 PM ISA that demonstrated inflammatory effects in animals.

6.2.12.1 Epidemiologic Studies

Several studies of long-term $PM_{2.5}$ exposure and C-reactive protein (CRP) were published since the 2009 PM ISA. CRP is an acute phase reactant, a well-known biomarker of inflammation and clinical tool that can be used to inform decisions regarding treatment of patients with an intermediate risk of atherosclerotic cardiovascular disease (Goff et al., 2014; Pearson et al., 2003). Findings from several recent studies that considered the temporality of the $PM_{2.5}$-CRP association generally found positive associations between one- to twelve-month mean $PM_{2.5}$ exposures and log-transformed CRP as

determined by a variety of methods. These longitudinal studies leveraged the availability of repeated, time-varying measures of both the exposure and outcome, applying multi-variable adjusted mixed models and were conducted in well characterized U.S. and European cohorts including the Study of Women's Health Across the Nation (SWAN) [12.75% change (95%CI: 5.1, 21.45)] (Ostro et al., 2014) and the HNR study [22.65% change (95%CI: 13.8, 31.65)] (Hennig et al., 2014) and [11.25% change (95% CI (1.25,21.88)] (Viehmann et al., 2015). Viehmann et al. (2015) also reported results indicating that white cell count (WCC) may increase with long-term exposure to $PM_{2.5}$ [3.13% change WCC 95%CI: 0.83, 5.42)] among the HNR study population. The longitudinal analysis of the MESA cohort provided little support for an association with CRP [1% change (95%CI: -4, 6)], although a 6% (95%CI: 2, 9) higher IL-6, another indicator of systemic inflammation, was reported (Hajat et al., 2015). A meta-analysis of cross-sectional results from the ESCAPE cohorts (Lanki et al., 2015) provides little support for an association between long-term exposure to $PM_{2.5}$ and CRP [2.4% difference (95%CI: -7.5, 13.4)]. A cross-sectional analysis of the NHANES participants reported small magnitude associations of annual average $PM_{2.5}$ exposure, with CRP which was stronger in people with diabetes (Dabass et al., 2016b).

6.2.12.2 Toxicology Studies

The 2009 PM ISA included findings from several studies that pointed to inflammation in response to long-term $PM_{2.5}$ exposure, particularly in association with atherosclerotic progression (2009 PM ISA). More recent animal toxicological studies continue to provide evidence that long-term exposure to $PM_{2.5}$ may result in inflammatory effects. More specifically, a recent study demonstrated statistically significant ($p < 0.05$) changes in circulating T-cell populations in mice following long-term $PM_{2.5}$ exposure (Deiuliis et al., 2012). Similarly, in mice Kampfrath et al. (2011) demonstrated that long-term exposure to $PM_{2.5}$ results in increased ($p < 0.05$) inflammatory monocytes in the blood from the bone marrow, and that this increase in monocytes is at least partially dependent on TLR4 expression.

When examining cytokines and other inflammatory mediators, Tanwar et al. (2017) reported increased mRNA expression of the cytokines IL-1β and IL-6, as well as the matrix metalloproteinases MMP-9 and MMP-13 at birth in heart tissue of mice exposed to $PM_{2.5}$ in utero. In addition, Aztatzi-Aguilar et al. (2015) found increased ($p < 0.05$) IL-6 protein levels in mouse hearts, and Ying et al. (2013) reported increased ($p < 0.05$) Il-6, TNFα, and MCP-1 mRNA, but not e selectin, ICAM-1 or VCAM-1 in mesenteric arteries when compared to control mice exposed to FA. Similarly, an additional study in mice reported that long-term exposure to $PM_{2.5}$ was found to statistically significantly increase ($p < 0.05$) plasma levels of TNF-α and MCP-1, but not IL-6, IL 12 or Il-10, or IFN-γ when compared to control animals (Kampfrath et al., 2011). Moreover, Kampfrath et al. (2011) also demonstrated upregulation of these cytokines was at least partially dependent on TLR4 expression. In $ApoE^{-/-}$ mice, Lippmann et al. (2013a) reported increased IL-10 ($p < 0.05$) following 3 months of exposure in Manhattan, NY and decreased ($p < 0.05$) IL-6 and IL-10 at 6 months in Irvine, CA relative to control mice. Other locations did not have statistically significant changes in IL-6 or IL-10 and no location

reported appreciable changes in CRP, TNF-α, IL-13, MCP-1 or Il-12. In addition, in Irvine, CA was there a statistically significant change (increase; p >0.05) in GM-CSF. Taken together, these studies may appear somewhat inconsistent, however it should be noted that markers of systemic inflammation are often transiently expressed, thus making it difficult to consistently report changes across studies that use different study designs and a variety of methodological approaches. Thus, it can be concluded that the animal toxicological evidence presented above supports long-term exposure to $PM_{2.5}$ resulting in increased markers of systemic inflammation. Moreover, there is also evidence to support that the location from which the $PM_{2.5}$ is collected influences the inflammatory response.

With respect to oxidative stress, Rao et al. (2014) reported that relative to FA, long-term exposure of $ApoE^{-/-}$ mice to $PM_{2.5}$ in resulted in increased oxidation of cholesterol. Moreover, Kampfrath et al. (2011) demonstrated that long-term exposure to $PM_{2.5}$ in mice results in an increase in NADPH oxidase derived O_2- production in the aorta. In contrast, Ying et al. (2013) did not find that long-term $PM_{2.5}$ exposure resulted in a statistically significant effect on the oxidative stress marker 8-isoprostane. Thus, there is limited evidence of oxidative stress following long-term $PM_{2.5}$ exposure. More information on studies published since the 2009 ISA can be found in Table 6-49 below.

Table 6-49 Study-specific details from toxicological studies of long-term $PM_{2.5}$ exposure and inflammation and oxidative stress.

Study	Study Population	Exposure Details	Endpoints Examined
(Tanwar et al., 2017)	FVB mice, pregnant F, and offspring	In utero inhalation of 73.61 µg/m^3 $PM_{2.5}$ CAPs for 6h/day, 7 days/week throughout pregnancy.	Markers of inflammation in hearts of mice at birth after exposure in utero
(Lippmann et al., 2013a) NPACT Study 1	$ApoE^{-/-}$ mice, M, n = 4-8 per treatment group,	CAPs from Irvine, CA; Tuxedo, NY; Manhattan, NY, Lansing, MI; or Seattle, WA (138, 136, 123, 68, or 60 µg/m^3, respectively) for 6 h/day, 5 days/week for 6 mo	Markers of inflammation in blood at 3 and 6 mo post-exposure
(Aztatzi-Aguilar et al., 2015)	Adult Sprague-Dawley rats, M, n = 4 per treatment group	Inhalation of 178 µg/m^3 $PM_{2.5}$ from a high traffic and industrial area north of Mexico City in early summer for 5 h/day for 8 weeks (4 days/week).	Markers of inflammation in heart tissue collected 24 h post-exposure
(Ying et al., 2013)	Adult $ApoE^{-/-}$ mice, M	Inhalation of 69.6 µg/m^3 $PM_{2.5}$ CAPs for 6 h/day, 5 days/week for 12 week.	Markers of systemic inflammation in mesenteric artery tissue Marker of oxidative stress

Table 6-49 (Continued): Study-specific details from toxicological studies of long-term $PM_{2.5}$ exposure and inflammation and oxidative stress.

Study	Study Population	Exposure Details	Endpoints Examined
(Kampfrath et al., 2011)	Balb/c mice, M TLR4 null mice, M TRR4 wt mice, M	Inhalation of 92.4 µg/m^3 $PM_{2.5}$ for 6 h/day 5days/week for 20 weeks from Columbus, OH	Monocyte population counts and egress from bone marrow to blood post exposure Markers of systemic inflammation post exposure Markers of oxidative stress
(Rao et al., 2014)	ApoE$^{-/-}$ mice, M	9.1 ± 7.3 µg/m^3 from Columbus, OH fro 6 mo	Cholesterol oxidation
(Deiuliis et al., 2012)	C57BL/6 mice, M,	Inhalation of 115.5 µg/m^3 $PM_{2.5}$ for 6 h/day 5days/week for 24- 28 weeks	Changes in circulating T-cell populations post exposure

n = number, h = hour, d = day, week = week, M = male, f = female, SH = spontaneously hypertensive, CAP = concentrated ambient particle, TLR = toll like receptor

6.2.13 Coagulation

Systemic inflammation is associated with pro-coagulation effects. Fibrinogen, a soluble glycoprotein and acute phase reactant that can be proteolytically converted to fibrin, cross-linked into clots, and degraded into dimerized fragments called D-dimers, are potential predictors of cardiovascular thrombosis. There were no studies of long-term exposure to $PM_{2.5}$ and markers of coagulation in the 2009 PM ISA (U.S. EPA, 2009). Several recent epidemiologic studies provide evidence that long-term exposure to $PM_{2.5}$ can affect fibrinogen, D-dimer and platelet count.

6.2.13.1 Epidemiologic Studies

Longitudinal analyses of the U.S. or European cohorts are available. Viehmann et al. (2015) reported a positive association between $PM_{2.5}$ and fibrinogen among the HNR study population [0.21% change (95% CI: -2.08, 2.29)] and a positive, $PM_{2.5}$- platelet count association [4.79% change (95%CI: 2.92, 6.88)]. Hajat et al. (2015) observed a positive $PM_{2.5}$-D-dimer association [7% change (95% CI: 2, 13)] and inverse $PM_{2.5}$-fibrinogen association [-3.45 % change (-7.43, 0.52)] among MESA participants. In addition, 28-day $PM_{2.5}$ was not associated with increased fibrinogen in a longitudinal analysis of the NAS cohort (Bind et al., 2012). Cross-sectional studies do not generally support an association. A meta-analyses of cross-sectional, study-specific results, from the ESCAPE cohorts does not indicate an association between $PM_{2.5}$ and fibrinogen [0.5% change (95%CI: -1.1, 2)] (Lanki et al., 2015). A cross-sectional analysis of the NHANES participants reported no association of annual average exposure to $PM_{2.5}$ with fibrinogen (Dabass et al., 2016b).

6.2.14 Impaired Vascular Function and Arterial Stiffness

Endothelial dysfunction is the physiological impairment of the inner lining of the blood vessels. Endothelial dysfunction is typically measured by flow mediated dilation percent (FMD%). This method is a noninvasive technique involving measurement of the percent change in brachial artery diameter (BAD) after reactive hyperemia (increased blood flow following removal of an artery-occluding blood pressure cuff) (Thijssen et al., 2011). Biomarkers of endothelial activation, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin, soluble forms of which are released in response to inflammation-induced endothelium damage, are also examined in epidemiologic studies.

Arterial stiffness is associated with a variety of cardiovascular risk factors and outcomes (Laurent et al., 2006). Carotid-femoral pulse wave velocity (PWV) is the gold standard for directly and noninvasively measuring arterial stiffness. PWV measures the velocity at which the pulse generated by the heart travels through the arteries, typically measured by the foot-to-foot method (end diastole of the wave in the carotid artery to end diastole of the wave in the femoral artery). Increases in PWV are indicative of increased arterial stiffness. Several tools can be used to detect the pulse wave as it travels, including pressure, distension, and Doppler, allowing PWV to be calculated as the distance divided by change in time between the two points. Augmentation index is an indirect measure of arterial stiffness and cannot be used in place of PWV in assessing regional stiffness; however, its measurement in concert with PWV can provide additional evidence for arterial stiffness. Large and small artery compliance and Young's modulus (a measure of elasticity adjusted for wall thickness) are measures of local arterial stiffness, which require more advanced measurement techniques. Aside from PWV, evidence supporting the validity of arterial stiffness measures as predictors of cardiovascular outcomes is not extensive.

6.2.14.1 Epidemiologic Studies

There were no epidemiologic studies of long-term exposure to $PM_{2.5}$ and FMD, BAD or markers of endothelial activation reviewed in the 2009 PM ISA. A limited number of studies have been published subsequently. In an analysis of MESA data, Krishnan et al. (2012) reported that $PM_{2.5}$ was inversely associated with FMD% [-0.50% change FMD (95% CI: -1.00, -0.05)] with potential effect modification by sex, smoking status, age, and hypertensive status but not associated with BAD [0.00% difference BAD (95% CI: -0.10, 1.00)]. Wilker et al. (2014) reported a comparable inverse association [-0.40 % change (95% CI: -0.68, -0.13)] between $PM_{2.5}$ and FMD% among a subset of participants in the Framingham Offspring Study and Third Generation Studies. Wilker et al. (2014) also examined associations with measures of arterial and microvascular function, BAD, baseline mean flow velocity, and mean hyperemic flow velocity. Only hyperemic flow velocity was additionally associated with $PM_{2.5}$ [-1.80 % change (95%CI: -3.45, -0.15)] These effects are relatively large given that normal ranges are between 5-10% (Järhult et al., 2009). Hajat et al. (2015) observed no association of annual $PM_{2.5}$ exposure with soluble

ICAM-1 [-2.07% (95% CI: -7.69, 3.56)] or E-selectin [1.08 % (95%CI: -0.66, 2.82)]. In addition, Tallon et al. (2017) reported an association [OR: 1.27 (95%CI:0.87, 1.84)] with erectile dysfunction, which may be a consequence of $PM_{2.5}$-mediated effects on vascular function.

There were no studies of long-term $PM_{2.5}$ exposure and PWV reviewed in the 2009 PM ISA. Currently available studies do not provide evidence of an effect of $PM_{2.5}$ on arterial stiffness. A cross-sectional analysis of the Atherosclerosis Risk in Young Adults study in which PWV could only be measured in a subset of participants (Lenters et al., 2010) reported no association [−0.99 % change PWV (95% CI: -6.7, 4.71)]. Similarly, O'Neill et al. (2011) measured large and small artery compliance as well as Young's modulus among participants in the MESA population and found no associations between $PM_{2.5}$ and arterial stiffness overall or stratified by sites [0.4% difference PWV (95% CI: 0.7, -0.15)]. There was evidence of possible effect modification by race and diabetes (O'Neill et al., 2011).

6.2.14.2 Toxicology Studies

Since the publication of the 2009 PM ISA, Ying et al. (2015) reported that in SH rats, long-term exposure to $PM_{2.5}$ resulted in statistically significant ($p < 0.05$) reduced vasodilation in response to the vasodilator acetylcholine. Similarly, these authors also demonstrated that long-term exposure to $PM_{2.5}$ resulted in a statistically significant ($p < 0.05$) increase in the contractile response following treatment of aortic rings with vasoconstrictors. Thus, long-term $PM_{2.5}$ exposure can result in greater contractility and reduced dilation in SH rats. These results are in agreement with an additional study in mouse aortic rings that reported both reduced vasodilation in response to acetylcholine as well as increased contractile response following vasoconstrictor treatment (Kampfrath et al., 2011). Thus there is some evidence that long-term exposure to $PM_{2.5}$ can result in impaired vascular function. More information on these studies can be found in Table 6-50 below.

Table 6-50 Study specific details from toxicological studies of long-term $PM_{2.5}$ exposure and impaired vascular function.

Study	Study Population	Exposure Details	Endpoints Examined
(Ying et al., 2015)	4 week old SH rats, M, n = 6/treatment group	Inhalation of 128.3 ± 60.4 $\mu g/m^3$ $PM_{2.5}$ CAPs Exposed 6 h/day, 5 days/week for 15 week from Columbus, OH	contractility of rat aortic rings, Hypertrophic markers 15 week post
(Kampfrath et al., 2011)	Balb/c mice, M TLR4 null mice, male TRR4 wt mice, male	Inhalation of 92.4 $\mu g/m^3$ $PM_{2.5}$ for 6 h/day 5 days/week for 20 weeks from Columbus, OH	contractility of mouse aortic rings

n = number, m = male, h = hour, week = week, CAP = concentrated ambient particle.

6.2.15 Copollutant Confounding

The independence of the association between long-term exposure to $PM_{2.5}$ and cardiovascular health effects can be examined through the use of copollutant models. A change in the $PM_{2.5}$ risk estimates, after adjustment for copollutants, may indicate the potential for confounding. Recent studies presenting copollutant model results address a previously identified data gap by informing the extent to which effects associated with exposure to $PM_{2.5}$ are independent of co-exposure to correlated copollutants in long-term analyses. A limited number of studies are available to assess copollutant confounding of the association between long-term exposure to $PM_{2.5}$ and cardiovascular morbidity (Figure 6-20). Overall, risk estimates from these few studies remain largely unchanged after adjustment for $PM_{10-2.5}$, NO_2, and $PM_{2.5}$ from traffic sources.

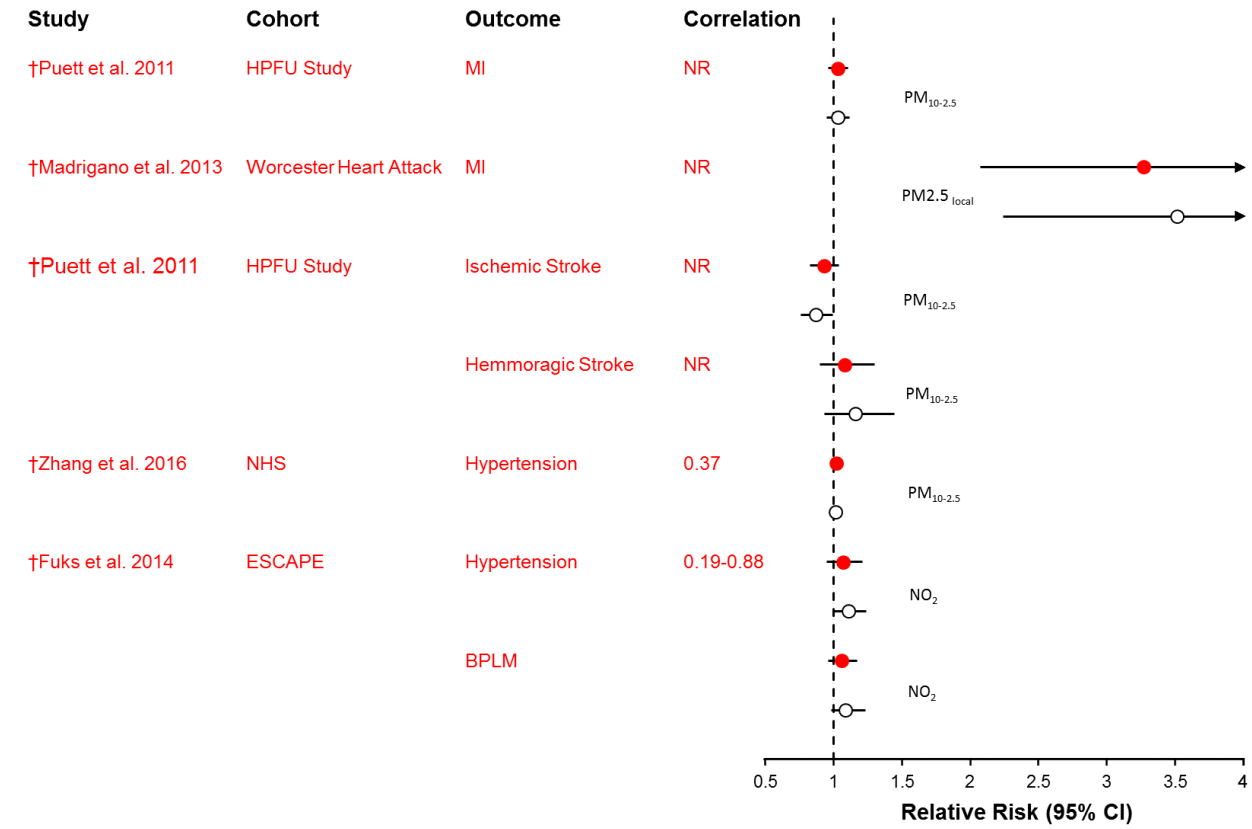
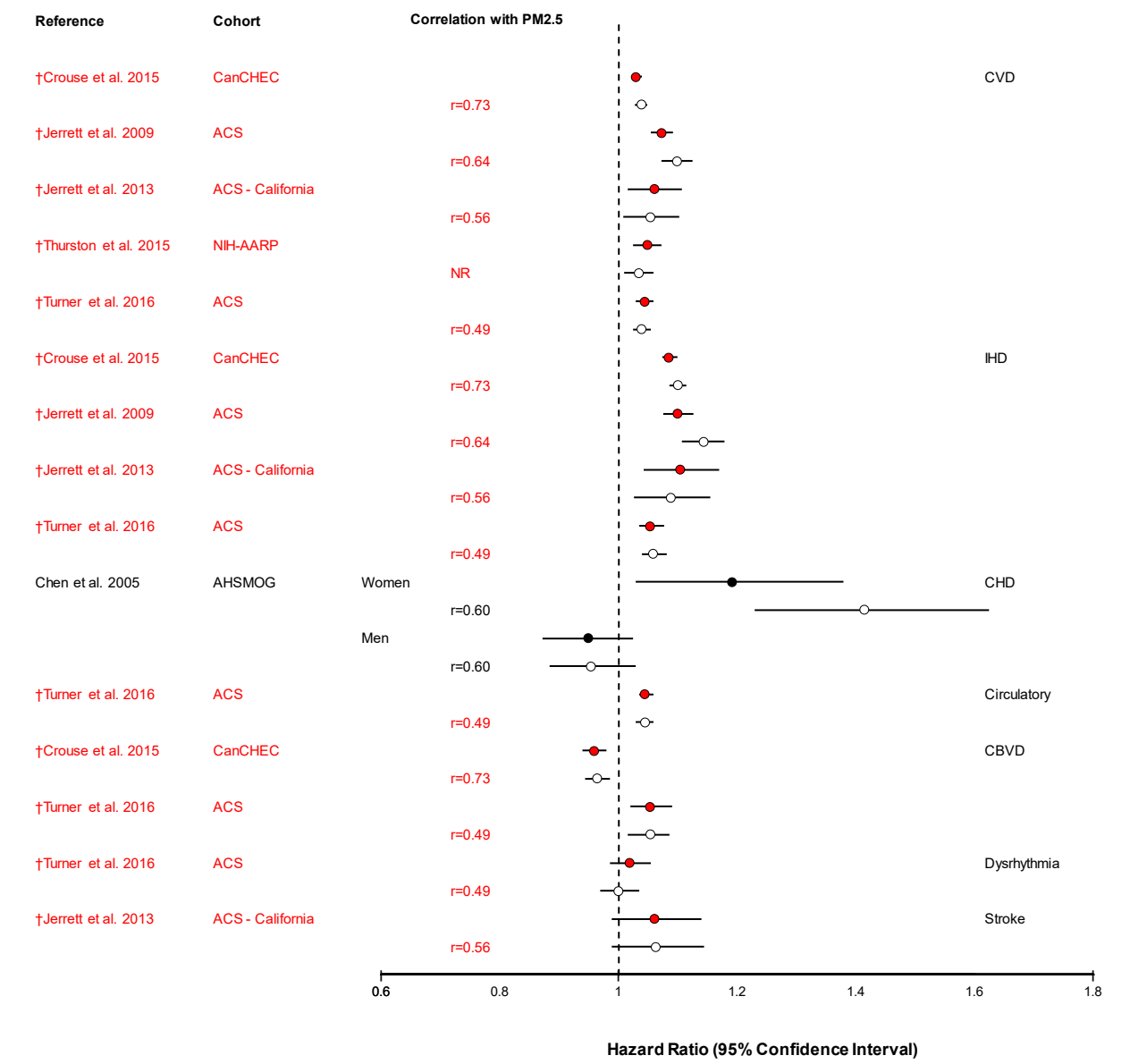


Figure 6-20 Associations between long-term exposure to $PM_{2.5}$ and cardiovascular morbidity in single pollutant models and models adjusted for copollutants.

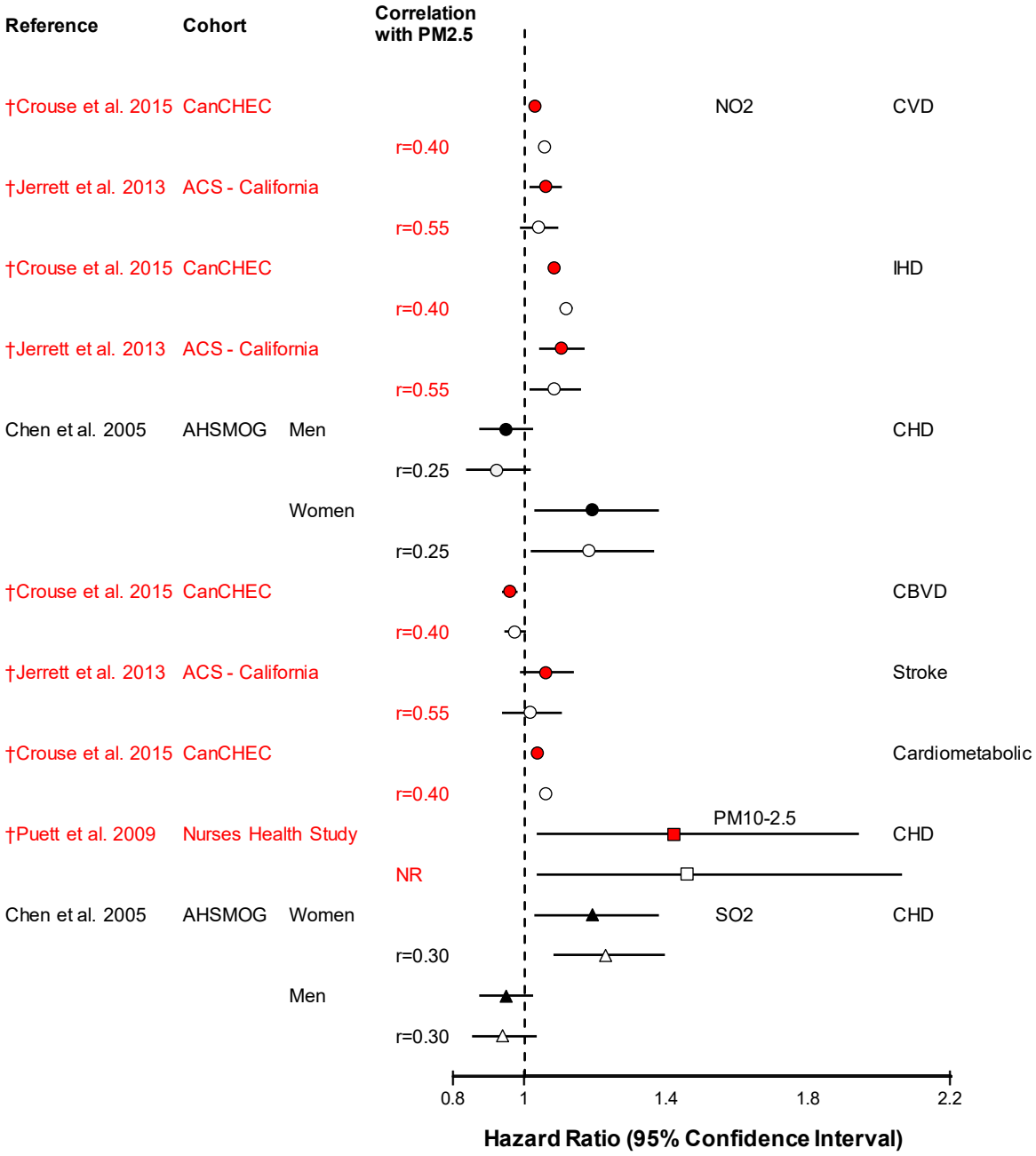
There is a larger body of studies that examined the potential for copollutant confounding of the association between long-term exposure to $PM_{2.5}$ and mortality from cardiovascular causes. The results for associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality in single pollutant models and copollutant models adjusted for ozone are shown in Figure 6-21. The correlations between $PM_{2.5}$ and ozone exposures in the studies that conducted copollutant analyses were generally positive and moderate to strong, ranging from $r = 0.49$ to 0.73. Generally, the $PM_{2.5}$ effect estimates remained relatively unchanged in copollutant models adjusted for ozone. The trend persisted across different specific causes of cardiovascular mortality. There was one exception to the trend. The effect of long-term $PM_{2.5}$ exposure on CHD mortality among women in the AHSMOG cohort (Chen et al., 2005) increased after adjusting for ozone in the model. The results for associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality in single pollutant models and copollutant models adjusted for NO_2, $PM_{10-2.5}$, or

SO_2 are shown in Figure 6-22. The correlations between $PM_{2.5}$ and NO_2 exposures in studies that conducted copollutant analyses were positive and weak ($r = 0.25$) or moderate ($r = 0.40$; $r = 0.55$). The correlations between $PM_{2.5}$ and $PM_{10-2.5}$ were not reported in the single study evaluating coarse particles (Puett et al., 2009). One study evaluated SO_2 (Chen et al., 2005) in copollutant models and reported a correlation of $r = 0.30$. Generally, the $PM_{2.5}$ effect estimates remained relatively unchanged in copollutant models adjusted for NO_2, $PM_{10-2.5}$, or SO_2.



Associations are presented per 5 µg/m^3 increase in pollutant concentration. Circles represent point estimates, horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black circles represent effect of $PM_{2.5}$ in single pollutant models, white circles represent effect of $PM_{2.5}$ adjusted for ozone. ACS: American Cancer Society Cohort; CanCHEC = Canadian Census Health and Environment Cohort; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet & Health Cohort; AHSMOG: Adventist Health Air Pollution Study; CVD: cardiovascular; IHD: ischemic heart disease; CHD: coronary heart disease; CBVD: cerebrovascular disease; CPD: cardiopulmonary disease; COPD: chronic obstructive pulmonary disease; NR: not reported.
†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Figure 6-21 Associations between long-term exposure to $PM_{2.5}$ and cardiovascular mortality in single pollutant models and models adjusted for ozone.



Associations are presented per 5 μg/m^3 increase in pollutant concentration. Circles, squares, and triangles represent point estimates, horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Filled symbols represent effect of $PM_{2.5}$ in single pollutant models, open circles represent effect of $PM_{2.5}$ adjusted for NO_2; open squares represent effect of $PM_{2.5}$ adjusted for $PM_{10-2.5}$; open triangles represent effect of $PM_{2.5}$ adjusted for SO_2. ACS: American Cancer Society Cohort; AHSMOG: Adventist Health Air Pollution Study; CanCHEC = Canadian Census Health and Environment Cohort; CVD: cardiovascular; IHD: ischemic heart disease; CHD: coronary heart disease; CBVD: cerebrovascular disease; NR: not reported. †Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Figure 6-22 Long-term exposure to $PM_{2.5}$ and cardiovascular mortality in single pollutant models and models adjusted for other pollutants.

6.2.16 Shape of the Concentration-Response Function

An important consideration in characterizing the association between long-term $PM_{2.5}$ exposure and mortality is whether the concentration-response relationship is linear across the full concentration range that is encountered, or if there are concentration ranges where there are departures from linearity. The 2009 PM ISA characterized the results of an analysis by Miller et al. (2007) that demonstrated that the shape of the concentration-response curve for cardiovascular mortality was generally linear. Recent studies add to the evidence base on the C-*R* relationships for cardiovascular morbidity (Table 6-51) and mortality (Table 6-52) outcomes. However, complicating the interpretation of these results is both the lack of thorough empirical evaluations of alternatives to linearity as well as the results from cut-point analyses that provide some potential indication for nonlinearity in the relationship between long-term $PM_{2.5}$ exposure and cardiovascular disease.

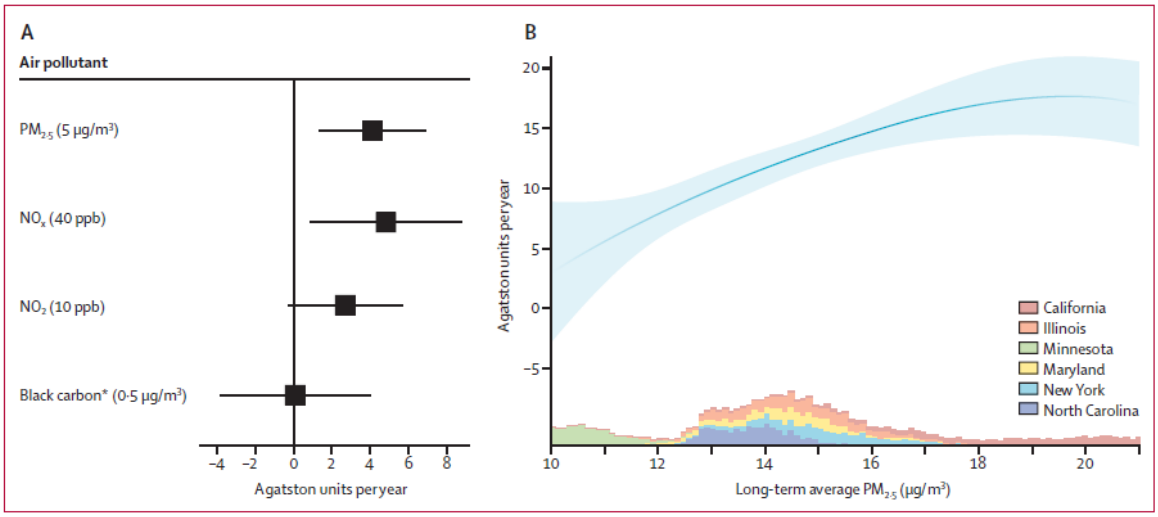
Two analyses of the C-*R* function for the relationship between $PM_{2.5}$ and CAC are available. Kaufman et al. (2016) generated a C-*R* curve using a thin plate regression spline with 5 degrees of freedom. The curve shows an increase in CAC with increasing long-term exposure to $PM_{2.5}$ and attenuation of the curve at higher concentrations (Figure 6-23). Dorans et al. (2016) reported a deviation from linearity such that log transformed CAC increased with increasing $PM_{2.5}$ concentrations at lower concentrations (<~10µg/m^3) while log transformed CAC decreased with increasing $PM_{2.5}$ at higher concentrations (Figure 6-24). A restricted cubic spline with 5 knots was used to examine the shape curve. The concentration and variability in the $PM_{2.5}$ concentrations were notably lower in the Framingham Heart Study cohort compared to the MESA population.

Chen et al. (2014a) examined the shape of the C-*R* function or the relationship between long-term $PM_{2.5}$ exposure and hypertension using a natural cubic spline with 2 degrees of freedom, is shown in Figure 6-25. The reference concentration for the HRs, which generally increase in a linear fashion, was 2.9 µg/m^3. In an analysis of IHD incidence, Cesaroni et al. (2014) restricted the data used in their meta-analysis of ESCAPE cohorts to include only those exposed below various thresholds. For the cohorts with participants exposed to <15 µg/m^3 average annual $PM_{2.5}$, the meta-analyzed HR for the association of long-term $PM_{2.5}$ exposure and IHD incidence was like the HR for the entire range of concentrations [1.19 (95%CI: 1.00, 1.42)].

Table 6-51 Summary of studies examining the concentration-response relationship or conduction threshold analyses for long-term exposure to $PM_{2.5}$ and cardiovascular morbidity.

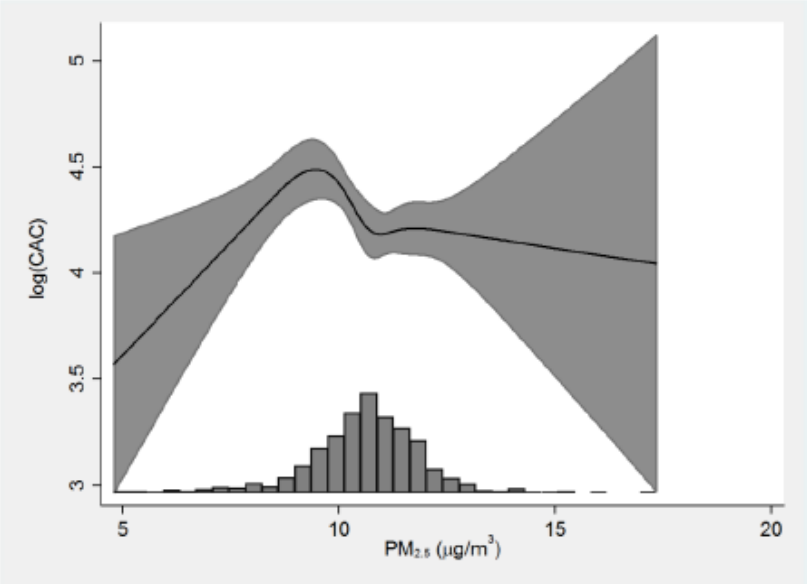
Study Location – Cohort (Table/Figure from Reference)	Outcome	Exposure $PM_{2.5}$ Mean: (Range) in $\mu g/m^3$	Statistical Analysis Summary
Cesaroni et al. (2014) 11 Cohorts Europe ESCAPE	IHD Incidence	NR	Restricted the meta-analysis to persons exposed below various thresholds. HR <15 $\mu g/m^3$ similar to HR across the full range of concentrations
Kaufman et al. (2016) 6 Urban sites U.S. MESA	CAC	Mean: 14.2 (range: 9.2-22.6)	Thin plate regression spline with 5 degrees of freedom. Attenuation at higher concentrations suggested
Dorans et al. (2016) Framingham Heart Study Offspring	CAC	Median (IQR) = 10.7 (1.4) for 2003	Restricted cubic spline with 5 knots. Non-linear relationship of log CAC with long-term $PM_{2.5}$ concentration observed
Chen et al. (2014a) Ontario, Canada	Hypertension	Mean 10.7 (range 2.9-19.2)	Natural cubic spline with 2 degrees of freedom (reference concentration 2.9 $\mu g/m^3$). No evidence of departure from linearity across the range of concentrations

CAC = coronary artery calcium, ESCAPE = European Study of Cohorts for Air Pollution Effects, HR = hazard ration, IHD = ischemic heart disease, IQR = interquartile range.



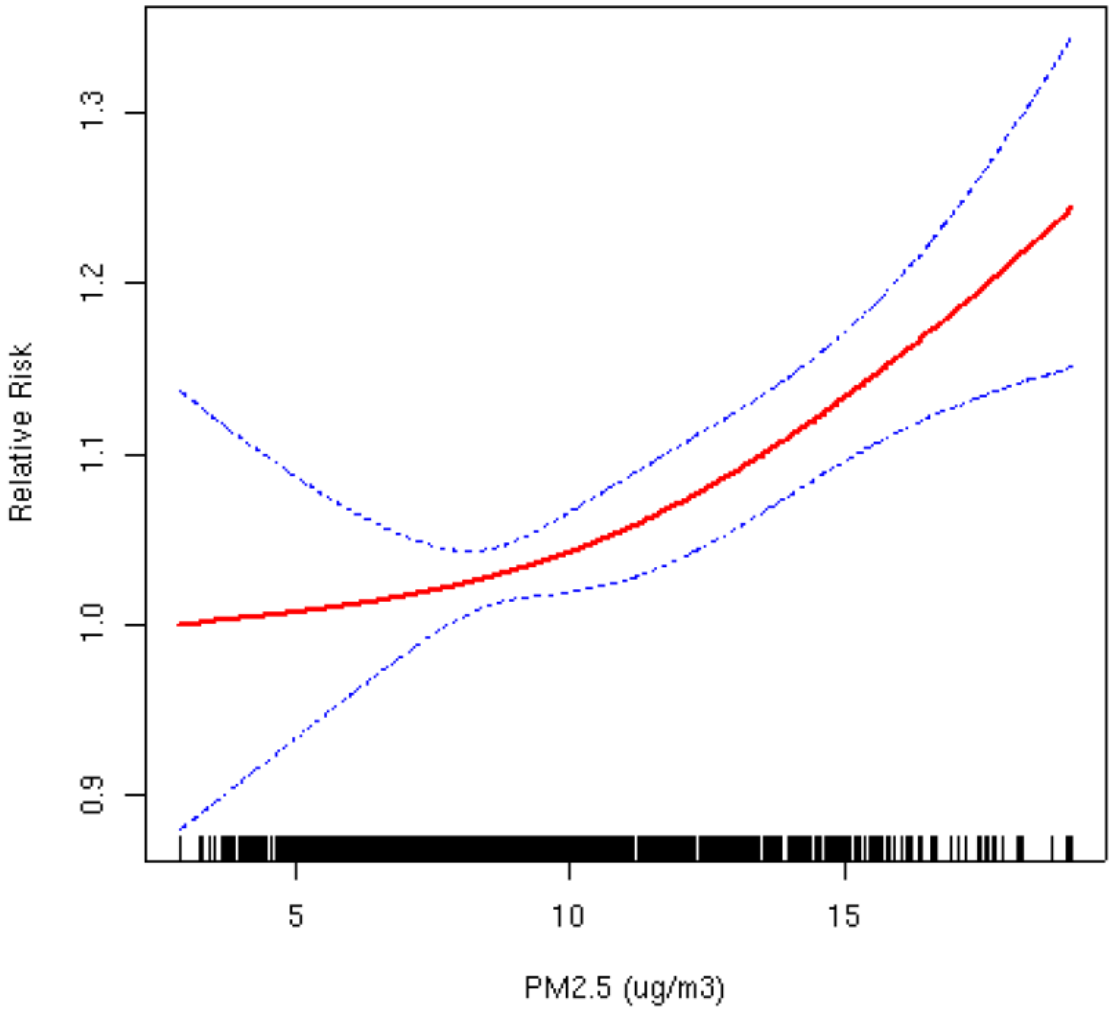
Source: Permission pending, (Kaufman et al., 2016)

Figure 6-23 The linear longitudinal association of long-term average $PM_{2.5}$ concentrations with coronary artery calcification (CAC) progression (Agatston units per year) across the range of concentrations.



Source: Permission pending, (Dorans et al., 2016)

Figure 6-24 Non-linear association of annual average $PM_{2.5}$ concentration (2003) and natural log-transformed coronary artery calcification (CAC).



Source: Permission pending, (Chen et al., 2014a)

Figure 6-25 Concentration-response relationship between the concentration of $PM_{2.5}$ and incident hypertension. The relative risks are adjusted covariates including sex, marital status, education, income body mass index (BMI), physical activity, smoking alcohol, diet race, urban residency neighborhood level socioeconomic status (SES) and unemployment rate, diabetes and COPD.

A number of recent studies have conducted analyses to inform the shape of the concentration-response relationship for the association between long-term exposure to $PM_{2.5}$ and mortality, and are summarized in Table 6-52. Generally, the majority of the results from these analyses continue to support a

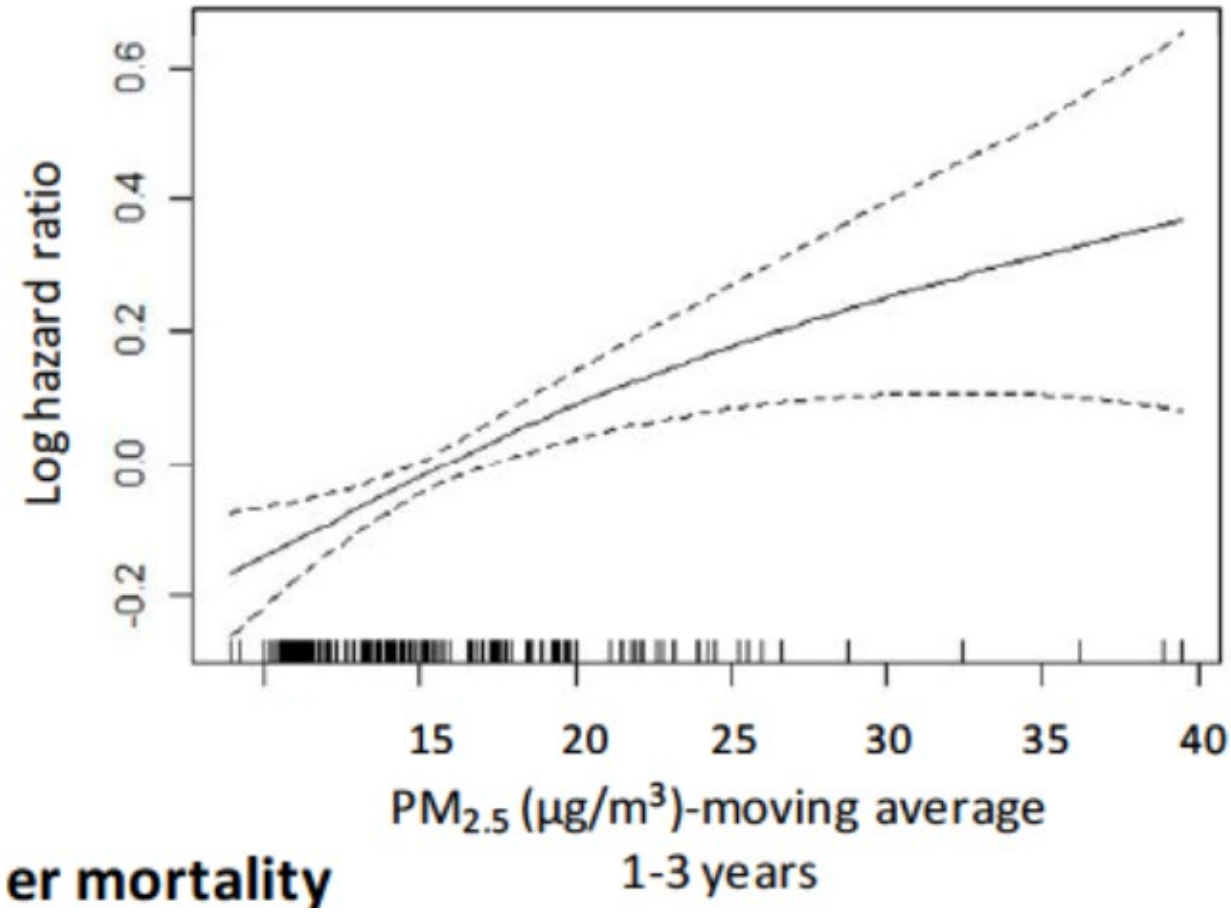
linear, no-threshold relationship for cardiovascular mortality, especially at lower ambient concentrations of $PM_{2.5}$. A number of the concentration-response analyses include concentration ranges ≤12 μg/m^3. For example, Lepeule et al. (2012) observed a linear, no-threshold concentration-response relationship for cardiovascular mortality in the most recent analysis of the Harvard Six Cities study, with confidence in the relationship down to a concentration of 8 μg/m^3 (Figure 6-26). Similar linear, no-threshold concentration-response curves were observed for cardiovascular mortality in other studies (Thurston et al., 2015; Villeneuve et al., 2015; Cesaroni et al., 2013; Gan et al., 2011). However, some studies reported that the slope of the concentration-response function tended to be steeper at lower concentrations, especially for IHD mortality. For example, in Crouse et al. (2012) statistical tests did not provide evidence for departure from linearity in the concentration-response function for IHD, but the risk was greater (HR = 1.20) at lower concentrations (<10 μg/m^3) compared to higher concentrations (10-15 μg/m^3) of $PM_{2.5}$ (Figure 6-27). Similar results were observed in other studies (Jerrett et al., 2016; Weichenthal et al., 2014b). Additional evidence to support a supralinear concentration-response relationship comes from a series of studies that looked at exposure to $PM_{2.5}$ from both ambient air pollution and cigarette smoke (Pope et al., 2011; Pope et al., 2009). These studies concluded that including the full concentration range of $PM_{2.5}$ from both ambient air pollution and cigarette smoking, it is clear that the relationship between long-term exposure and cardiovascular mortality cannot be adequately characterized as linear with no threshold. The concentration-response relationship is much steeper at lower $PM_{2.5}$ concentrations (such as those due to ambient air pollution) compared to the higher concentrations associated with cigarette smoking. This indicates the importance of considering the cause of death when characterizing the concentration-response relationship between long-term $PM_{2.5}$ exposure and cardiovascular mortality.

Table 6-52 Summary of studies examining the concentration-response relationship or conduction threshold analyses for long-term exposure to $PM_{2.5}$ and cardiovascular mortality.

Study Location – Cohort (Table or Figure from Reference)	Exposure $PM_{2.5}$ Mean; (Range) in μg/m^3	Statistical Analysis Summary
Cesaroni et al. (2013) Italy–RoLS (Figure 2B)	Eulerian Dispersion Model (1 km x 1 km) 23.0; (7.2-32.1)	Natural splines with 2, 3, or 4 df, compared goodness of fit using BIC and likelihood ratio test No evidence of deviation from linearity; Results similar for 2, 3 or 4 df

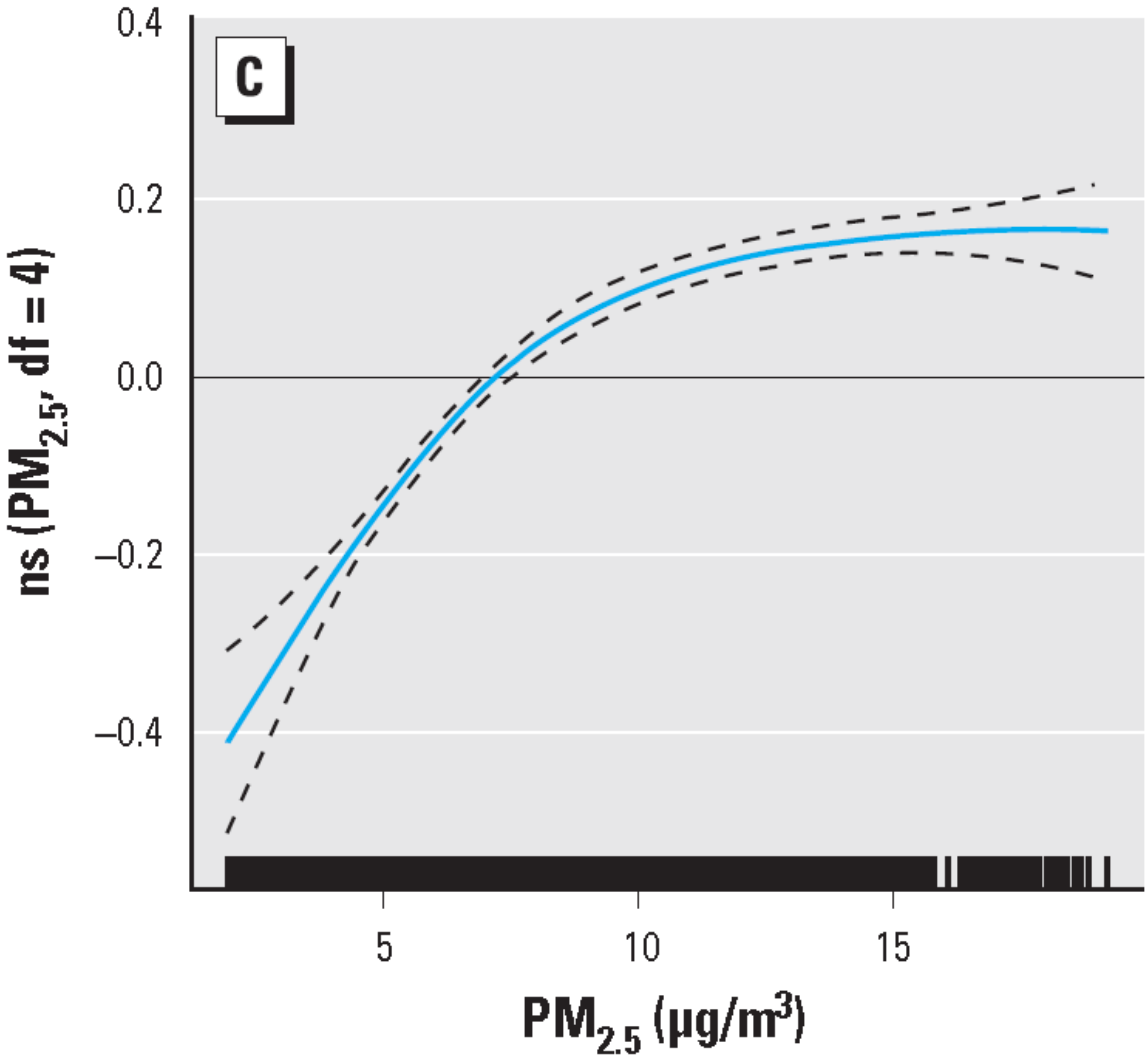
Table 6-52 (Continued): Summary of studies examining the concentration-response relationship or conduction threshold analyses for long-term exposure to $PM_{2.5}$ and cardiovascular mortality.

Study Location – Cohort (Table or Figure from Reference)	Exposure $PM_{2.5}$ Mean; (Range) in $\mu g/m^3$	Statistical Analysis Summary
Crouse et al. (2012) Canada – CanCHEC (Figure 2A-D)	Ground monitors in 11 cities; Satellite RS (10 km x 10 km) 11.2; (1.9-19.2)	Natural splines with 2, 3, or 4 df, compared goodness of fit using BIC. Log function of $PM_{2.5}$ (ln[$PM_{2.5}$ + 1]) yielded lower BIC than each of the spline models No evidence for departure from linearity for, CVD or CBVD. Risk was higher (HR = 1.20) from 5 $\mu g/m^3$ to 10 $\mu g/m^3$, and lower (HR = 1.12) from 10 $\mu g/m^3$ to 15 $\mu g/m^3$ for IHD mortality
Gan et al. (2011) Canada – Metro Vancouver (Figure 1b)	LUR 4.08; (0-10.24)	Study subjects divided into quintiles based on $PM_{2.5}$ concentration Consistent magnitude of RRs across quintiles suggests linearity. (Magnitude of effect is near null)
Jerrett et al. (2016) U.S. – ACS (Figures S2 and S3)	BME LUR: 12.0; (1.5-26.6) Satellite RS: 11.9; (1.9–24.6)	Natural splines with 2 df BME LUR curve is generally linear and has a steeper slope compared to the satellite RS curve, though slope decreases at concentrations above 20 $\mu g/m^3$; satellite RS curve is generally linear though slope begins to flatten for concentrations above has 13 - 15 $\mu g/m^3$
Lepeule et al. (2012) U.S.–HSC (Supplemental Figure 1)	Ground Monitor 15.9; (11.4-23.6)	Penalized spline models Linear relationship with exposures down to 8 $\mu g/m^3$. No evidence of a threshold. Highest confidence from 10 – 20 $\mu g/m^3$ based on greatest data density
Thurston et al. (2015) U.S.–NIH–AARP (Figure 2)	Hybrid LUR geo-statistical model 12.2; (2.9 – 28.0)	Natural spline plots with 4 df (Referent HR = 1.0 at mean exposure level) Observed linear relationship
Villeneuve et al. (2015) Canada–CNBSS (Figure 3)	Satellite RS (10 km x 10 km) 9.1; (0.1 – 20.0)	C-*R*: Natural cubic spline functions with 3 df; Threshold analysis: newly defined exposure variables based on concentration corresponding to the largest log-likelihood value from the Cox model Linear relationships for CVD and IHD mortality; Threshold analysis demonstrates no improvement in fit over a no-threshold linear model for CVD and IHD mortality
Weichenthal et al. (2014b) U.S.–Ag Health (Figure 2)	Satellite RS (10 km x 10 km) 8.84; (5.7-19.2)	Natural splines with 2 df. Natural splines with 3 and 4 df were examined but didn't not improve model fit Linear increase observed from 6 to 10 $\mu g/m^3$, with slope flattening out for concentrations between 10 and 14 $\mu g/m^3$



Source: Reprinted with permission from (Lepeule et al., 2012)

Figure 6-26 Concentration-response relationship between long-term $PM_{2.5}$ exposure and cardiovascular mortality in the Harvard Six Cities Study using penalized splines (1974−2009).



Source: Reprinted with Permission from (Crouse et al., 2012)

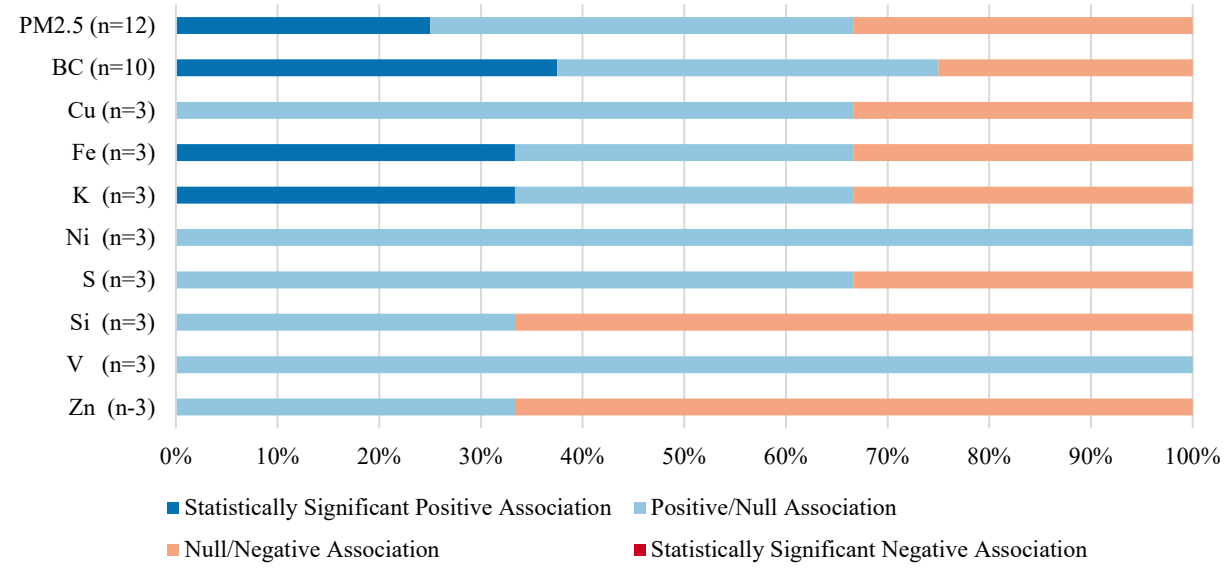
Figure 6-27 Concentration-response curve for IHD mortality in the CanCHEC cohort study. (Mean $PM_{2.5}$: 8.7 µg/m^3; natural splines with four degrees of freedom). Dotted lines indicate 95% confidence intervals.

6.2.17 Associations between $PM_{2.5}$ Components and Sources and Cardiovascular Effects

There were no studies that examined the association between $PM_{2.5}$ components and cardiovascular outcomes available for review in the 2009 PM ISA. A limited number of studies have been published since the previous review. Overall, this set of studies reports a range of findings from positive and statistically significant to null or negative (Figure 6-28). Figure 6-29 presents associations for specific

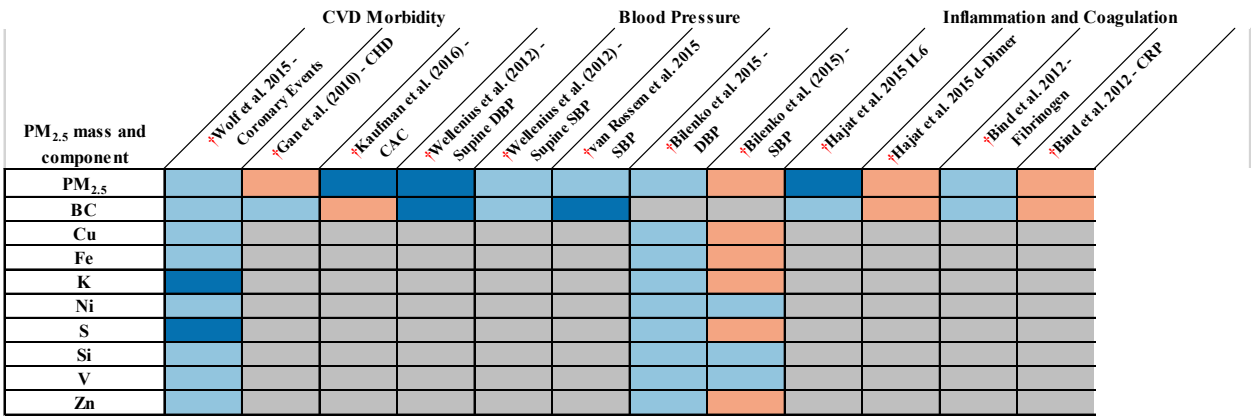
studies showing the lack of comparability across studies regarding the cardiovascular outcome and the component examined.

Wolf et al. (2015b) positive associations of $PM_{2.5}$ and $PM_{2.5}$ components with coronary events in the ESCAPE cohort. Gan et al. (2011) reported an association between long-term black carbon (BC) exposure and CHD hospitalizations but not between long-term $PM_{2.5}$ exposure and CHD hospitalizations in Vancouver, Canada. As discussed in Section 6.2.4 on atherosclerosis, Kaufman et al. (2016) reported a longitudinal association between exposure to $PM_{2.5}$ and CAC, but not between $PM_{2.5}$ and cIMT as indicated in the interim analysis of Adar et al. (2013). Consequently, associations of $PM_{2.5}$ components with cIMT (Kim et al., 2014; Sun et al., 2013) are not pictured in Figure 6-28. Kaufman et al. (2016) did not observe an association between black carbon (BC) and increased CAC. Wellenius et al. (2012b) reported significant associations of both 28-day average $PM_{2.5}$ and 28-day average BC exposure with resting supine DBP. Non-significant increases between both pollutants and resting supine SBP were also observed. Association between $PM_{2.5}$ and most measured components and DBP were observed among children (12 years old) participating in the PIAMA cohort in the Netherlands (Bilenko et al., 2015a). Positive associations between IL-6 and fibrinogen but not CRP or d-Dimer were observed for both $PM_{2.5}$ and BC (Hajat et al., 2015; Bind et al., 2012).



Note: Bars represent the percent of associations across studies for $PM_{2.5}$ mass or $PM_{2.5}$ components for long-term exposure studies of cardiovascular outcomes where dark blue = statistically significantly positive, light blue = positive/null, light orange = null/negative, red = statistically significantly negative N = number of studies that provided an estimate. $PM_{2.5}$ = particulate matter with mean aerodynamic diameter 2.5 µm, BC = black carbon, Cu = copper, Fe = iron, K = potassium, Ni = nickel, S = sulfur, Si = silica, V = vanadium, Zn = zinc

Figure 6-28 Distribution of associations of long-term exposure to $PM_{2.5}$ and $PM_{2.5}$ component concentrations with cardiovascular outcomes.



Note: Cells represent associations examined for studies of long-term exposure to $PM_{2.5}$ mass and $PM_{2.5}$ components and cardiovascular outcomes. Dark blue = statistically significant positive association; light blue = positive or null association; light orange = null or negative association; red = statistically significant negative association; grey = component not examined. Only $PM_{2.5}$ components for which there were at least three studies available were included in the table. $PM_{2.5}$ = particulate matter with mean aerodynamic diameter 2.5 μm, BC = black carbon, Cu = copper, Fe = iron, K = potassium, Ni = nickel, S = sulfur, Si = silica, V = vanadium, Zn = zinc.

Figure 6-29 Results of studies of long-term exposure to $PM_{2.5}$ and $PM_{2.5}$ component concentrations and cardiovascular outcomes.

Regional Heterogeneity

The 2009 PM ISA concluded that there is variation in both $PM_{2.5}$ mass and composition between cities and that the variation may be due, in part to differences in $PM_{2.5}$ sources as well as meteorology and topography. Although east-west gradients were observed for PM components including SO_4^{2-}, OC, and NO_3^-, the amount of city-specific speciated $PM_{2.5}$ data was limited and did not explain the heterogeneous effect estimates for PM across locations. There were no national-scale studies that examined regional differences in the associations between long-term exposure to $PM_{2.5}$ and cardiovascular effects included in the 2009 PM ISA, however, a large U.S.-based multicity study of short-term exposure and CVD hospital admissions provided evidence indicating larger risks in the Northeast compared to the West and multicity epidemiologic studies of cardiovascular mortality generally observed a similar pattern.

A limited number of studies published since the 2009 PM ISA examine regional differences in the associations between long-term exposure and cardiovascular outcomes including CHD and stroke. An analysis of region specific HRs in the NHS indicated slight increases in the Northeast and the South compared to the Midwest and West, although confidence intervals were wide. In a sensitivity analyses restricted to more recent years (2000-2006) the regional differences were more pronounced. Note that Hart et al. (2015b) observed no of association between long-term exposure to $PM_{2.5}$ and incident CHD [HR: 1.01 95%CI: 0.96,1.07], overall. Feng and Yang (2012) compared prevalence odds ratios across nine U.S. regions reporting that the largest ORs for the associations with MI and CHD were in "east central" region of the US.

Sources

The literature examining the relationship between sources of $PM_{2.5}$ and health effects that was included in the 2009 PM ISA was limited to a small number of studies examining the associations of traffic-related sources with mortality. The evidence provided by these studies was not sufficient to distinguish specific sources that could be linked to health effects. The currently available studies on this topic are tabulated below. Aguilera et al. (2016) reported an association between cIMT and $PM_{2.5}$ from traffic but not between cIMT and $PM_{2.5}$ from crustal sources. Positive cross-sectional associations of cIMT with traffic load and traffic intensity were reported in a meta-analysis of four ESCAPE cohorts. $PM_{2.5}$ from traffic exhaust was associated with readmission for MI in MINAP study in London (Tonne et al., 2015). Overall, these studies were not designed to evaluate whether long-term exposure to $PM_{2.5}$ traffic sources was more strongly or independently associated with cardiovascular health effects, however.

6.2.17.1 Toxicology Studies of Individual Components and Sources as Part of a PM Mixture

Campen et al. (2014) exposed young, male $ApoE^{-/-}$ mice on a high fat, high cholesterol diet to motor vehicle exhaust (MVE), MVE with particles removed, sulfate particles, ammonium nitrate particles or paved road dust at target concentrations of 300 $\mu g/m^3$ for 50 days (6 hr/day, 7 day/week). Given that the MVE exposures included gases, the focus of the discussion on this study is on those exposures that contained particles only. Measurements informative for biologic pathways of vascular toxicity, atherosclerosis, and coronary artery disease were obtained the day following the last exposure. Multiple Additive Regression Tree (MART) analysis was performed to assess the relationship between concentrations of individual components with the measurements of biological endpoints. Ultimately a "predictor values" of ranked components is produced based on the strength of their association with each biological marker. In addition, an estimated concentration-response curve is generated using the biological outcome and the predictor after accounting for the average effects of all other chemical predictors across their experimental exposure ranges. MART analysis chemical predictor variables include particle mass, ammonium, elements, nitrate, sulfate, EC, OC, particle phase organics (i.e., organic acids, organic phenols, organic sterols, organic sugars, organic hopanes, organic steranes, organic PAHs, organic nitro-PAHs, and organic alkanes). There were very few changes in biologic endpoints compared to control animals exposed to air for the sulfate, ammonium nitrate or road dust exposures. The sulfate exposure did result in significant enhancement of PE-induced contraction in mouse aortas compared to air controls, with ammonium nitrate exposure resulting in significantly diminished PE-induced contraction compared to air controls. Plaque area was also increased and linked to ammonium nitrate, albeit the group size was quite small (as low as 3). Two measurements appeared dependent on PM (more so than the gases) – oxidized low-density lipoprotein and vasoconstriction. However, in general, MVE gases were

required to elicit significant responses in toxicological measurements and the PM alone did not appear to drive any of the statistically significant effects observed.

Chen et al. (2010) examined mice exposed to Manhattan and Sterling Forest (aka Tuxedo) CAPs as a part of the NPACT study. They evaluated changes in HR and HRV parameters with source categories identified using factor analysis of 17 components (including NO_2 to identify a traffic factor). Seven factors were identified for Manhattan and four factors for Sterling Forest.

Table 6-53 shows general ECG results over the exposure period for each location and identified source category. This is a semi-quantitative evaluation of the number of significant associations, given that there were 6 HR/HRV parameters (HR, SDNN, rMSSD, LF, HF, and LF/HF) analyzed over 4 different time periods (9:00 a.m.−2:00 p.m., 7:00 p.m.−10:00 p.m., 10:00 p.m.−1:00 a.m., 1:00 a.m.−3:00 a.m.) and three different lags (0, 1 and 2).

Table 6-53 Study results for identified source categories and occurrence of heart rate (HR) and heart rate variability (HRV) changes (Chen et al., 2010).

Location	Identified Source Categories	General HR and HRV Results
Manhattan	Incineration (Cu, Zn, Pb); Soil (Al, Si, Ca); Long-range transport (S, Se, Br, EC); Iron-manganese (Fe, Mn); Residual oil (V, Ni, EC); Traffic (EC, NO_2); Fireworks (K, Cu, Ba)	Residual oil had the most number of changes in HR/HRV (59) that were fairly evenly split across lags and time periods; long-range transport had the second most changes (45), with the majority at lag 0 and 1; traffic (30), FeMn (22) and incineration (21) were 3rd, 4th and 5th for number of changes; FeMn had the greatest number of responses on lag 0 and incineration had the greatest number of responses at lag 1; HR/HRV changes attributed to soil (14) were nearly all observed on lag 0; fireworks was associated with 1 HR/HRV change at lag 0 during the 7 PM-10 PM time period
Sterling Forest	Long-range transport (S, Se, Br, EC); Residual oil/traffic (V, BC); Ni-refinery (Ni, Cr, Fe); Soil (Al, Si, Ca)	Long range transport had double the number of occurrences of HR/HRV changes (34) compared to the next source factor, Ni refinery (17); the most numerous changes were at lag 0 and 1 for long-range transport; the most number of changes in HR/HRV for soil were observed at lag 1 (7 of 11); residual oil/traffic had the fewest counts of HR/HRV changes (3), all of which were observed at lag 0 in the 1 AM-4 AM time period

In looking at the two sites, long-range transport was associated with changes in cardiac function with both Manhattan and Sterling Forest CAPS. In contrast, the residual oil source factor was associated with the most number of changes in HR and HRV in Manhattan and the least in Sterling Forest (albeit it

was a combined residual oil and traffic source factor). The number of occurrences of HR and HRV changes associated with soil was similar in across the two sites, with the majority at lag 0 in Manhattan and lag 1 in Sterling Forest.

In another study of rats exposed to $PM_{2.5}$ CAPs in Detroit, for the summer months, 29 components were analyzed and PMF was used to investigate source factors (Rohr et al., 2011). Decreases in SDNN using 30-minute data in the summer were associated with 4 of 6 identified source factors - iron/steel manufacturing, sludge incinerator, cement/lime production and gasoline and diesel-powered vehicles. The strongest association was with the vehicle source factor and no association was observed with the refinery or secondary sulfate source factors. Similar to summer, 6 source factors were identified in winter. However, there were differences in that sludge incinerator source was only identified in summer and the iron/steel manufacturing was a part of the gasoline and diesel powered-vehicles and metal processing in winter. Increased HR in winter was associated with a refinery source factor and decreased HR was associated with the sludge incineration, cement/lime production and coal/secondary sulfate factors. For rMSSD, increases were associated with two factors - coal/secondary sulfate and gasoline and diesel-powered vehicles and iron/steel manufacturing.

In a study akin to (Rohr et al., 2011) that took place in Steubenville, OH, approximately 30 $PM_{2.5}$ components were measured and used to identify source factors using PMF (Kamal et al., 2011). Six factors were identified – coal/secondary, incineration, lead, metal coating/processing, mobile sources, and iron/steel manufacturing. There was a distinct difference in source contribution and ECG effects based on wind direction. Increased HR was associated with SW winds and the metal processing factor, whereas decreased HR was associated with NE winds and incineration, lead and iron/steel manufacturing factors. Decreased SDNN was associated with NE winds and the incineration factor and with SW winds and the metal factor. Increased rMSSD was only associated with combined winds and the iron/steel manufacturing factor.

6.2.18 Summary and Causality Determination

The evidence reviewed in the 2009 PM ISA provided the rationale to conclude that there is "a causal relationship between long-term $PM_{2.5}$ exposure and cardiovascular effects" (U.S. EPA, 2009). Studies of mortality from cardiovascular causes provided the strongest evidence in support of this conclusion. While several studies included in the 2009 PM ISA reported associations between long-term PM_{10} exposure and morbidity outcomes such as post-MI CHF and DVT, studies of $PM_{2.5}$ were limited. One large prospective study of post-menopausal women reported an increased risk of cardiovascular events, including CHD and stroke, in association with long-term exposure to $PM_{2.5}$ (Miller et al., 2007). Cross-sectional analyses provided supporting evidence and experimental studies demonstrating enhanced atherosclerotic plaque development and inflammation following long-term exposures to $PM_{2.5}$ CAPs provided biological plausibility for the epidemiologic findings. In addition, a limited number of

toxicological studies reporting CAPs-induced effects on hypertension and vascular reactivity were drawn upon to support the causal conclusion. With respect to the current review, the evidence for the relationship between long-term exposure to $PM_{2.5}$ and cardiovascular effects is described below and summarized in Table 6-54, using the framework for causality determination described in the Preamble to the ISAs (U.S. EPA, 2015).

The studies of long-term exposure to $PM_{2.5}$ and cardiovascular mortality continue to provide strong evidence that there is a causal relationship between long-term exposure to $PM_{2.5}$ and cardiovascular effects. Results from recent U.S. and Canadian cohort studies demonstrate consistent, positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality (see Figure 6-19). Overall, studies reporting positive associations examine the relationship at varying spatial scales and employ different exposure assessment and statistical methods (Section 6.2.10). The studies were conducted in locations where mean annual average concentrations ranged from 4.08-17.9 $\mu g/m^3$. Generally, most of the $PM_{2.5}$ effect estimates relating long-term $PM_{2.5}$ exposure and cardiovascular mortality remained relatively unchanged or increased in copollutant models adjusted for ozone, NO_2, $PM_{10-2.5}$, or SO_2. In addition, most the results from analyses examining the C-R function for cardiovascular mortality supported a linear, no-threshold relationship for cardiovascular mortality, especially at lower ambient concentrations of $PM_{2.5}$ (Table 6-52).

The body of literature examining the relationship between long-term $PM_{2.5}$ exposure and cardiovascular morbidity has greatly expanded since the 2009 PM ISA, with positive associations reported in several cohorts. The findings from the WHI cohort of post-menopausal women (Miller et al., 2007), reporting associations of long-term $PM_{2.5}$ and coronary events, were strengthened through a subsequent analysis that considered potential confounding and modification by SES and applied enhanced exposure assessment methods (Chi et al., 2016a). Analyses of the NHS and CTS, which are both cohorts of women and include extensive data on covariates (i.e., hormone use, menopausal status and SES), were not entirely consistent with the WHI findings, however. Although the NHS cohort is comparable to WHI in that it is made of predominantly post-menopausal women, no associations with CHD or stroke were observed in this population (Hart et al., 2015b). An association with stroke, but not CHD, that was stronger among post-menopausal women was observed in the CTS (Lipsett et al., 2011). Several studies conducted among cardiovascular disease patient populations generally reported positive associations with MI (Hartiala et al., 2016; Tonne et al., 2015; Koton et al., 2013) and a sensitivity analysis of the NHS restricted to women with diabetes detected a positive association with CHD. Although the evidence is not consistent across the populations studied, heterogeneity is expected when the methods, or the underlying distribution of covariates vary across studies (Higgins, 2008).

Longitudinal change in measures of atherosclerosis in relation to long-term exposure to $PM_{2.5}$ add to the collective evidence base (Hartiala et al., 2016; Kaufman et al., 2016; Gan et al., 2014; Künzli et al., 2010). Findings were somewhat variable across cohorts and depended, in part, on the vascular bed in which atherosclerosis was evaluated. Kaufman et al. (2016) reported an association of $PM_{2.5}$ with CAC

among middle to older aged adults in the MESA study, while Dorans et al. (2016) reported no association in the Framingham Heart Study. Associations of long-term exposure to $PM_{2.5}$ with cIMT were not consistently observed across cohorts or between analyses of the same cohort with variable methods. Relationships between $PM_{2.5}$ and CIMT at younger ages were not observed. However, a recent toxicological study adds to similar evidence from the 2009 PM ISA by demonstrating increased plaque progression in $ApoE^{-/-}$ mice following long-term exposure to $PM_{2.5}$ collected from multiple locations across the U.S. (Section 6.2.4.2). Thus, this study provides direct evidence that long-term exposure to $PM_{2.5}$ may result in atherosclerotic plaque progression. This study is also coherent with those epidemiologic studies discussed above reporting positive associations between long-term exposure to $PM_{2.5}$ and indicators of atherosclerosis.

A small number of epidemiologic studies also report positive associations between long-term $PM_{2.5}$ exposure and HF (Section 6.2.5), blood pressure and hypertension (Section 6.2.7). These HF studies are in agreement with animal toxicological studies demonstrating decreased cardiac contractility and function, and increased coronary artery wall thickness following long-term $PM_{2.5}$ exposure (Section 6.2.5.2). Similarly, a limited number of animal toxicological studies demonstrating a relationship between long-term exposure to $PM_{2.5}$ and consistent increases in BP in rats and mice are coherent with epidemiologic studies reporting positive associations between long-term exposure to $PM_{2.5}$ and hypertension.

Longitudinal epidemiologic analyses also support the observation of positive associations with markers of systemic inflammation (Section 6.2.12), coagulation (Section 6.2.13), and endothelial dysfunction (Section 6.2.14). These results are in coherence with animal toxicological studies generally reporting increased markers of systemic inflammation and oxidative stress (Section 6.2.12.2), as well as with toxicological studies generally demonstrating endothelial dysfunction as evidenced by reduced vasodilation in response to acetylcholine (Section 6.2.14).

There is also consistent evidence from multiple, high-quality epidemiologic studies that long-term exposure to $PM_{2.5}$ is associated with mortality from cardiovascular causes. Associations with CHD, stroke and atherosclerosis progression were observed in several additional high-quality epidemiologic studies providing coherence with the mortality findings. Results from copollutant models generally support the independence of the $PM_{2.5}$ associations. Additional evidence of the direct effect of $PM_{2.5}$ on the cardiovascular system is provided by experimental studies in animals, which in part, demonstrate biologically plausible pathways by which long-term inhalation exposure to $PM_{2.5}$ could potentially result in outcomes such as CHD, stroke, CHF and cardiovascular mortality (Section 6.2.1). Taken together, these epidemiologic and experimental studies constitute strong evidence that **a causal relationship exists between long-term exposure to $PM_{2.5}$ and cardiovascular effects.**

Table 6-54 Summary of evidence for a causal relationship between long-term $PM_{2.5}$ exposure and cardiovascular effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Consistent epidemiologic evidence from multiple, high-quality studies at relevant $PM_{2.5}$ concentrations	Positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality in U.S. and Canadian cohorts; positive associations persisted after adjustment for common confounders.	Section 6.2.10 Figure 6-19	Mean concentrations ranged from 4.08 $\mu g/m^3$ (CCHS) – 17.9 $\mu g/m^3$ CA Teachers
	Positive associations observed in studies examining varying spatial scales and across different exposure assessment and statistical methods.	Section 6.3.10.1	
Evidence from copollutant models generally supports an independent $PM_{2.5}$ association	Positive associations observed between long-term $PM_{2.5}$ exposure and cardiovascular mortality remain relatively unchanged after adjustment for copollutants. Correlations with ozone were generally moderate to high (0.49-0.73). When reported, correlations with SO_2, NO_2 and $PM_{10-2.5}$ ranged from weak to moderate (r = 0.25-0.55).	Section 6.3.10.25 Figure 6-21 Figure 6-22	
Epidemiologic evidence supports a linear no-threshold concentration response (C-R) relationship.	Majority of analyses support a linear, no-threshold relationship for cardiovascular mortality, especially at lower ambient concentrations of $PM_{2.5}$. Confidence in C-*R* relationship extends to 8 $\mu g/m^3$ in Harvard Six Cities study	Section 6.2.10 Lepeule et al. (2012)	
Inconsistent evidence from epidemiologic studies of CHD or stroke	High quality epidemiologic study reports association with coronary events, CHD and stroke (mortality and morbidity combined) among post-menopausal women that persist after adjustment for SES. Association with stroke but not CHD in the CA Teachers cohort No association with CHD or stroke in the NHS or HPFU	(Chi et al., 2016a; Miller et al., 2007) Lipsett et al. (2011) Puett et al. (2011) Hart et al. (2015b)	Mean: 13.4 $\mu g/m^3$ Mean: 15.6 $\mu g/m^3$ Mean: 17.8 $\mu g/m^3$ Mean: 13.4 $\mu g/m^3$

Table 6-54 (Continued): Summary of evidence indicating that a causal relationship exists between long-term $PM_{2.5}$ exposure and cardiovascular effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Generally consistent evidence of an association with CHD or stroke among those with preexisting disease	Consistent associations with MI in patient populations Association among women with diabetes in NHS	Hartiala et al. (2016) Tonne et al. (2015) Koton et al. (2013) Hart et al. (2015b)	Mean: 15.5 $\mu g/m^3$ Mean: 14.6 $\mu g/m^3$ Mean: 23.9 $\mu g/m^3$ Mean: 13.4 $\mu g/m^3$
Some but not all high quality epidemiologic studies provide evidence for effect of long-term $PM_{2.5}$ on CAC	Longitudinal change in CAC observed in MESA but not in Framingham Heart Offspring study	Kaufman et al. (2016) Dorans et al. (2016)	Mean: 14.2 $\mu g/m^3$ Median: 9.8 $\mu g/m^3$
Consistent evidence from animal toxicological studies at relevant $PM_{2.5}$ concentrations	Consistent changes in measures of impaired heart function and blood pressure Additional evidence of atherosclerosis, systemic inflammation, changes in endothelial function	Section 0 Section 6.2.4.2 Section 6.2.7.2 Section 6.2.12.2 Section 6.2.14.2	~85- 130 $\mu g/m^3$ See Tables in identified sections
Generally consistent evidence for biological plausibility of cardiovascular effects	Strong evidence for coherence of effects across scientific disciplines and biological plausibility for a range of cardiovascular effects in response to long-term $PM_{2.5}$ exposure. Includes evidence for impaired heart function, atherosclerosis, and increased blood pressure.	Section 6.2.1	

$PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than a nominal diameter of 2.5 µm; SO_2 = sulfur dioxide.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

6.3 Short-Term $PM_{10-2.5}$ Exposure and Cardiovascular Effects

The 2009 PM ISA concluded that the available evidence for short-term $PM_{10-2.5}$ exposure and cardiovascular effects was "suggestive of a causal relationship." This conclusion was based on several epidemiologic studies reporting associations between short-term $PM_{10-2.5}$ exposure and cardiovascular

effects including ischemic heart disease (IHD) hospitalizations, supraventricular ectopy, and changes in heart rate variability (HRV). In addition, dust storm events resulting in high concentrations of crustal material were linked to increases in cardiovascular disease emergency department (ED) visits and hospital admissions. However, it was noted in the last review that there were concerns with respect to the potential for exposure measurement error in these epidemiologic studies because of the methods employed to estimate $PM_{10-2.5}$ concentrations. In addition, there was limited evidence of cardiovascular effects from the few experimental studies that examined short-term $PM_{10-2.5}$ exposures. Thus, in the last review, key uncertainties included the potential for exposure measurement error and biological plausibility of associations reported in epidemiologic studies.

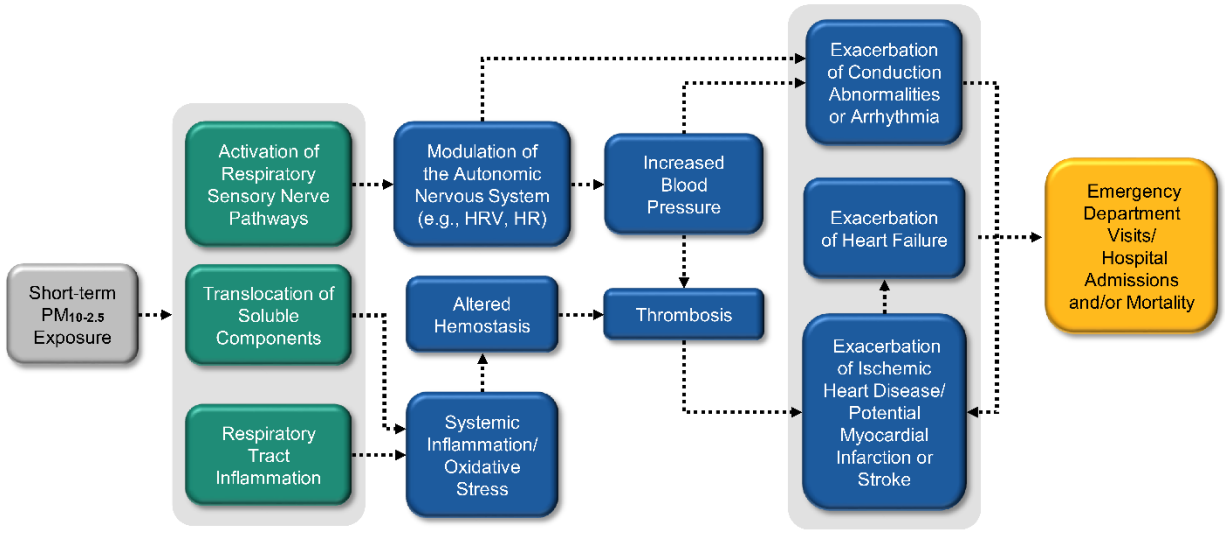
Evidence published since the completion of the 2009 PM ISA continues to be suggestive of a causal relationship between short-term exposures to $PM_{10-2.5}$ and cardiovascular effects. Since the publication of the 2009 PM ISA, there were a small number of epidemiologic studies reporting positive associations between exposure to $PM_{10-2.5}$ and IHD ED visits and hospital admissions. However, there is only limited evidence to suggest that these associations are independent of copollutant confounding. Similarly, there is only limited biological plausibility for IHD ED visits or hospital admissions from CHE, epidemiologic panel, and animal toxicological studies. Finally, similar to those studies evaluated in the 2009 PM ISA, the approaches used to estimate $PM_{10-2.5}$ concentrations continue to vary across studies leading to uncertainty regarding the extent to which exposure measurement error might be impacting the epidemiologic results.

The subsections below provide an evaluation of the most policy relevant scientific evidence relating-short-term $PM_{10-2.5}$ exposure to cardiovascular health effects. To clearly characterize and put this evidence into context, there is first a discussion of the biological plausibility of cardiovascular effects following short-term $PM_{10-2.5}$ exposure (Section 6.3.1). Following this discussion, the health evidence relating short-term $PM_{10-2.5}$ exposure and specific cardiovascular health outcomes is discussed in detail: ischemic heart disease and myocardial infarction (Section 6.3.2), heart failure and impaired heart function (Section 6.3.3) cardiac electrophysiology and arrhythmia (Section 6.3.4), cerebrovascular disease and stroke (Section 6.3.5), increased blood pressure and hypertension (Section 6.3.6), aggregated cardiovascular outcomes (Section 6.3.7), and cardiovascular-related mortality (Section 6.3.8). The evidence for an effect of $PM_{10-2.5}$ exposures on endpoints such as changes in heart rate variability (HRV) and endothelial function are then discussed (Section 6.3.9, Section 6.3.10, Section 6.3.11, and Section 6.3.12). Finally, considering the all of the information presented above, summary and causal determinations are presented (Section 6.3.13).

6.3.1 Biological Plausibility

This subsection describes the biological pathways that potentially underlie cardiovascular health effects resulting from short-term inhalation exposure to $PM_{10-2.5}$. Figure 6-30 graphically depicts these

proposed pathways as a continuum of pathophysiological responses—connected by arrows—that may ultimately lead to the apical cardiovascular events observed in epidemiologic studies. This discussion of "how" short-term exposure to $PM_{10-2.5}$ may lead these cardiovascular events also provides at least some biological plausibility for the epidemiologic results reported later in Section 6.3. In addition, most studies cited in this subsection are discussed in greater detail throughout Section 6.3.



Note: the boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes.

Figure 6-30 Potential biological pathways for cardiovascular effects following short-term exposure to $PM_{10-2.5}$.

When considering the available health evidence, plausible pathways connecting short-term exposure to $PM_{10-2.5}$ to the apical events reported in epidemiologic studies are proposed in Figure 6-30. The first pathway begins as respiratory tract inflammation leading to systemic inflammation.[64] The second pathway involves activation of sensory nerves in the respiratory tract that leads to modulation of the autonomic nervous system. Once these pathways are initiated, there is evidence from experimental and observational studies that short-term exposure to $PM_{10-2.5}$ may result in a series of pathophysiological

[64] It is also possible that soluble particle components can translocate directly into the circulatory system (Chapter 4) and lead to systemic inflammation, although the extent to which particle translocation occurs remains unclear.

responses that could lead to cardiovascular events such as ED visits and hospital admissions for IHD and HF, and ultimately mortality.

Short-term exposure to $PM_{10-2.5}$ may result in respiratory tract inflammation (Section 5.2). Inflammatory mediators such as cytokines produced in the respiratory tract may then enter into the circulatory system where they can cause distal pathophysiological responses and can contribute to overt cardiovascular disease (see Section 6.1.1). There is some evidence from a controlled human exposure study (Behbod et al., 2013) that following short-term exposure to $PM_{10-2.5}$, systemic inflammation may occur. Once in the circulation, inflammatory cytokines such as IL-6 can stimulate the liver to release coagulation factors that can alter hemostasis and increase the potential for thrombosis (see Section 6.1.1). It is therefore important to note that there is some evidence from a CHE (Graff et al., 2009) and an epidemiologic panel study (Huttunen et al., 2012) that following short-term exposure to $PM_{10-2.5}$, altered hemostasis may occur. Thus, the IHD and HF-related ED visit and hospital admission associations reported in epidemiologic studies are at least plausible through a pathway that includes thrombosis (Figure 6-30). This potential pathway could also plausibly contribute to the development of MI or stroke (Figure 6-30).

In addition to short-term $PM_{10-2.5}$ exposure potentially leading to worsening of cardiovascular disease through respiratory tract inflammation, there is also evidence that short-term exposure to $PM_{10-2.5}$ could potentially lead to worsening of cardiovascular disease through the activation of sensory nerves in the respiratory tract (CHAPTER 5). Sensory nerve activation can potentially result in modulation of the autonomic nervous system which may lead to changes in BP, conduction abnormalities, or arrhythmia (see Section 6.1.1). Thus, it is notable that there is a CHE study (Brook et al., 2014) that demonstrates autonomic nervous system modulation (as evidenced by changes in HRV and HR) following short-term $PM_{10-2.5}$ exposure. There is also evidence from CHE (Byrd et al., 2016; Zhong et al.; Brook et al., 2014; Bellavia et al., 2013), epidemiologic panel (Zhao et al., 2015) and animal toxicological (Aztatzi-Aguilar et al., 2015) studies that short-term exposure to $PM_{10-2.5}$ is associated with increases in BP. Similarly, there is evidence from epidemiologic panel studies for indicators of arrhythmia (Bartell et al., 2013; Hampel et al., 2010) following short-term $PM_{10-2.5}$ exposure. This is important given that increases in BP (e.g., through shear stress induced thrombosis) and arrhythmia may worsen IHD and set the stage for HF.

Taken together, there are plausible pathways by which short-term exposure to $PM_{10-2.5}$ may worsen IHD or HF as well as contribute to the development of MI or stroke (Figure 6-30). These proposed pathways also provide biological plausibility for ED visits and hospital admissions following short-term $PM_{10-2.5}$ exposure. That said, the evidence supporting most of the individual events in these pathways is quite limited. This information will be used to inform a causal determination, which is discussed later in the chapter (Section 6.3.13).

6.3.2 Ischemic Heart Disease and Myocardial Infarction

As noted above, (Section 6.1.2) IHD is characterized by reduced blood flow to the heart. The majority of IHD cases are caused by atherosclerosis (Section 6.2.4), which can result in the blockage of the coronary arteries and restrict of blood flow to the heart muscle. Also noted above (Section 6.1.2), an MI occurs as a consequence of IHD, resulting in insufficient blood flow to the heart that overwhelms myocardial repair mechanisms and leads to muscle tissue death. Additional information on IHD and MI can be found in Section 6.1.2.

As detailed below, recent studies add to existing evidence from the 2009 PM ISA that increases in $PM_{10-2.5}$ concentrations are associated with increases in ED visits and hospital admissions for IHD. However, results from copollutant models provide limited evidence that the observed associations are independent of other examined copollutants, including $PM_{2.5}$. Moreover, exposure measurement error remains an important uncertainty. There were no CHE or animal toxicological studies examining the relationship between short-term exposure to $PM_{10-2.5}$ and indicators of IHD or MI.

6.3.2.1 Emergency Department Visits and Hospital Admissions

The 2009 PM ISA reviewed a handful of studies that considered the association between $PM_{10-2.5}$ and IHD ED visits and hospital admissions that reported generally positive associations. A multicity study in France observed a 6.4% (95% CI: 1.6, 11.4%) increase in hospital admissions for IHD at lag 0-1 (Host et al., 2007). Associations were also recorded in single-city studies in Detroit (Ito, 2003) and Toronto (Burnett et al., 1999). On the other hand, one study in Atlanta observed no evidence of an association (Metzger et al., 2004). Additionally, one study examined $PM_{10-2.5}$ concentrations in relation to MI, and observed a positive but imprecise (i.e., wide 95% CI) association (Peters et al., 2001).

Several recent studies provide additional evidence for a positive association between short-term $PM_{10-2.5}$ exposure and IHD ED visits and HA. Specifically, $PM_{10-2.5}$ exposure was associated with IHD hospital admissions among U.S. Medicare beneficiaries in a multicity MCAPS study (Powell et al., 2015), as well as in single-city studies of IHD hospital admissions in Hong Kong, China and Kaohsiung, Taiwan (Chen et al., 2015b; Qiu et al., 2013). In the MCAPS study, $PM_{10-2.5}$ exposure was associated with a 0.74% (95% CI: 0.29, 1.20%) increase in hospital admissions for IHD on the same day (Powell et al., 2015). The association was unchanged in copollutant models adjusting for $PM_{2.5}$. Qiu et al. (2013) also observed a positive association, which persisted but lost precision after adjustment for $PM_{2.5}$. In Kaohsiung, Taiwan, Chen et al. (2015b) considered nearly 23,000 hospital admissions for IHD and reported positive associations on cool and warm days. The observed associations were generally robust to adjustment for NO_2, SO_2, CO, and O_3 in copollutant models. One additional important uncertainty across the available studies remains exposure measurement error for $PM_{10-2.5}$. All studies used an indirect measure of $PM_{10-2.5}$ (the difference between county- or area-averaged PM_{10} and $PM_{2.5}$ measurements or

the difference between concentrations measured at single PM_{10} and $PM_{2.5}$ monitors). Chen et al. (2015b) indicate the monitors were collocated, though it was unclear if these authors relied on the difference from collocated monitors before the spatial averaging was done, or if the spatial averaging of the PM_{10} and $PM_{2.5}$ monitors was done first, and then the difference was taken. Overall, it remains unclear how exposure measurement error may be affected by differing approaches for assigning $PM_{10-2.5}$ exposure in these studies (Section 3.3.1).

6.3.3 Heart Failure and Impaired Heart Function

As noted above (Section 6.1.3), HF refers to a set of conditions in which the heart's pumping action is weakened. In congestive heart failure (CHF), the flow of blood from the heart slows, failing to meet the oxygen demands of the body, and returning blood can back up, causing swelling or edema in the lungs or other tissues (typically in the legs and ankles). Additional information on HF can be found in Section 6.1.3.

As detailed below, recent studies add to existing evidence from the 2009 PM ISA that increases in $PM_{10-2.5}$ concentrations are associated with increases in ED visits and hospital admissions for HF. However, results from copollutant models provide limited evidence that the observed associations are independent of other examined copollutants, including $PM_{2.5}$. Moreover, exposure measurement error remains an important uncertainty. There were no CHE or animal toxicological studies examining the relationship between short-term exposure to $PM_{10-2.5}$ and indicators of HF included in the 2009 PM ISA.

6.3.3.1 Emergency Department Visits and Hospital Admissions

The 2009 PM ISA reviewed one study examining the association between $PM_{10-2.5}$ and ED visits and hospital admissions for heart failure. In the Atlanta-based SOPHIA study, Metzger et al. (2004) observed weak and imprecise positive associations between coarse PM concentrations and ED visits for congestive heart failure (CHF). Since the release of the 2009 PM ISA, few recent studies are available for review. In the 110-county national Medicare cohort (MCAPS) study, Powell et al. (2015) reported a 0.40% (95% CI: -0.06, 0.87%) increase in heart failure hospitalizations associated with $PM_{10-2.5}$ concentrations on the same day (measured by the difference of collocated PM_{10} and $PM_{2.5}$ monitors). The association was attenuated in magnitude and precision, but still positive, in a two-pollutant model adjusting for $PM_{2.5}$. In a much smaller study in Taipei, Taiwan, Chen et al. (2015b) also observed positive associations between $PM_{10-2.5}$ (measured by the difference of collocated PM_{10} and $PM_{2.5}$ monitors) and CHF hospitalizations on both warm and cold days. The associations were robust in copollutant models adjusting for SO_2, and attenuated but still positive in two-pollutant models adjusting for NO_2, CO, and O_3. Overall, recent studies provide limited evidence supporting an association between $PM_{10-2.5}$ and ED visits and hospital admissions for heart failure. Results from copollutant models also provide limited evidence

that the observed associations are independent of other examined copollutants; however, additional studies would be useful in providing more certainty regarding the nature of the association and addressing potential exposure measurement error from $PM_{10-2.5}$ measurements.

6.3.3.2 Toxicology Studies of Impaired Heart Function

There were no animal toxicological studies in the 2009 PM ISA (U.S. EPA, 2009) that examined the effect of short-term exposure to $PM_{10-2.5}$ on heart function. Since the publication of that document, Aztatzi-Aguilar et al. (2015) did not find an appreciable difference relative to control animals in expression of alpha skeletal actin (Acta1), or collagen-3 (Col3a1), two genes know to respond during pathological states of cardiac damage. Thus, this study does not provide evidence of potential decreases in heart function following short-term $PM_{10-2.5}$ exposure. More information on this recently published study can be found in Table 6-55 below.

Table 6-55 Study specific details from toxicological studies of short-term $PM_{10-2.5}$ exposure and impaired heart function.

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult Sprague-Dawley rats, M, n = 4 per treatment group	$PM_{10-2.5}$: 107 µg/m^3 collected from a high traffic and industrial area north of Mexico City in early summer. 5 h/day for 3 days. Animals were sacrificed 24 h after final exposure.	Acta1 and Col3a1 gene expression

d = day, h = hour, n = number, f = female, M = male, Acta1 = skeletal alpha-actin, Col3a1 = collagen Type 3 alpha

6.3.4 Cardiac Electrophysiology, Arrhythmia, and Cardiac Arrest

Experimental and epidemiologic panel studies typically use surface ECGs to measure electrical activity in the heart resulting from depolarization and repolarization of the atria and ventricles. The *P* wave of the ECG represents atrial depolarization, while the QRS represents ventricular depolarization and the T wave, ventricular repolarization. See Section 6.1.4 for more information on ECG, arrhythmia, and experimental measures of conduction abnormalities.

In the 2009 PM ISA, the evidence for arrhythmia related to short-term exposures to $PM_{10-2.5}$ was limited to a study reporting no associations between short-term $PM_{10-2.5}$ exposure and the risk of hospitalization for arrhythmia, and a panel studies demonstrating positive associations for ventricular arrhythmias. Since the 2009 PM ISA, there have been a few epidemiologic studies examining the

relationship between short-term PM 10-2.5 exposure and arrhythmia related HA. Although these studies generally show positive associations, uncertainties with respect to copollutant confounding and exposure measurement error remain. In addition, two panel epidemiologic studies only provide limited evidence of associations between short-term exposure to $PM_{10-2.5}$ and indicators of arrhythmia.

With respect to cardiac arrest, there were no studies included in the 2009 PM ISA and studies published since the last review are limited and inconsistent. That is, there are only a few studies that examined this endpoint, and the results of those few studies are not in agreement.

6.3.4.1 Emergency Department Visits and Hospital Admissions for Arrhythmia and Out-of-Hospital Cardiac Arrest

A number of studies based on administrative databases evaluate the association between short-term $PM_{10-2.5}$ concentrations and the risk of hospital admissions for cardiac arrhythmias (also known as dysrhythmias). In these studies, a primary discharge diagnosis of ICD-9 427 has typically been used to identify hospital admissions for cardiac arrhythmias. ICD-9 427 includes a heterogeneous group of arrhythmias including paroxysmal ventricular or supraventricular tachycardia, atrial fibrillation and flutter, ventricular fibrillation and flutter, cardiac arrest, premature beats, and sinoatrial node dysfunction.

As reported in the 2009 PM ISA, Halonen et al. (2009) did not observe a positive association between $PM_{10-2.5}$ and risk of hospital admissions for arrhythmias in Helsinki, Finland. Since the 2009 PM ISA, there have been few recent studies published on the association between $PM_{10-2.5}$ exposure and arrhythmia. In a large national Medicare cohort (MCAPS) study, Powell et al. (2015) found a positive association between $PM_{10-2.5}$ and arrhythmia-related hospital admissions (ERR: 0.94% [95% CI: 0.40, 1.48%] associated with $PM_{10-2.5}$ concentrations on the same day, measured by the difference of collocated PM_{10} and $PM_{2.5}$ monitors). The association was robust to adjustment for $PM_{2.5}$ in a two-pollutant model. In Kaohsiung, Taiwan, Chen et al. (2015b) reported positive associations between $PM_{10-2.5}$ (measured by the difference of collocated PM_{10} and $PM_{2.5}$ monitors) and hospital admissions for arrhythmias on cool days. In copollutant models, the observed association was robust to adjustment for SO_2, NO_2, and O_3, and attenuated but still positive after adjustment for CO.

6.3.4.1.1 Out-of-Hospital Cardiac Arrest

The majority of out-of-hospital cardiac arrests are due to cardiac arrhythmias. The 2009 PM ISA did not review any epidemiologic studies of ambient $PM_{10-2.5}$ concentrations and risk of OHCA. More recent evidence is limited and inconsistent. In two recent studies, Rosenthal et al. (2013) and Raza et al. (2014) did not observe positive associations between $PM_{10-2.5}$ (measured by the difference of collocated PM_{10} and $PM_{2.5}$ monitors) and OHCA in Helsinki, Finland and Stockholm, Sweden, respectively. In contrast, Dennekamp et al. (2010) and Wichmann et al. (2013) observed positive and imprecise

associations between $PM_{10-2.5}$ and OHCA. Dennekamp et al. (2010) reported a 1.7% (95% CI: -1.8, 5.3%) increase in hospital admissions on the same day in Melbourne, Australia, while Wichmann et al. (2013) observed a 9.0% (95% CI: -0.7, 19.5%) increase in hospital admissions at Lag 3 in Copenhagen, Denmark.

6.3.4.2 Panel Epidemiologic Studies for Arrhythmia and Conduction Abnormalities

The evidence for associations between arrhythmia and conduction abnormalities and $PM_{10-2.5}$ is very limited across the current review and in the 2009 PM ISA (U.S. EPA, 2009). Metzger et al. (2007) published a study demonstrating positive associations between ventricular arrhythmias and exposure to $PM_{10-2.5}$ in patients in Atlanta, GA, as described in the 2009 PM ISA (U.S. EPA, 2009). A recently published study by Bartell et al. (2013) used personal, size-fractionated PM measurements and found that 24-hour $PM_{10-2.5}$ was associated with ventricular tachyarrhythmia (RR = 1.20; 95% CI: 0.90, 1.59), but null associations were observed for 1-day (RR = 0.87; 95% CI: 0.71, 1.06) or 2-day lags (RR = 0.97; 95% CI: 0.66, 1.44). Hampel et al. (2010) reported positive associations between 24-47-hour average $PM_{10-2.5}$, determined using the difference method, with QTc (0.8%; 95% CI: 0.3%, 1.3%), but not for 0-23-hour averages or 3- to 5-day averages.

6.3.5 Cerebrovascular Disease and Stroke

Cerebrovascular disease typically includes conditions classified under ICD10 codes I60-I69 (ICD 9: 430-438) such as hemorrhagic stroke, cerebral infarction (i.e., ischemic stroke) and occlusion of the pre-cerebral and cerebral arteries. Ischemic stroke results from an obstruction within a blood vessel that supplies oxygen to the brain, potentially leading to infarction, and accounts for the majority of all strokes (Goldberger et al., 2008). Hemorrhagic stroke is less common but results to a disproportionate amount of fatalities. Additional information on cerebrovascular disease and stroke can be found in Section 6.1.5.

The 2009 PM ISA did not review any epidemiologic studies of short-term exposure to $PM_{10-2.5}$ emergency department visits and hospital admissions visits for cerebrovascular disease (CBVD). In the current review, a limited number of studies provide inconsistent evidence regarding the presence of an association. Moreover, there are uncertainties with respect to copollutant confounding and exposure measurement error.

6.3.5.1 Emergency Department Visits and Hospital Admissions

A limited number of recent studies provide inconsistent evidence regarding the presence of an association between short-term $PM_{10-2.5}$ exposure and ED visits and hospital admissions for CBVD.

Studies in Rome, Italy (Alessandrini et al., 2013) and Kaohsiung, Taiwan (Chen et al., 2015b) reported some evidence of an association between short-term $PM_{10-2.5}$ concentrations and ED visits and hospital admissions for CBVD. Alessandrini et al. (2013) considered 26,557 hospital admissions for CBVD in the context of Saharan dust outbreaks, and observed a 1.6% (95% CI: -0.6, 3.8%) increase in risk of hospital admissions associated with $PM_{10-2.5}$ concentrations measured on the same day. The association was larger in magnitude, but less precise (i.e., wide 95% CIs) on days with high Saharan dust levels, though effect measure modification by Saharan dust level was not statistically significant. Chen et al. (2015b) also evaluated approximately 25,000 hospitalizations for CBVD and reported associations with $PM_{10-2.5}$ concentrations on both warm and cool days, with a larger magnitude association observed on warm days. The observed association on warm days was robust to adjustment for SO_2 and O_3, and attenuated but still positive after adjustment for NO_2 and CO in copollutant models. Additional studies conducted in China reported inconsistent evidence of an association (Huang et al., 2016; Qiu et al., 2013). Huang et al. (2016) reported a positive association between $PM_{10-2.5}$ concentrations and stroke ED visits (lag 0) when adjusted for CO, or NO_2 in Beijing, China. Additionally, when examining ischemic and hemorrhagic stroke subtypes Huang et al. (2016) observed positive associations at lag 0, while associations were attenuated but still positive, or null, at longer lag periods (lag 1 to lag 3). Furthermore, the authors also reported consistently stronger associations across lag periods for ED visits on days when the temperature was greater than 13.5ºC. In contrast to the studies in Rome, Kaohsiung and Beijing, a study of over 100,000 ED visits in Hong Kong, China reported a null association between CBVD hospital admissions and $PM_{10-2.5}$ concentrations (Qiu et al., 2013). One additional important uncertainty across the available studies remains the use of an indirect measure of $PM_{10-2.5}$ and the potential for exposure measurement error for $PM_{10-2.5}$ (Section 3.3.1). Overall, there remains limited and inconsistent evidence of an association between $PM_{10-2.5}$ and CBVD.

6.3.6 Blood Pressure and Hypertension

High blood pressure results in the increased force on the artery walls and can damage the blood vessels and increase risk for cardiovascular disease and stroke. Hypertension typically develops over years and is the clinically relevant blood pressure outcome, defined as SBP above 140 mm hg or DBP above 90 mm hg. That being said, small population-level changes in blood pressure, even in the absence of clinical hypertension, can have large effects on clinical outcome prevalence (Rose, 1985). Additional information on blood pressure and hypertension can be found in Section 6.1.6 and Section 6.2.7.

There was a single epidemiologic panel study in the 2009 PM ISA finding a decrease in SBP following short-term $PM_{10-2.5}$ exposure (U.S. EPA, 2009). Since the publication of the 2009 PM ISA, an epidemiologic panel study and a few CHE studies provide some evidence of an effect of short-term PM 10-2.5 exposure on measurements of blood pressure. In addition, an animal toxicological study also reported that short-term exposure to $PM_{10-2.5}$ could result in changes in the blood pressure regulating renin-angiotensin system at the mRNA level. Thus, studies published since the completion of the 2009

PM ISA provide some additional evidence that short-term exposure to $PM_{10-2.5}$ may result in changes in BP.

6.3.6.1 Panel Epidemiologic Studies of Changes in Blood Pressure (BP)

For the 2009 PM ISA (U.S. EPA, 2009), a single study was evaluated (Ebelt et al., 2005) that examined the association between BP and $PM_{10-2.5}$. Ebelt et al. (2005) reported decreases in SBP relative to $PM_{10-2.5}$ determined using the subtraction method. A recent panel study examined cardiovascular effects among people with diabetes and short-term exposure to $PM_{10-2.5}$ (calculated by the subtraction method) in Shanghai where daily averages of $PM_{2.5}$ and $PM_{10-2.5}$ during the study period were 60 ug/m^3 and 19 ug/m^3, respectively. Specific lags of 0-2, 3-6, 7-12, and 13-24 hours were positively associated with DBP but associations with SBP and PP across lags were null (Zhao et al., 2015).

6.3.6.2 Controlled Human Exposure Studies of Changes in Blood Pressure (BP)

In the 2009 PM ISA (U.S. EPA, 2009), there were no CHE studies that examined the effect of $PM_{10-2.5}$ on blood pressure. Since the last review, there have been studies examining changes in blood pressure in response to short-term exposure to urban (Byrd et al., 2016; Bellavia et al., 2013), as well as rural (Brook et al., 2014) $PM_{10-2.5}$.

In response to urban $PM_{10-2.5}$, Bellavia et al. (2013) reported small, but significant ($p = 0.03$) elevations in SBP, but not DBP. These results are generally in agreement with an additional study of urban $PM_{10-2.5}$. Byrd et al. (2016) found exposure to urban $PM_{10-2.5}$ resulted in small (~1-3 mm hg), increases in SBP ($p < 0.001$), DBP ($p < 0.001$), and pulse pressure ($p = 0.03$) when compared to FA.

Changes in blood pressure were also demonstrated in a CHE study of rural $PM_{10-2.5}$. Brook et al. (2014) reported an increase in both SBP ($p = 0.021$) and DBP ($p = 0.05$) during the exposure period when compared to FA (results were reiterated in (Morishita et al., 2015b)). In addition, pooled blood pressure results from (Brook et al., 2014)and (Byrd et al., 2016) showed that changes in blood pressure in response to urban $PM_{10-2.5}$ were on average significantly greater throughout $PM_{10-2.5}$ exposure than those changes observed throughout the exposure to rural $PM_{10-2.5}$ (Byrd et al., 2016) ($p < 0.001$).

The CHE studies presented in the current ISA provide evidence of a small, but reproducible effect of urban and rural $PM_{10-2.5}$ exposure on BP elevation in healthy adults. Biological components present in PM may at least partially account for changes in BP. That is, Zhong et al. (2015) examined whether PM effects on BP were associated with endotoxin and β-1,3-d-glucan present in PM. After adjusting for total exposure mass, results indicated endotoxin was associated with increases in SBP 30-minutes post exposure, and DBP for up to 20 hours post exposure. β-1,3-d-glucan was only associated with an increase

in DBP 30 minutes post exposure. Finally, increases in BP could also be associated with hypomethylation. Bellavia et al. (2013) found Toll Like Receptor 4 (TLR4) hypomethylation (which can be a marker for increased inflammation) in response to $PM_{10-2.5}$ CAP exposure and an association between TLR4 hypomethylation and increases in SBP and DBP. More information on studies published since the 2009 ISA can be found in Table 6-56 below.

Table 6-56 Study-specific details from controlled human exposure (CHE) studies of short-term $PM_{10-2.5}$ exposure and blood pressure (BP).

Study	Population	Exposure Details (Concentration; Duration)	Endpoints Examined
Bellavia et al. (2013)	Healthy adults n = 8 M, 7 F 18-60 yr old 27.7 ± NA	~200 µg/m^3 $PM_{10-2.5}$ for 130 min at rest PM collected from a busy street in Toronto, Canada	BP: 10 min pre, 5 min post DNA methylation: 1 h post
Byrd et al. (2016)	Healthy adults 20 M, 9 F; 18-50 yrs 30 ± 8.2,	164.2 ± 80.4 µg/m^3 $PM_{10-2.5}$ CAP for 2 h CAP from urban Dearborn, MI	BP: every 7 min during exposure, post, 2 h post Vascular function: post, 2 h post
Brook et al. (2014)	Healthy adults n = 16 M, 16 F; 18-46 yr 25.9 ± 6.6,	76.2 ± 51.5 µg/m^3 $PM_{10-2.5}$ for 2 h CAPs from rural Dexter, MI	BP: every 10 min during exposure, post, and 2 h post
Morishita et al. (2015b)	Healthy adults n = 16 M, 16 F; 18-46 yr 25.9 ± 6.6	76.2 ± 51.5 µg/m^3 $PM_{10-2.5}$ CAP for 2 h CAP from rural Dexter, MI	Relationship between $PM_{10-2.5}$ components and changes in BP
Zhong et al. (2015)	Healthy adults n = 23 M, 27 F; 18-60 yr	Endotoxin and B-1,3-d-glucan associated with 200 µg/m^3 $PM_{10-2.5}$ CAP exposure for 130 min at rest CAP collected from a heavy-traffic 4-lane street in Toronto	BP: pre, 0.5 h and 20 h post

Note: SD = standard deviation, M = male, F = female, n = number, h = hour, yr = year, CAP = concentrated ambient particle, BP = blood pressure.

6.3.6.3 Toxicology Studies of Changes in Blood Pressure (BP)

There were no animal toxicological studies in the 2009 PM ISA examining the effect of $PM_{10-2.5}$ CAP exposure on measures of BP. Since the publication of that document, Aztatzi-Aguilar et al. (2015) exposed rats to $PM_{10-2.5}$ and reported that Ace and B1r, but not At1r mRNA levels in the heart were increased ($p < 0.05$). Thus, there is limited evidence at the mRNA level that exposure to $PM_{10-2.5}$ can result in changes to the renin-angiotensin system which could then, effect blood pressure. More information on this study can be found in Table 6-57 below.

Table 6-57 Study specific details from toxicological studies of short-term $PM_{10-2.5}$ exposure and blood pressure (BP).

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult Sprague-Dawley rats, M, n = 4 per treatment group	Inhalation of 107 μg/m^3 $PM_{10-2.5}$ for 5 h/day for 3 days	angiotensin and bradykinin system gene expression

Notes: n = number, h = hour, d = day, M = male

6.3.7 Emergency Department Visits and Hospital Admission Studies of Cardiovascular-Related Effects

Many epidemiologic studies consider the composite endpoint of ED visits and hospital admissions for all cardiovascular diseases, including diseases of the circulatory system. This endpoint generally encompasses ED visits and hospital admissions for ischemic heart disease, MI, PVD, heart failure, arrhythmia, CBVD and stroke, and diseases of pulmonary circulation. A smaller body of studies examines the endpoint of cardiac diseases, a subset of CVD that specifically excludes hospitalizations for cerebrovascular disease, peripheral vascular disease, and other circulatory diseases not involving the heart or coronary circulation. The 2009 PM ISA reviewed a limited number of studies on $PM_{10-2.5}$ and CVD ED visits and HA. In 108 U.S. counties with collocated PM_{10} and $PM_{2.5}$ monitors, Peng et al. (2008) reported a 0.8% (95%: 0.6, 1.0%) increase in risk of CVD hospital admissions among Medicare beneficiaries associated with $PM_{10-2.5}$ concentrations on the same day. A positive association was also observed in six French cities, but the association was much less precise (Host et al., 2008). Tolbert et al. (2007) did not find evidence of an association between $PM_{10-2.5}$ exposure and CVD ED visits and hospital admissions in Atlanta, Georgia. Recent multicity studies focus on overall CVD visits and provide some evidence that $PM_{10-2.5}$ may be associated with increased risk of cardiovascular-related HA, while results from single-city studies are inconsistent (Table 6-58).

Table 6-58 Epidemiologic studies of short-term $PM_{10-2.5}$ exposure and hospital admission and emergency department visits for cardiovascular disease.

Study Reference, Location, Study Period, ICD Codes for Outcomes	Exposure Assessment	Mean $PM_{10-2.5}$ Concentrations $\mu g/m^3$	Effect Estimates (95% CI)	Copollutant Examination
†Powell et al. (2015) 110 U.S. Counties (1999-2010) ICD: 430-438, 428, 426-427, 410-414, 429, 440-448	Concentrations from monitors in county averaged Number NR $PM_{10-2.5}$ calculated by difference in PM_{10} and $PM_{2.5}$ (collocated)	24-h avg:12.78 75th: 15.84	Lag 0: 1.007 (1.005, 1.009)	Correlation (*r*): NA Copollutant models with: $PM_{2.5}$
†Stafoggia et al. (2013b) Eight European Cities (2001-2010) ICD: 390-459/I00-I99	Concentrations from monitors in city averaged Number NR $PM_{10-2.5}$ calculated by difference in PM_{10} and $PM_{2.5}$ (collocated)	24-h avg: 9.3 to 17.5 (across eight cities)	Lag 0-1: 1.007 (1.002, 1.013)	Correlation (*r*): NO_2: 0.17-0.57, $PM_{2.5}$: >0.5 Copollutant models with: O_3, NO_2, $PM_{2.5}$
†Lanzinger et al. (2016b) Five Central and Eastern European Cities (2011-2012; 2012-2013; 2013-2014 vary by city) ICD: I00-I99	1 monitor in Prague, other cities NR. $PM_{10-2.5}$ calculated by difference in PM_{10} and $PM_{2.5}$ (collocated)	24-h avg: 9.3 to 17.5 (across eight cities)	Lag 2-5: 1.030 (0.989, 1.074)	Correlation (*r*): $PM_{2.5}$: 0.40-0.61, PM_{10}: 0.58-0.78, NO_2: 0.37-0.43 Copollutant models with: NA
†Alessandrini et al. (2013) Rome, Italy (2001-2004) ICD: 390-429	1 monitor $PM_{10-2.5}$ calculated by difference in PM_{10} and $PM_{2.5}$ (collocated)	24-h avg: 14.6 and 20.7 on Saharan dust-free and dust-affected days, respectively	Lag 0-1: 1.036 (1.015, 1.058)	Correlation (*r*): $PM_{2.5}$: 0.25, PM_{10}: 0.83 Copollutant models with: NA
†Atkinson et al. (2010) London, England (2000-2005) ICD: I00-I99	1 monitor $PM_{10-2.5}$ calculated by difference in PM_{10} and $PM_{2.5}$ (collocated) Non-primary PM considered regional source, measured from primary to NO_X ratio	24-h avg Median: 7.0 IQR: 5.0 75th: 10.0	No quantitative results; results presented graphically. Null or negative associations at individual lags 0 through 6.	Correlation (*r*): PM_{10}: 0.52, $PM_{2.5}$: 0.22 Copollutant models with: NA

Table 6-58 (Continued): Epidemiologic studies of short-term $PM_{10-2.5}$ exposure and hospital admission and emergency department visits for cardiovascular disease.

Study Reference, Location, Study Period, ICD Codes for Outcomes	Exposure Assessment	Mean $PM_{10-2.5}$ Concentrations $\mu g/m^3$	Effect Estimates (95% CI)	Copollutant Examination
†Rodopoulou et al. (2014) Dona Ana County, New Mexico (2007-2010) ICD: 390-459	Concentrations from monitors in county averaged 3 monitors $PM_{10-2.5}$ calculated by difference in PM_{10} and $PM_{2.5}$	24-h avg: 9.4 Max: 368.5	Lag 1: 1.015 (0.993, 1.039)	Correlation (*r*): NA Copollutant models with: NA
†Qiu et al. (2013) Hong Kong, China (2000-2005) ICD: 390-459	1 monitor $PM_{10-2.5}$ calculated by difference in PM_{10} and $PM_{2.5}$ (collocated)	24-h avg: 16.6 75th: 20.9	Lag 0-1: 1.014 (1.005, 1.022)	Correlation (*r*): NA Copollutant models with: $PM_{2.5}$

NR = not reported, RR = relative risk, OR = odds ratio, HR = hazard ratio, IQR = interquartile range, max = maximum, %ile = percentile, SD = standard deviation, $PM_{2.5}$ = particulate matter with mean aerodynamic diameter $_{2.5}$ µm, $PM_{10-2.5}$ = particulate matter with mean aerodynamic diameter between $_{2.5}$ µm and 10 µm, PM_{10} = particulate matter with mean aerodynamic diameter 10 µm, CO = carbon monoxide, NO_2 = nitrogen dioxide, SO_2 = sulfur dioxide.

Studies are listed in the order that they are discussed in the text. †Studies published since the 2009 PM ISA. Effect estimates are standardized to a 10 $\mu g/m^3$ for 24-h avg. $PM_{2.5}$.

Several multicity studies provide evidence of an association between $PM_{10-2.5}$ concentrations and cardiovascular-related HA. In the U.S. MCAPS study, Powell et al. (2015) observed increases in same-day (lag 0) $PM_{10-2.5}$ concentrations were associated with a 0.69% (95% CI: 0.45%, 0.92%) higher rate of cardiovascular-related hospital admissions among Medicare beneficiaries. The association was diminished when longer lag periods were evaluated, and was unchanged after adjustment for $PM_{2.5}$ in copollutant models. The authors did not observe differences in associations between study regions in the observed associations when stratifying counties into Eastern and Western regions. The MED-PARTICLES study reported a similar positive association between $PM_{10-2.5}$ concentrations (lag 0-1) and cardiovascular-related hospital admissions in eight southern European cities (Stafoggia et al., 2013b). Similar to the findings from the U.S. MCAPS study, the association was not present at longer lags (0-5 and 2-5). The observed association was attenuated but still positive in copollutant models adjusted for $PM_{2.5}$ and NO_2. Conversely, in a study of five cities in Central and Eastern Europe, Lanzinger et al. (2016b) reported a positive association with a wide confidence interval for $PM_{10-2.5}$ concentrations averaged over a longer lag period (0-5), though no evidence of an association at a shorter lag period (0-1). In city-specific analyses, while effect estimates had wider confidence intervals, there was evidence of a higher-magnitude association in Augsburg, Germany compared to the other four cities (Lanzinger et al., 2016c).

Results from single-city studies have shown less consistent evidence for the relationship between short-term $PM_{10-2.5}$ exposure and cardiovascular-related ED visits and HA. In Rome, Italy, Alessandrini et

al. (2013) considered 26,557 hospital admissions for CVD in the context of Saharan dust outbreaks, and observed a 3.6% (95% CI: 1.5, 5.9%) increase in risk of hospitalization at lag 0-1. There was no evidence of effect modification by Saharan dust level. In another European study, Atkinson et al. (2010) reported a null association between $PM_{10-2.5}$ exposure and cardiovascular-related hospital admissions in London, England. In Dona Ana County, New Mexico, Rodopoulou et al. (2014) reported a positive association with ED visits (RR: 1.015, 95% CI: 0.993, 1.039, lag 1). A study in Hong Kong, China considered $PM_{10-2.5}$ concentrations in relation to cardiac diseases (Qiu et al., 2013). Qiu et al. (2013) observed a positive association, but the association attenuated to the null after adjustment for $PM_{2.5}$.

Overall, several recent studies report positive association between $PM_{10-2.5}$ and cardiovascular-related ED visits and HA; however, there is limited evidence to support that this association is independent of copollutant confounding. Based on limited evidence from these studies, observed associations tend to be most pronounced on the same day or previous day, with diminishing associations at longer lags. Results from recent single-city studies provide inconsistent evidence of an association. Additionally, it remains unclear how exposure measurement error may be affected by how $PM_{10-2.5}$ exposure is being assigned in these studies (Section 3.3.1).

6.3.8 Epidemiologic Studies of Cardiovascular Mortality

Studies that examine the association between short-term $PM_{10-2.5}$ exposure and cause-specific mortality outcomes, such as cardiovascular mortality, provide additional evidence for $PM_{10-2.5}$-related cardiovascular effects, specifically whether there is evidence of an overall continuum of effects. In the 2009 PM ISA, the majority of studies evaluated consisted of single-city studies, with only one U.S. based multicity study (Zanobetti and Schwartz, 2009) that examined the relationship between short-term $PM_{10-2.5}$ exposure and cardiovascular mortality. Across studies there was evidence of consistent positive associations with cardiovascular mortality even though studies used a variety of approaches to estimate $PM_{10-2.5}$ concentrations. Overall there was a limited evaluation of the potential confounding effects of gaseous pollutants and the influence of model specification on the associations observed.

Recent multicity epidemiologic studies provide additional evidence of consistent positive associations between short-term $PM_{10-2.5}$ exposure and cardiovascular mortality with the majority of evidence at lags 0-1 days. Unlike the studies evaluated in the 2009 PM ISA, some recent studies have also further evaluated the $PM_{10-2.5}$-cardiovascular mortality relationship by examining cause-specific cardiovascular mortality outcomes (e.g., stroke, heart failure, IHD) (Pascal et al., 2014; Samoli et al., 2014), but overall these studies are still limited in number. As a result, this section focuses on studies that examine the combination of all cardiovascular mortality outcomes and address uncertainties and limitations in the relationship between short-term $PM_{10-2.5}$ exposure and cardiovascular mortality, specifically: potential copollutant confounding, lag structure of associations, and effect modification by season and temperature.

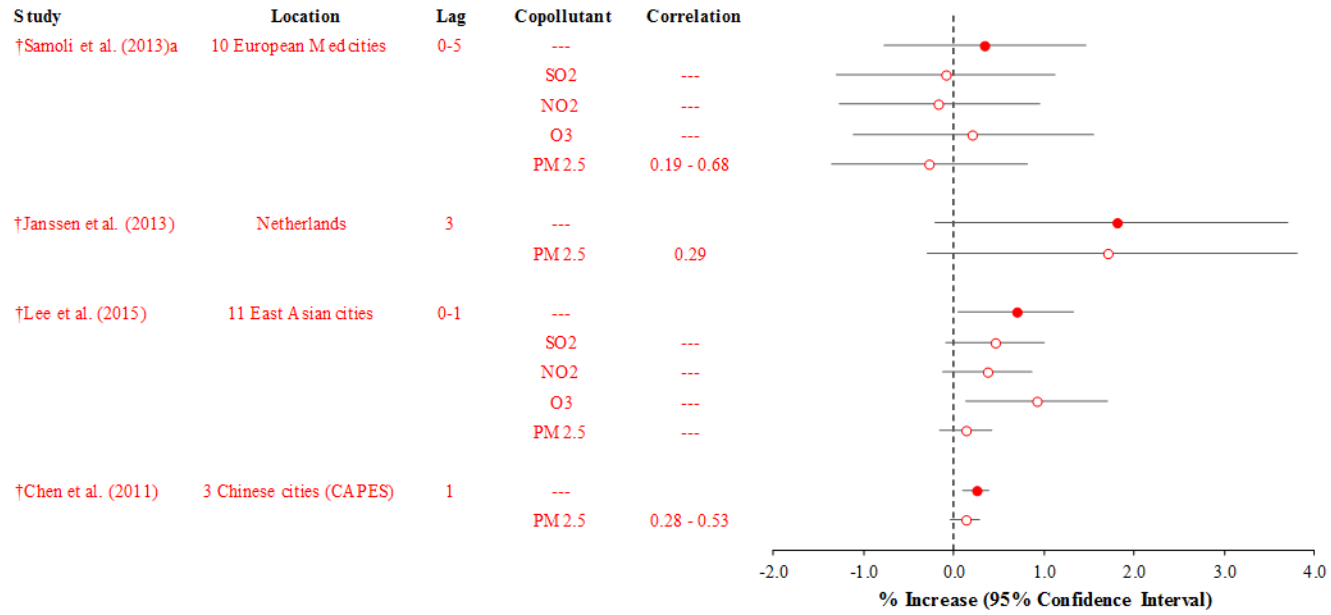
Characterizing the $PM_{10-2.5}$ Cardiovascular Mortality Relationship

Recent epidemiologic studies conducted additional analyses that address some of the uncertainties and limitations of the $PM_{10-2.5}$ – cardiovascular mortality relationship identified in the 2009 PM ISA. Specifically, recent studies provide additional information on copollutant confounding, lag structure of associations, and seasonal associations. However, similar to those studies evaluated in the 2009 PM ISA, the approaches used to estimate $PM_{10-2.5}$ concentrations varies across studies and it remains unclear if the level of exposure measurement error varies by each approach (see Table 11-9, Section 11.3). Overall, these studies provide initial evidence that: $PM_{10-2.5}$-cardiovascular mortality associations remain positive, but may be attenuated in copollutant models; $PM_{10-2.5}$ effects on cardiovascular mortality tend to occur within the first few days of exposure (i.e., lags 1 to 3 days), and associations are larger in magnitude during warmer months.

Copollutant Confounding

Consistent with the evaluation of total (nonaccidental) mortality, the studies evaluated in the 2009 PM ISA provided limited information on the potential confounding effects of gaseous pollutants and $PM_{2.5}$ on the relationship between short-term $PM_{10-2.5}$ exposure and cardiovascular mortality. Recent multicity studies (Lee et al., 2015a; Pascal et al., 2014; Janssen et al., 2013; Samoli et al., 2013; Malig and Ostro, 2009) and a meta-analysis (Adar et al., 2014) provide additional information concerning the role of copollutants on the $PM_{10-2.5}$-cardiovascular mortality relationship.

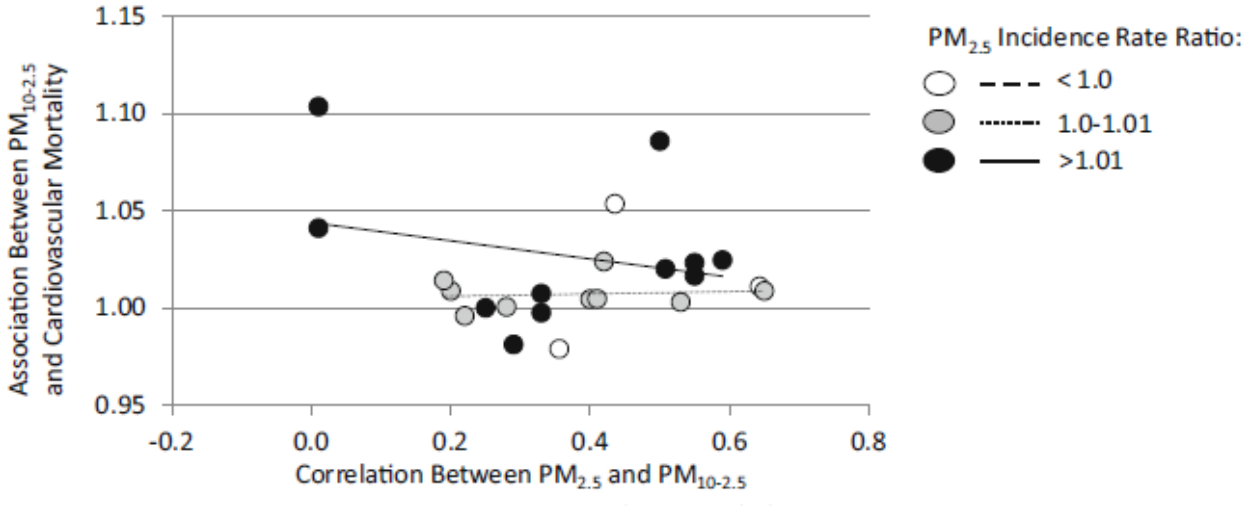
When focusing on potential copollutant confounding of the $PM_{10-2.5}$-cardiovascular mortality relationship by $PM_{2.5}$, there is evidence that the association generally remains positive, but is attenuated in some instances (Figure 6-31). Within the U.S., Malig and Ostro (2009) in a study of 15 California counties examined copollutant confounding, but only by $PM_{2.5}$. The authors observed that the pattern and magnitude of associations over single-day lags of 0 to 2 days was relatively unchanged in both models (quantitative results not presented), which is supported by the low correlation between $PM_{2.5}$ and $PM_{10-2.5}$ observed in this study (r = -0.03 to 0.35). The copollutant model results with $PM_{2.5}$ in Malig and Ostro (2009) are consistent with Janssen et al. (2013) in a study conducted in the Netherlands and Chen et al. (2011) in the CAPS study. However, these results are inconsistent with Lee et al. (2015a) in a study of 11 east Asian cities and Samoli et al. (2013) in a study of 10 European Mediterranean cities within the MED-PARTICLES project (Figure 6-31). The interpretation of $PM_{2.5}$ copollutant model results in Lee et al. (2015a) and Samoli et al. (2013) is complicated by the lack of information on the correlation between $PM_{2.5}$ and $PM_{10-2.5}$, and the examination of a longer lag (i.e., lag 0-5 days), respectively.



Note: †Studies published since the 2009 PM ISA. a = Copollutant results only presented for a lag of 0-5 days. Corresponding quantitative results are reported in Supplemental Table S6-22 (U.S. EPA, 2018).

Figure 6-31 Percent increase in cardiovascular mortality for a 10 μg/m^3 increase in 24-hour average $PM_{10-2.5}$ concentrations in single- and copollutant models.

The studies that provide evidence of a $PM_{10-2.5}$-cardiovascular mortality association that remains positive in copollutant models with $PM_{2.5}$ is supported by analyses conducted by Adar et al. (2014) in the context of a meta-analysis. When examining studies that conducted copollutant models with $PM_{2.5}$, Adar et al. (2014) observed that the $PM_{10-2.5}$-cardiovascular mortality association was similar in magnitude to that observed in single-pollutant models (quantitative results not provided). The results from copollutant models were further supported when stratifying $PM_{10-2.5}$-mortality estimates by the correlation with $PM_{2.5}$ (low, $r < 0.35$; medium, $r = 0.35$ to < 0.5; high, $r > 0.5$). The authors observed evidence of positive associations for the low and high correlation categories that were similar in magnitude, but had wide confidence intervals. However, there was no evidence of an association for the medium correlations. Adar et al. (2014) further examined potential copollutant confounding by $PM_{2.5}$ through an analysis focusing on whether $PM_{10-2.5}$-mortality associations were present when the correlation between $PM_{2.5}$ and $PM_{10-2.5}$ increased and when $PM_{2.5}$ was also associated with mortality. As highlighted in Figure 6-32 there was evidence of positive $PM_{10-2.5}$-cardiovascular mortality associations at both low and high correlations as well as low and high magnitudes of the $PM_{2.5}$-cardiovascular mortality association (Figure 6-32).



Source: Permission pending, Adapted from (Adar et al., 2014)

Figure 6-32 Associations between short-term $PM_{10-2.5}$ exposure and cardiovascular mortality as a function of the correlation between $PM_{10-2.5}$ and $PM_{2.5}$ stratified by strength of the association with $PM_{2.5}$.

Compared to the examination of potential copollutant confounding by $PM_{2.5}$, fewer studies examined the potential confounding effects of gaseous pollutants. Across studies there remains a limited evaluation of copollutant models with gaseous pollutants and their impact on the $PM_{10-2.5}$ – cardiovascular mortality relationship remains unclear (Figure 6-31). Similar to the analysis of potential copollutant confounding by $PM_{2.5}$, the assessment of gaseous pollutants is complicated by the lack of correlation information and the lag examined (i.e., lag 0-5 days).

Collectively, the recent epidemiologic studies that examined potential copollutant confounding along with the analyses conducted by Adar et al. (2014) provide initial evidence that $PM_{10-2.5}$-cardiovascular mortality associations remain positive in copollutant models with $PM_{2.5}$, but in some cases there is evidence of no association. Additionally, the limited number of studies that examined potential copollutant confounding by gaseous pollutants along with the lack of information on the correlation between $PM_{10-2.5}$ and gaseous pollutants does not allow for an adequate assessment as to whether they confound the $PM_{10-2.5}$-cardiovascular mortality association.

Lag Structure of Associations

Multicity epidemiologic studies that examined cause-specific mortality in the 2009 PM ISA observed immediate effects on cardiovascular mortality attributed to short-term $PM_{10-2.5}$ exposure with consistent positive associations observed at lags ranging from 0 to 1 day. However, the majority of these

studies either examined single-day lags or selected lags a prior. Recent multicity studies have conducted more extensive examinations of the lag structure of associations by examining multiple sequential single-day lags, or examining whether there is evidence of immediate (i.e., lag 0-1 days), delayed (i.e., lag 2-5 days), or prolonged (i.e., lag 0-5 days) effects of short-term $PM_{10-2.5}$ exposure on cardiovascular mortality.

Across the studies that examined single-Lag days, most of the studies focused on lags within the range of 0 to 2 days. Although a few studies extended out to a longer duration, collectively the studies provided evidence that was generally in agreement with one another. In the lone U.S. study, Malig and Ostro (2009) in 15 California counties observed the largest association at lag 2 (0.7% [95% CI: 0.1, 1.5]). These results are consistent with two studies conducted in Europe, Janssen et al. (2013) in the Netherlands where the largest association in terms of magnitude and precision was observed for lag 3 (1.8% [95% CI: -0.2, 3.7]), and Samoli et al. (2013) in the MED-PARTICLES project where the largest associations were observed at lags 1 and 2 (quantitative results not presented). Additionally, in a study conducted in Asia (i.e., CAPES) Chen et al. (2011) observed the largest association at lag 1. While the previous studies focused on a narrower number of single-day lags, Stafoggia et al. (2017), in a study of 8 European cities, examined single-day lags ranging from 0 to 10 days. Although the authors reported an association largest in magnitude at lag 1, they also found evidence of positive associations at lags 2 and 3, but no evidence of an association at longer lags. Instead of focusing on multiple single-day lags, Lee et al. (2015a) when examining 11 east Asian cities, examined a series of multi-day lags ranging from 0 to 4 days. Although positive associations were observed across all combinations of lags, the strongest association in terms of magnitude and precision was observed at lag 0-2 days (quantitative results not presented). The results across the studies that examined a series of single- and multi-day lags is confirmed by the meta-analysis by Adar et al. (2014) where an examination of single-day lag risk estimates across studies found positive associations across lags ranging from 0 to 2 days with the strongest association in terms of magnitude and precision occurring at lag 2.

Along with the examination of single-day lags, some studies also focused on a priori multi-day lag structures defined to be representative of immediate, delayed, and prolonged effects. However, in light of the single-day lag results the a priori lag structures institute breakpoints that complicate the interpretation of the combination of single-day and multi-day lag results. Lanzinger et al. (2016a) in the UFIREG study observed positive associations across all lag structures, but the confidence intervals were large due to the short study duration (lag 0-1: 1.9 % [95% CI: -4.8, 9.4]; lag 2-5: 8.9% [95% CI: 0.85, 17.8]; lag 0-5: 9.1% [95% CI: -1.3, 20.4]). The magnitude of associations in Lanzinger et al. (2016a) is much larger and shows a different pattern of associations than that observed in Samoli et al. (2013) where results tended to indicate that the majority of the effect on cardiovascular mortality due to short-term $PM_{10-2.5}$ exposures is immediate (lag 0-1: 0.28% [95% CI: -0.37, 0.93]; lag 2-5 and lag 0-5: 0.33%). Additionally, as noted above when examining single-day lags through a polynomial distributed lag model, Samoli et al. (2013) observed that associations were largest at lag 1 and 2 days.

Overall, studies that examined the lag structure of associations generally support that short-term $PM_{10-2.5}$ exposure contributes to cardiovascular mortality effects within the first few days after exposure, ranging from 1 to 3 days. Even though studies of multi-day lags that examined the timing of effects provide some initial evidence for a potential longer duration between exposure and effect, an examination of single-day lags over the same multi-day lag does not support this initial observation.

Effect Modification

Season

An examination of potential seasonal differences in associations between short-term $PM_{10-2.5}$ exposure and cardiovascular mortality in the 2009 PM ISA was limited to one U.S. multicity study (Zanobetti and Schwartz, 2009) that provided initial evidence of associations being larger in magnitude in the spring and summer. Although still limited in number, some recent multicity studies conducted an examination of potential seasonal differences in associations (Lee et al., 2015a; Pascal et al., 2014; Samoli et al., 2013).

Pascal et al. (2014) in a study of nine French cities examined associations at lag 0-1 across the four seasons and reported the largest associations in the summer (4.6% [95% CI: 2.3, 6.9]) and fall (3.3% [95% CI: 1.3, 5.1]) with no evidence of an association in the winter and spring. Instead of examining each individual season, Samoli et al. (2013) in the MED-PARTICLES project only examined warm (April – September) and cold months (October – March). When examining lag 0-5 days, the authors only observed evidence of an association during the warm season (0.48% [95% CI: -1.2, 2.2]), but confidence intervals were wide.

Although the studies that examined European cities provide consistent evidence of $PM_{10-2.5}$-cardiovasculr mortality associations being larger in magnitude during warmer months (i.e., summer), a study conducted in 11 east Asian cities observed a different pattern of associations. Lee et al. (2015a) reported that $PM_{10-2.5}$ associations with cardiovascular mortality were larger in the cold season (1.0% [95% CI: 0.26, 1.8]) compared to the warm (0.30% [95% CI: -0.30, 0.91]). It is unclear why these results differ from the other studies, but mean $PM_{10-2.5}$ concentrations and mean temperature tended to be higher across the cities in Lee et al. (2015a) compared to the cities in the other studies evaluated in this section. Overall, across studies the evidence for seasonal associations remains limited, but results indicate potentially larger associations during the warmer months.

Temperature

In addition to examining whether there is evidence that warm temperatures modify the $PM_{10-2.5}$-cardivoascular mortality relationship by conducting seasonal analyses, a recent study also examined whether there is evidence that high temperature days modify the $PM_{10-2.5}$-cardiovascular mortality relationship. Pascal et al. (2014) examined the impact of temperature on the $PM_{10-2.5}$-cardiovascular

mortality relationship across 9 French cities by comparing associations on warm and non-warm days where warm days were defined as those days where the mean temperature exceed the 97.5th percentile of the mean temperature distribution. When calculating the interaction ratio, which estimated the extra PM effect due to warm days, the authors observed no evidence of a positive or negative modifying effect of warm days on cardiovascular mortality.

6.3.9 Heart Rate (HR) and Heart Rate Variability (HRV)

Measured by ECG, HRV represents the degree of difference in the inter-beat intervals of successive heartbeats, and is an indicator of the balance between the sympathetic and parasympathetic arms of the autonomic nervous system (Rowan III et al., 2007). More information on HRV and measures of HRV can be found in Section 6.1.10.

In the 2009 PM ISA, there was limited evidence examining the relationship between short-term exposure to $PM_{10-2.5}$ and measurements of HRV and HR. Since the last review, results from a CHE study provides limited evidence that rural, but not urban $PM_{10-2.5}$ may alter HR and HRV.

6.3.9.1 Epidemiologic Panel Studies of Heart Rate (HR) and Heart Rate Variability (HRV)

In the 2009 PM ISA (U.S. EPA, 2009), there was limited evidence with inconsistent results for changes in HRV relative to short-term exposures to $PM_{10-2.5}$. One additional study has recently been published and found no association was observed between $PM_{10-2.5}$ (calculated as the difference between co-located monitors) and heart rate in asthma and COPD patients in New York City and Seattle; HRV was not examined (Hsu et al., 2011).

6.3.9.2 Controlled Human Exposure Studies of Heart Rate (HR) and Heart Rate Variability (HRV)

In the previous ISA, there were no CHE studies examining the effect of $PM_{10-2.5}$ on heart rate. More recently, Brook et al. (2014) reported significant, but modest increases in HR in response to rural $PM_{10-2.5}$ exposures ($P < 0.0001$). However, similar results were not observed in response to urban $PM_{10-2.5}$ exposure (Byrd et al., 2016). In total, there is some evidence from CHE studies relating modest changes in HR to rural, but not urban $PM_{10-2.5}$ exposure.

With respect to HRV, in the 2009 PM ISA a controlled human exposure study reported decreased SDNN after exposure to $PM_{10-2.5}$ CAPs (Graff et al., 2009). In a study published since the 2009 PM ISA, Brook et al. (2014) reported a decrease in HF ($p = 0.006$) and an increase in the LF/HF ratio ($p = 0.007$)

during exposure to rural $PM_{10-2.5}$. Statistically significant changes in SDNN and LF were not observed. In an additional study, no changes in time or frequency HRV metrics were reported in response to urban $PM_{10-2.5}$ exposure (Byrd et al., 2016). Taken together, the above CHE studies provide limited evidence relating changes in HRV to rural, but not urban $PM_{10-2.5}$. More information on studies published since the 2009 ISA can be found in Table 6-59 below.

Table 6-59 Study-specific details from controlled human exposure (CHE) studies of short-term $PM_{10-2.5}$ exposure and heart rate (HR) and heart rate variability (HRV).

Study	Population N, Sex; Age (Mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
Byrd et al. (2016)	Healthy adults 20 M, 9 F; 18-50 yrs 30 ± 8.2,	164.2 ± 80.4 µg/m^3 $PM_{10-2.5}$ CAP for 2 h from urban Dearborn, MI	HR: every 7 min during exposure, post, 2 h post HRV: during exposure
Brook et al. (2014)	Healthy adults n = 16 M, 16 F; 18-46 yrs 25.9 ± 6.6,	76.2 ± 51.5 µg/m^3 $PM_{10-2.5}$ for 2 h CAP from rural Dexter, MI	HR: every 10 min during exposure, post, and 2 h post HRV: during exposure, Vascular function: post, and 2h post

n = number, M = male, F = female, n = number, h = hour, CAP = concentrated ambient particle, HR = heart rate, HRV = heart rate variability

6.3.10 Systemic Inflammation and Oxidative Stress

As discussed in Section 6.1.1 and Section 6.1.11 systemic inflammation and oxidative stress have been linked to a number of cardiovascular-related outcomes. For example, circulating cytokines such as IL-6 can stimulate the liver to release inflammatory proteins and coagulation factors that can ultimately increase the risk of thrombosis and embolism. Similarly, oxidative stress can result in damage to healthy cells and blood vessels and a further increase in the inflammatory response. Thus, this section discusses the evidence for markers of systemic inflammation and oxidative stress following short-term $PM_{10-2.5}$ exposures.

In the previous review, one CHE study reported no change in plasma CRP following short-term $PM_{10-2.5}$ exposure. Since the last review, a few additional studies have examined this relationship and the results of these studies have largely been inconsistent. That being said, given the transient nature of markers of systemic inflammation (e.g., cytokine release) and the differences in methodological approaches across studies, this is to be expected.

6.3.10.1 Epidemiologic Panel Studies of Systemic Inflammation and Oxidative Stress

Wittkopp et al. (2013) and Huttunen et al. (2012) have recently published studies examining the relationship between $PM_{10-2.5}$ and biomarkers of inflammation and oxidative stress. Both studies included repeated measures in panels of older adults with pre-existing cardiovascular disease and reported that 1- to 5-day averages of $PM_{10-2.5}$ or 1- to 3-day lags of $PM_{10-2.5}$ were not associated with a number of biomarkers including CRP, IL12, IL8, IL6sR, and sTNFRII. While Wittkopp et al. (2013) conducted size-fractionated, residential monitoring for $PM_{10-2.5}$ at retirement communities where participants lived, Huttunen et al. (2012) used the difference method to estimate $PM_{10-2.5}$ from differentially located monitors, contributing to greater uncertainty in exposure measurement.

6.3.10.2 Controlled Human Exposure Studies of Systemic Inflammation and Oxidative Stress

Controlled human exposure studies from the 2009 PM ISA (U.S. EPA, 2009) examining systemic inflammation reported no change in plasma CRP levels following exposure to $PM_{10-2.5}$ CAPs with exercise (Graff et al., 2009).

A few recent CHE studies examined the potential for short-term exposure to $PM_{10-2.5}$ CAP to induce a variety of inflammatory markers such as white blood cells, cytokines, adhesion molecules, or blood markers of inflammation such as CRP. A couple of these studies did not find an association between $PM_{10-2.5}$ and the markers or inflammatory cells they examined (Liu et al., 2015a; Brook et al., 2013a). However, Behbod et al. (2013) reported increased leukocytes and neutrophils at 24 hours, but not 3-hours post exposure to urban $PM_{10-2.5}$ ($p < 0.05$). They also reported that increases in accompanying ambient endotoxin were associated with the increases in leukocytes. However, no changes in the inflammatory markers IL-6, or hs-CRP were reported.

In a different type of study, Maiseyeu et al. (2014) looked at the potential for exposure to $PM_{10-2.5}$ to result in increased inflammation and decreased anti-oxidant activity by impairing high density lipoprotein (HDL) function. Indeed, HDL plays an important role in vascular homeostasis through anti-inflammatory and anti-oxidant activities (Maiseyeu et al., 2014). Exposure to coarse CAP did not impair HDL function. Additional information on lipoproteins and lipedema can be found in the Metabolic Effects Chapter (CHAPTER 7).

Considered together, there is limited evidence that exposure to $PM_{10-2.5}$ may result in systemic inflammation. However, it should be noted that due to the transient nature of some of the inflammatory biomarkers analyzed, it is possible that different results would have been reported if samples had been analyzed at different time points.

With respect to oxidative stress, a single study since the 2009 PM ISA has addressed systemic oxidative stress after exposure to coarse PM. Liu et al. (2015a) studied the potential for exposure to $PM_{10-2.5}$ and endotoxin to change levels of biomarkers for lipid peroxidation (malondialdehyde [MDA]) or DNA oxidative damage (8-OHdG). Short-term exposure to $PM_{10-2.5}$ was not associated with levels of MDA in blood or in urine. However, exposure to $PM_{10-2.5}$ was associated with 8-OHdG levels in urine 1-hour post exposure. It was further noted that endotoxin present in the coarse fraction was also associated with 8-OHdG levels. Thus, there is limited evidence that short-term exposure to $PM_{10-2.5}$ and/or endotoxin can alter markers of oxidative stress. More information on studies published since the 2009 ISA can be found in Table 6-60 below.

Table 6-60 Study-specific details from CHE studies of short-term $PM_{10-2.5}$ exposure and inflammation and oxidative stress.

Study	Population N, Sex; Age Mean ± SD	Exposure Details (Concentration; Duration)	Endpoints Examined
Behbod et al. (2013)	Healthy adults N = 19 M; 16 F 18-60 yrs	~250 µg/m^3 fine CAP (0.1 to 2.5 microns) ~200 µg/m^3 course CAP (2.5 to 10 microns) For 130 min CAP from busy Toronto street Correlated effects with presence of endotoxin	Inflammatory cells and markers ~45 pre and 3h and 24 h after start of each exposure
(Brook et al., 2013a)	Healthy adults n = 16 M, 16 F; 18-50 yrs 25.9 ± 6.6,	76.2 ± 51.5 µg/m^3 $PM_{10-2.5}$ for 2 h CAPs from rural Dexter, MI	Inflammatory cells and markers of inflammation, circulating endothelial progenitor cells collected 2 and 20 h post
Liu et al. (2015a)	Healthy adults n = 50; 18-60 yrs 28 ± 9	238.4 ± 62.0 µg/m^3 fine cap 212.9 ± 52µg/m^3 course cap 135.8 ± 67.2 µg/m^3 ultrafine cap for 130 min individually	Inflammatory markers and Oxidative stress markers pre, 1 h, and 21 h post
Maiseyeu et al. (2014)	Healthy adults n = 16 M, 16 F; 18-46 yrs 25.9 ± 6.6	76.2 ± 51.5 µg/m3 $PM_{10-2.5}$ CAP for 2 h CAP from rural Dexter, MI	HDL lipoprotein function: post, 20 h post

Note: SD = standard deviation, M = male, F = female, n = number, h = hour, CAP = concentrated ambient particle, HDL = high density lipoproteins

6.3.11 Coagulation

Coagulation refers to the process by which blood changes from a liquid to a semi-solid state in order to form a clot. Increases in coagulation factors (e.g., fibrinogen) or decreases in anti-coagulation factors can promote clot formation, and thus, increase the potential for an embolism.

In the last review, there was limited and inconsistent evidence for coagulation following $PM_{10-2.5}$ exposure. Since the 2009 PM ISA, no new CHE studies have been published. However, there is limited evidence for coagulation following short-term $PM_{10-2.5}$ exposure across a few epidemiologic panel studies.

6.3.11.1 Panel Epidemiologic Studies of Coagulation

Overall, there is limited evidence examining associations between $PM_{10-2.5}$ and markers of coagulation in panel epidemiologic studies. There were no studies evaluated in the 2009 PM ISA, though there are some recently published studies. In a quasi-experimental study of 31 healthy volunteers in Utrecht assigned to different exposure locations, $PM_{10-2.5}$ was associated with a .22% increase in vWF (95% CI: 0.02, 0.41; per 13.50 $\mu g/m^3$) but not fibrinogen or platelet counts (Strak et al., 2013a). Another study examined associations between $PM_{10-2.5}$ in a panel of 52 older adult participants with ischemic heart disease and found positive associations between fibrinogen levels and 1-day lag of ambient $PM_{2.5}$-10 (Huttunen et al., 2012). Null associations were observed between short-term exposures to $PM_{10-2.5}$ and an array of circulating markers of coagulation among people with diabetes and short-term exposure to $PM_{10-2.5}$. Wang et al. (2015). These recently published studies all used $PM_{10-2.5}$ concentrations derived from the subtraction method, contributing to exposure measurement error.

6.3.11.2 Controlled Human Exposure Studies of Coagulation and Thrombosis

Thrombosis was discussed in one study from the 2009 PM ISA. Graff et al. (2009) reported a ~33% decrease in the clot dissolving protein tPA 20 hours post exposure per 10 $\mu g/m^3$ increase in $PM_{10-2.5}$ concentration ($p = 0.01$). However, levels of other clotting related proteins were unchanged in response to $PM_{10-2.5}$ exposure. Since the publication of the 2009 PM ISA, no additional CHE studies have examined the relationship between $PM_{10-2.5}$ exposure and coagulation or thrombosis.

6.3.12 Endothelial Dysfunction and Arterial Stiffness

Endothelial dysfunction is the physiological impairment of the inner lining of the blood vessels and is typically measured by FMD. Arterial stiffness is associated with a variety of cardiovascular risk

factors and outcomes (Laurent et al., 2006) and is best measured by pulse wave velocity (PWV). Both endothelial dysfunction and arterial stiffness are discussed in more detail in Section 6.1.13.

There were no studies from the 2009 PM ISA evaluating the relationship between short-term exposure to $PM_{10-2.5}$ and endothelial dysfunction or arterial stiffness. Since that document, CHE studies have examined measures of endothelial dysfunction following $PM_{10-2.5}$ exposure and found limited evidence of an effect only when evaluating biomarkers (i.e., no statistically significant effect was found on FMD). There was also no new evidence of arterial stiffness in recent studies examining the endpoint.

6.3.12.1 Controlled Human Exposure Studies of Impaired Vascular Function

In the current review there were studies that examined the relationship between short-term exposure to $PM_{10-2.5}$ and clinical measures of endothelial dysfunction, but no relationship was found (Byrd et al., 2016; Brook et al., 2014). In addition to these studies, there were a couple of CHE studies that examined biomarkers indicating the potential for endothelial dysfunction following short-term $PM_{10-2.5}$ exposure. Liu et al. (2015a) reported that exposure to $PM_{10-2.5}$ alone did not result in statistically significant increases in VEGF at 1-hour post-exposure in blood or urine. There were also no changes in blood for the biomarker ET-1. In an additional study, Brook et al. (2013a) reported an increase ($p = 0.008$) in endothelial progenitor cells (a potential indicator of vascular injury) at 20 hours relative to filtered air, but changes in neutrophils, lymphocytes, and VEGF levels at this time point were not statistically significant. Taken together there is limited evidence for an increase in biomarkers consistent with vascular dysfunction. However, in the studies that examined measures of dilation, no relationship was found. Thus, the relationship between endothelial dysfunction and short-term exposure to $PM_{10-2.5}$ remains uncertain.

Since the publication of the 2009 PM ISA, studies have examined whether $PM_{10-2.5}$ had appreciable effects on measures of arterial stiffness, but results were generally negative. More specifically, Byrd et al. (2016) found no changes in pulse wave velocity or the Aix. In addition, Brook et al. (2014) reported that exposure to rural coarse CAP resulted in no change in pulse wave velocity. More information on studies published since the 2009 ISA can be found in Table 6-61 below.

Table 6-61 Study-specific details from controlled human exposure (CHE) studies of short-term $PM_{10-2.5}$ exposure and impaired vascular function.

Study	Population N, Sex; Age Mean ± SD	Exposure Details Concentration; Duration	Endpoints Examined
Byrd et al. (2016)	Healthy adults 20 M, 9 F; 18-50 yrs 30 ± 8.2,	164.2 ± 80.4 µg/m^3 $PM_{10-2.5}$ CAPs for 2 h CAP from urban Dearborn, MI	Pulse wave analysis, pulse wave velocity, and pulse pressure: post, 2 h post
(Brook et al., 2013a)	Healthy adults n = 16 M, 16 F; 18-50 yrs 25.9 ± 6.6,	76.2 ± 51.5 µg/m^3 $PM_{10-2.5}$ for 2 h CAPs from rural Dexter, MI	VEGF and markers and circulating Endothelial progenitor cells from blood collected 2 and 20 h post
Brook et al. (2014)	Healthy adults n = 16 M, 16 F; 18-46 yrs 25.9 ± 6.6,	76.2 ± 51.5 µg/m^3 $PM_{10-2.5}$ for 2 h CAPs from rural Dexter, MI	Flow mediated dilation: post, and 2h post
Liu et al. (2015a)	Healthy adults n = 50; 18-60 yrs 28 ± 9	212.9 ± 52µg/m^3 $PM_{10-2.5}$ for 130 min	VEGF: 1 h and 21 h post

Note: SD = standard deviation, M = male, F = female, n = number, h = hour, CAP = concentrated ambient particle, VEGF = vascular endothelial growth factor

6.3.13 Summary and Causality Determination

The 2009 PM ISA found that the available evidence for short-term $PM_{10-2.5}$ exposure and cardiovascular effects was "suggestive of a causal relationship." This conclusion was based primarily on several epidemiologic studies reporting positive associations between short-term $PM_{10-2.5}$ exposure and cardiovascular effects including IHD hospitalizations, supraventricular ectopy, and changes in HRV. In addition, dust storm events resulting in high concentrations of crustal material were linked to increases in cardiovascular disease ED visits and hospital admissions. However, the 2009 PM ISA noted concerns with respect to the potential for exposure measurement error and copollutant confounding in these epidemiologic studies. In addition, there was limited evidence of cardiovascular effects from a small number of experimental studies that examined short-term $PM_{10-2.5}$ exposures. Thus, in the last review, key uncertainties included the potential for exposure measurement error, copollutant confounding, and limited evidence of biological plausibility for cardiovascular effects following inhalation exposure.

The evidence relating short-term $PM_{10-2.5}$ exposure and cardiovascular outcomes has expanded since the last review and now includes additional epidemiologic studies reporting positive associations with IHD, HA, and arrhythmia. However, key uncertainties related to copollutant confounding and exposure measurement error remain. In addition, uncertainties remain with respect to the biological plausibility of ED visits and hospital admissions for IHD and arrhythmia. Thus, when considered as a whole, the epidemiologic, CHE and animal toxicological evidence continues to be suggestive but not sufficient to infer a causal relationship between short-term $PM_{10-2.5}$ exposure and cardiovascular effects. The evidence supporting this determination of causality is discussed below and summarized in Table 6-62, using the framework for causality determination described in the Preamble to the ISAs (U.S. EPA, 2015).

Studies published since the 2009 PM ISA provide additional evidence of an association between short-term exposure to $PM_{10-2.5}$ and ED visits and/or hospital admissions for IHD. In the MCAPS study, $PM_{10-2.5}$ concentrations were associated with an increase in hospital admissions for IHD on the same day (Powell et al., 2015) and the association was unchanged in copollutant models adjusting for $PM_{2.5}$. Qiu et al. (2013) also observed a positive association, which persisted but lost precision after adjustment for $PM_{2.5}$. In Kaohsiung, Taiwan, Chen et al. (2015b) considered nearly 23,000 hospital admissions for IHD and reported positive associations on cool and warm days. The observed associations were generally robust to adjustment for NO_2, SO_2, CO, and O_3 in copollutant models. Thus, there are a few studies using copollutant models that suggest an independent effect of $PM_{10-2.5}$ on IHD-related HA. However, uncertainties with respect to copollutant confounding remain due to the overall evidence base for an independent effect of $PM_{10-2.5}$ being quite limited.

There are also a limited number of studies providing evidence of an associations between short-term exposure to $PM_{10-2.5}$ and ED visits and hospital admissions for arrhythmia (Section 6.3.4). However, appreciable uncertainties in these results remain given that none of these studies examined the potential for copollutant confounding with other size fractions of PM, and gaseous copollutant results are from a small number of studies conducted in Asia. It is also important to note that the approaches used to estimate $PM_{10-2.5}$ concentrations vary across the epidemiologic studies mentioned above (both for arrhythmia and IHD). Methods include using the difference of county-level averages of PM_{10} and $PM_{2.5}$ and the difference of PM_{10} and $PM_{2.5}$ measured at co-located monitors. It remains unclear how exposure measurement error might be impacted by each of these approaches.

A small number of CHE, epidemiologic panel, and animal toxicological studies provides some biological plausibility for a sequence of events that could potentially lead to $PM_{10-2.5}$-related ED visit and hospital admissions (Section 6.3.1). However, the evidence supporting most of the individual events in these pathways is quite limited and some of the epidemiologic panel studies used to support these pathways have the same measurement error uncertainties mentioned above. Also, when the evidence is evaluated as a whole, with the exception of small reproducible changes in BP (Section 6.3.6), the results of experimental and epidemiologic panel studies are largely inconsistent, or only provided limited

evidence of a relationship between cardiovascular endpoints and short-term $PM_{10-2.5}$ exposure. Thus, while there is more evidence for biological plausibility than in the 2009 PM ISA, this body of evidence is still quite limited and important uncertainties remain.

In summary, there were a small number of epidemiologic studies reporting positive associations between short-term exposure to $PM_{10-2.5}$ and cardiovascular-related ED visits and HA. However, there was limited evidence to suggest that these associations were biologically plausible, or independent of copollutant confounding. It also remains unclear how the approaches used to estimate $PM_{10-2.5}$ concentrations in epidemiologic studies may impact exposure measurement error. Taken together, the **evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10-2.5}$ exposures and cardiovascular effects.**

Table 6-62 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10-2.5}$ exposure and cardiovascular effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Evidence from multiple epidemiologic studies is generally supportive but not entirely consistent	Increases in ED visits and hospital admissions for IHD in multicity studies Increases in cardiovascular mortality in multicity studies conducted in the U.S., Europe, and Asia.	Powell et al. (2015); Section 6.3.2 Section 6.3.8	12.8 μg/m^3
Generally, consistent evidence from CHE studies	Small consistent changes in blood pressure	Section 6.3.6.2	~75.2-200 μg/m^3
Limited and supportive evidence from panel, controlled human exposure, and toxicological studies	Limited evidence for changes in HRV, systemic inflammation, coagulation factors, vascular function	Section 6.3.9 Section 6.3.10 Section 6.3.11 Section 6.3.12	See Tables in identified sections

Table 6-62 (Continued): Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10-2.5}$ exposure and cardiovascular effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Epidemiologic evidence from copollutant models provides some support for an independent $PM_{10-2.5}$ association	$PM_{10-2.5}$ associations are generally robust, but there are some instances of attenuation in copollutant models with gaseous pollutants and $PM_{2.5}$. However, there is limited information on the correlation between $PM_{10-2.5}$ and gaseous pollutants complicating the interpretation of results. Copollutant analyses with cardiovascular mortality are limited to studies conducted in Europe and Asia and indicate that $PM_{10-2.5}$ associations generally remain positive, although attenuated in some instances. When reported, correlations with gaseous copollutants were primarily in the low (r < 0.4) to moderate ($r \geq 0.4$ or < 0.7) range.	Powell et al. (2015); Qiu et al. (2013); Chen et al. (2015b) Figure 6-31	
Uncertainty regarding exposure measurement error	Across studies $PM_{10-2.5}$ concentrations are measured using a number of approaches (i.e., directly measured from dichotomous sampler, different between PM_{10} and $PM_{2.5}$ at collocated monitors, and difference of area-wide concentrations of PM_{10} and $PM_{2.5}$), which have not been compared in terms of whether they have similar spatial and temporal correlations.		
Limited evidence for biological plausibility of cardiovascular effects	Studies for a given health endpoint are largely inconsistent, or only provide limited evidence of a relationship between cardiovascular endpoints and $PM_{10-2.5}$ exposure. Some epidemiologic panel studies are also subject to the exposure measurement error discussed in this section.	Section 6.3.1 Figure 6-30	

a = Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

b = Describes the key evidence and references, supporting or contradicting, contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

c = Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

6.4 Long-Term $PM_{10-2.5}$ Exposure and Cardiovascular Effects

The evidence relating to the long-term effects of exposure to $PM_{10-2.5}$ on the cardiovascular system was characterized as "inadequate to infer the presence or absence of a causal relationship" in the 2009 PM ISA (U.S. EPA, 2009). A cause specific mortality study found a positive association with CHD

mortality among women enrolled in AHSMOG while another study of women (WHI) reported no association between $PM_{10-2.5}$ and cardiovascular events. Experimental studies demonstrating a direct effect of $PM_{10-2.5}$ on the cardiovascular system were lacking.

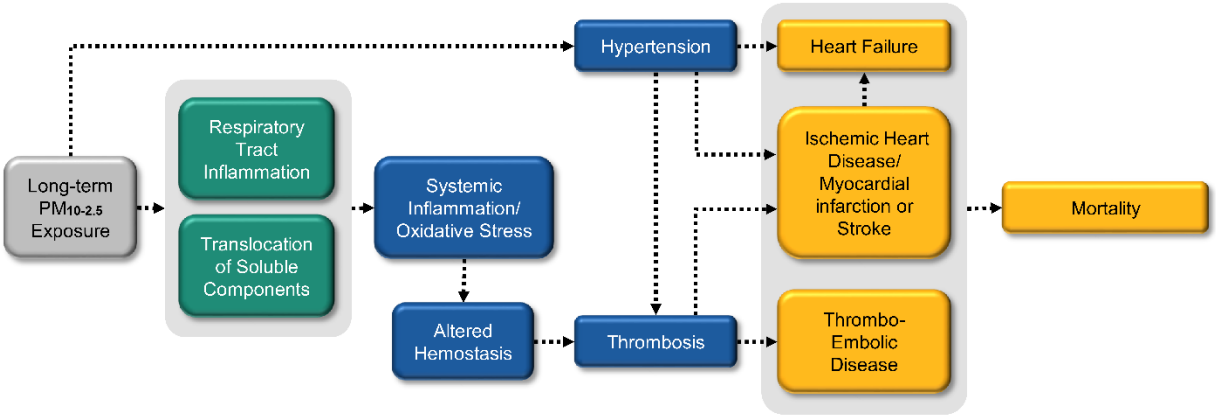
Evidence published since the completion of the 2009 PM ISA is also suggestive of a causal relationship between long-term exposures to $PM_{10-2.5}$ and cardiovascular effects. Since the publication of the 2009 PM ISA, the epidemiologic literature has grown and evidence is currently available on the relationship between exposure to long-term $PM_{10-2.5}$ and cardiovascular outcomes including MI and stroke, blood pressure and atherosclerosis. However, the overall epidemiologic evidence base is limited and uncertainties remain with respect to the potential for co-pollutant confounding. In addition, there continues to be a lack of toxicological evidence to support the associations reported in epidemiologic studies.

The subsections below provide an evaluation of the most policy relevant scientific evidence relating-long-tern $PM_{10-2.5}$ exposure to cardiovascular health effects. To clearly characterize and put this evidence into context, there is first a discussion of the biological plausibility of cardiovascular effects following long-tern $PM_{10-2.5}$ exposure (Section 6.4.1). Following this discussion, the health evidence relating long-tern $PM_{10-2.5}$ exposure and specific cardiovascular health outcomes is discussed in detail: ischemic heart disease and myocardial infarction (Section 6.4.2), heart failure and impaired heart function (Section 6.4.3), cerebral vascular disease and stroke (Section 6.4.4) atherosclerosis (Section 6.4.5), blood pressure and hypertension (Section 6.4.6), peripheral vascular disease (PVD), venous thromboembolism and pulmonary embolisms (Section 6.4.7) and cardiovascular-related mortality (Section 6.4.8). The evidence for an effect of $PM_{10-2.5}$ exposure on systemic inflammation and oxidative stress is also discussed (Section 6.4.9). Finally, the collective body of evidence is integrated across and within scientific disciplines[65], and the rationale for the causality determination is outlined in Section 6.4.10.

6.4.1 Biological Plausibility

This subsection describes the biological pathways that potentially underlie cardiovascular health effects resulting from long-term inhalation exposure to $PM_{10-2.5}$. Figure 6-33 graphically depicts these proposed pathways as a continuum of pathophysiological responses- connected by arrows- that may ultimately lead to the apical cardiovascular events observed in epidemiologic studies. This discussion of "how" long-term exposure to $PM_{10-2.5}$ may lead to these cardiovascular events also provides some biological plausibility for the epidemiologic results reported later in Section 6.4. In addition, most studies cited in this subsection are discussed in greater detail throughout Section 6.4.

[65] As detailed in the Preface, risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{10-2.5}$ concentrations unless otherwise noted.



Note: the boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 6-33 Potential biological pathways for cardiovascular effects following long-term exposure to $PM_{10-2.5}$.

When considering the available health evidence, there is a plausible pathway connecting long-term exposure to $PM_{10-2.5}$ to the apical events reported in epidemiologic studies (Figure 6-33). This pathway is described below and generally begins as respiratory tract inflammation leading to systemic inflammation.[66]

Long-term inhalation exposure to $PM_{10-2.5}$ may result in respiratory tract inflammation and oxidative stress (CHAPTER 5). Inflammatory mediators such as cytokines produced in the respiratory tract can potentially enter the circulatory system where they may cause distal pathophysiological responses such as changes in hemostasis (see Section 6.1.1). Thus, it noteworthy that following long-term exposure to $PM_{10-2.5}$, there is limited evidence from an epidemiologic study for systemic inflammation (Lanki et al., 2015) and altered hemostasis (Lanki et al., 2015). Therefore, thrombosis could conceivably occur, potentially contributing to the development of IHD, stroke, or thromboembolic disease elsewhere in the body (as previously described in Section 6.1.1). There is also evidence from epidemiologic studies that long-term exposure to $PM_{10-2.5}$ is associated with elevated blood pressure/hypertension risk (Chen et al., 2015a; Mu et al., 2014). Hypertension may also result in pathways that can contribute to the development of IHD, HF, stroke, or thromboembolic disease elsewhere in the body (as previously described in Section 6.1.1).

[66] It is also possible that soluble particle components can translocate directly into the circulatory system (Chapter 4) and lead to systemic inflammation, although the extent to which particle translocation occurs remains unclear.

Taken together, there is a small amount of evidence connecting long-term $PM_{10-2.5}$ exposure to cardiovascular health effects. That said, gaps in the proposed pathway exist. For example, there is a lack of evidence for how long-term $PM_{10-2.5}$ exposure may result in hypertension. Thus, there is only limited biological plausibility for the apical results reported in epidemiologic studies following long-term $PM_{10-2.5}$ exposure. This information will be used to inform a causal determination, which is discussed later in the chapter (Section 6.4.10).

6.4.2 Ischemic Heart Disease and Myocardial Infarction

Ischemic heart disease (IHD) is typically caused by atherosclerosis, which can result in the blockage of the coronary arteries and restriction of blood flow to the heart muscle potentially leading myocardial infarction (MI) or heart attack (Section 6.2.2). The evidence relating to the effect of $PM_{10-2.5}$ on the cardiovascular system included in the 2009 PM ISA was limited to a study of post-menopausal women enrolled in the WHI. The primary objective of this study (Miller et al., 2007) was to examine the cardiovascular health effects of long-term exposure to $PM_{2.5}$; however, results for $PM_{10-2.5}$ were also reported. No association between $PM_{10-2.5}$ and cardiovascular events was observed [HR: 0.99 (95%CI: 0.95, 1.03)]. Since the completion of the 2009 PM ISA, several epidemiologic studies reporting associations with $PM_{10-2.5}$, including some with comparable female populations, have been published. Among the limited number of studies currently available, positive associations were not consistently observed (Table 6-63, Figure 6-34).

Table 6-63 Characteristics of the studies examining the association between long-term $PM_{10-2.5}$ exposures and ischemic heart disease.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
(Miller et al., 2007) 36 metro areas, U.S. Prospective cohort $PM_{10-2.5}$: 2000 Follow-up: 1994-1998	WHI N = 65,893, women Median follow-up: 6 yrs	Annual avg of closest monitor (2000) Most participants within 10 km of monitor	NR	CVD event (MI, coronary revascularization, stroke, death from CHD, CBVD) Medical record review by physician adjudicators	Multipollutant model: $PM_{2.5}$, CO, SO2, NO_2, O_3 Copollutant correlations: NR
†(Hart et al., 2015b) U.S. (all contiguous states) Prospective cohort $PM_{10-2.5}$: 1989-2006 (sensitivity analyses restricting data to the years 2000-2006) Follow-up: 1988-2006	NHS N = 114,537 Follow-up: ~16 yrs	Annual avg, spatiotemporal model, $PM_{10-2.5}$ estimated by subtraction of monthly $PM_{2.5}$ from PM_{10}; time-varying exposure assigned based on residential address (C-V R^2 = 0.59, PM_{10}; 0.76 and 0.77 pre- (limited $PM_{2.5}$ data) and post 1999, respectively)	Mean 1989-2006: 8.7 (SD 4.5) Mean 2000-2006: 7.3 (SD 4.1)	Self-reported physician diagnosed CHD	Copollutant correlations: $PM_{2.5}$: r = 0.2; PM_{10}: r = 0.86
†(Puett et al., 2011) Northeast and Midwest, US (13 contiguous states) Prospective cohort $PM_{10-2.5}$: 1988-2002 Follow-up: 1989-Jan 2003	Health Professionals Follow-up Study N = 51,529 Avg follow-up NR	Annual avg estimated using spatiotemporal models for 2 time periods; C-V R^2 = 0.39, precision = 5.5 µg/m^3) see Yanosky et al. (2009) for details	Mean: 10.1 (SD: 3.3) IQR: 4.3	Non-fatal MI (medical record review)	Copollutant model: $PM_{2.5}$ Copollutant correlations: NR

Table 6-63 (Continued): Characteristics of the studies examining the association between long-term $PM_{10-2.5}$ exposures and ischemic heart disease.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Cesaroni et al. (2014) 11 Cohorts in Finland, Sweden, Italy, Denmark and Germany Prospective cohort $PM_{2.5}$: 2008-2011 Follow-up: 1992-2007, depending on cohort	ESCAPE N = 100,166 Avg follow-up: 11.5 yrs	Annual avg, LUR with measurements from 20 locations per study area Model performance R^2 ≥0.61	Mean ranged from 7.3 (SD = 1.3) to 31 (1.7)	IHD (hospital records) ICD9 410, 411	Copollutant model: $PM_{2.5}$ Copollutant correlations: NR
(Hoffmann et al., 2015) Prospective cohort $PM_{10-2.5}$: 2008-2009 Outcome: 2000/03-2012	HNR study N = 4,433	Multi-year avg (baseline) using LUR to estimate concentration at residential address	9.99 (SD: 1.83)	Self-reported coronary events with expert evaluation	Copollutant model: $PM_{2.5}$ Copollutant correlations: NR
†(Tonne et al., 2015) Greater, London Prospective cohort $PM_{10-2.5}$: 2003-2010 Follow-up: 2003/07 - 2010	MINAP (MI Survivors) N = 18,138 Avg follow-up 4 yrs	Annual avg estimated using dispersion models (20 by 20 m grid) time-varying exposure assigned within 100 m of patients' residential postal code centroid	Mean: 8.6 (SD: (0.7); IQR: 0.9	Readmission for STEMI or non-STEMI and death combined	Copollutant model: NR Copollutant correlations: $PM_{2.5}$ r = 0.70; PM_{10} r = 0.87; O_3 r = -0.88, NO_X r = 0.94; NO_2 r = 0.93

Avg = average, C-V = cross validation, ESCAPE = European Study of Air Pollution Exposure, HPFU = Health Professionals Follow-up Study, HNR = Heinz Nixdorf Recall study, LUR = land use regression, MI = myocardial infarction, NHS = Nurses' Health Study, N, n = number of subjects, NR = not reported, SD = standard deviation, STEMI = ST elevation myocardial infarction

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

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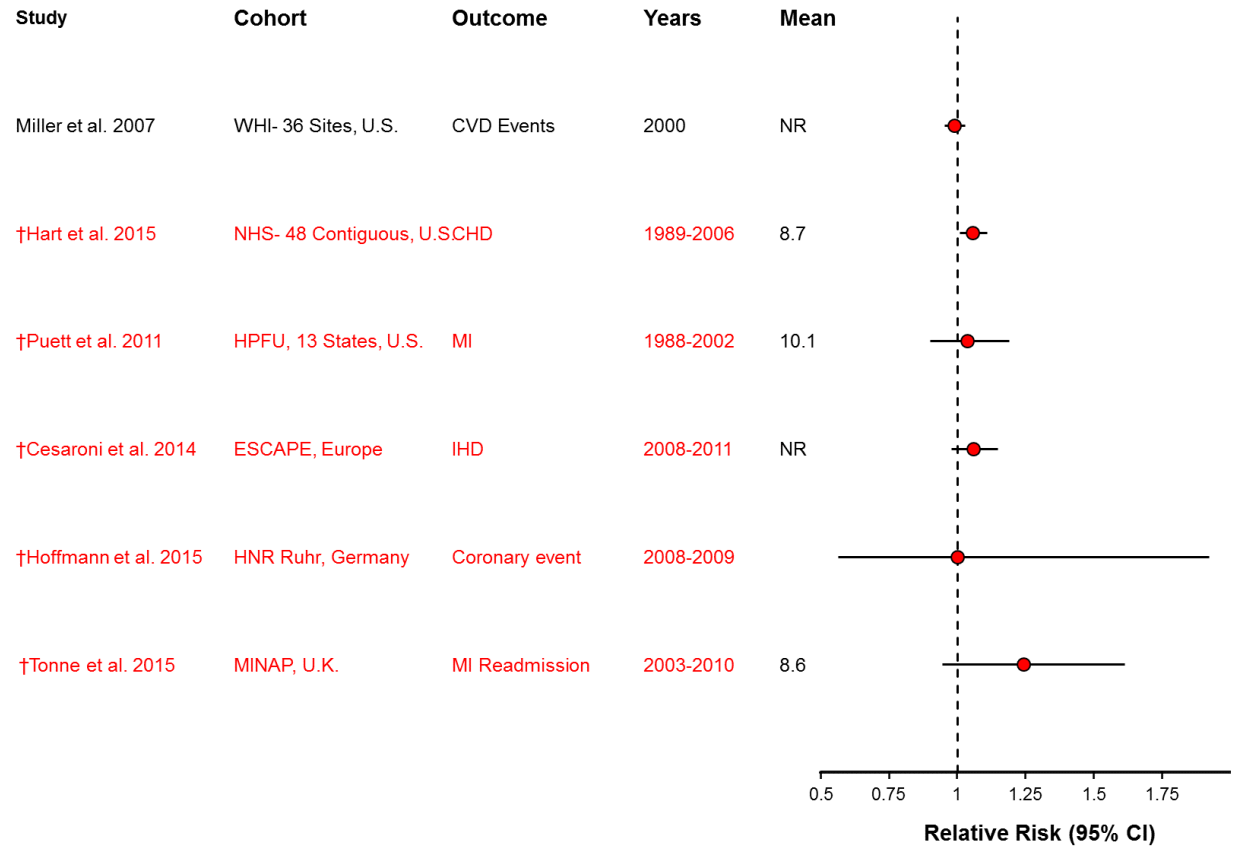
Hart et al. (2015b) examined data from the NHS, a cohort of women, 30-55 years old at enrollment, and observed positive associations of $PM_{10-2.5}$ with CHD [HR: 1.06 (95% CI: 1.01, 1.11)] Associations were less precise and somewhat attenuated in a sensitivity analysis restricted to exposure data that were relatively complete. Associations between $PM_{10-2.5}$ and CHD [HR: 1.07 (95%CI: 1.00, 1.14) vs. 0.96 (95%CI: 0.92, 1.0)] were present among women with diabetes, respectively. Effect modification by diabetes did not persist for CHD when analyses were restricted to the years with relatively complete exposure data. Larger associations of $PM_{10-2.5}$ with CHD were observed in the northeast compared to other regions. In a study of male health professionals Puett et al. (2011), a small increased risk for nonfatal MI was observed [HR: 1.04 (95%CI: 0.90, 1.19)]. There was no association after adjustment for $PM_{2.5}$, however [HR: 1.00 (95%CI: 0.85, 1.18)].

Cesaroni et al. (2014) reported an increased risk for the association between $PM_{10-2.5}$ and IHD [HR: 1.06 (0.98, 1.15)] in their meta-analysis of the 11 cohorts in the ESCAPE project. Heterogeneity in the effect estimates was observed across cohorts. In a separate analysis of one of the ESCAPE cohorts, Hoffmann et al. (2015) reported an inverse association of $PM_{10-2.5}$ exposure with coronary events [HR: 0.78 (95%CI: 0.33, 1.82)] in fully adjusted models that considered covariates including noise. Tonne et al. (2015) reported an association between $PM_{10-2.5}$ and readmission for MI in the MINAP study in the U.K. [HR: 1.24 (95%CI: 0.95, 1.61)].



†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Mean concentrations in $\mu g/m^3$. Hazard Ratios are standardized to a 5 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations. Corresponding quantitative results are reported in Supplemental Table 6S-16 (U.S. EPA, 2018). CTS = California Teachers Study; ESCAPE = European Study of Cohorts for Air Pollution; HPFU = Health Professionals Follow-up Study; IHD = Ischemic Heart Disease; HNR = Heinz Nixdorf Recall study; MINAP = Myocardial Ischemia National Audit Project; MI = Myocardial Infarction; NR=not reported; NHS = Nurses' Health Study; WHI = Women's Health Initiative.

Figure 6-34 Associations between long-term exposure to $PM_{10-2.5}$ and ischemic heart disease. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration.

6.4.3 Heart Failure and Impaired Heart Function

There were no studies of the effect of long-term exposure to $PM_{10-2.5}$ on heart failure or impaired heart function in the 2009 PM ISA (U.S. EPA, 2009).

6.4.3.1 Epidemiologic Studies

The E/E ratio is the ratio of peak early diastolic filling velocity to peak early diastolic mitral annulus velocity and a value less than eight indicates normal diastolic function and left atrial volume index (LAVI) is an indicator of diastolic function severity (Section 6.3.5). D'Souza et al. (2017) reported small imprecise increases in RV mass overall [0.91 g (95%CI: -2.95, 5.00] but larger increases were found among current smokers [2.05 g (95%CI: 0.23, 3.86] and those with emphysema [3.18 g [95%CI: 0.91, 5.68]. Ohlwein et al. (2016) conducted a cross-sectional analysis of the SALIA cohort to determine the association of long-term $PM_{10-2.5}$ with these two metrics. The mean ratios comparing 3rd to the 1st quartile of exposure for $PM_{10-2.5}$ were 1.03 (95%CI: 0.89, 1.18) for E/E and 1.06 (95%CI: 0.92, 1.21) for LAVI.

Table 6-64 Characteristics of the studies examining the association between long-term $PM_{10-2.5}$ exposures and heart failure.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†(Ohlwein et al., 2016) Cross-sectional $PM_{10-2.5}$: 2008-2009 Baseline: 2007/10	SALIA N = 402 69-79 yrs	LUR fit from differences between PM_{10} and $PM_{2.5}$ concentrations to estimate exposure at residence Model fit R2 = 0.66, cross-validation R2 = 0.57	Median: 9.1 (IQR: 8.6-10.4)	E/E" ratio LAVI (Tissue Doppler)	Correlations: NR
†(D'Souza et al., 2017) $PM_{10-2.5}$ mass and components	MESA N = 1,490 45-84 yrs	LUR fit from differences between P_{M10} and $PM_{2.5}$ concentrations to estimate 5-yr concentration at residence	Mean: 4.9 SD: 1.6	RV mass, volume, EF	2-pollutant models $PM_{2.5}$ and NO_2

MESA = Multi Ethnic Study of Atherosclerosis; SALIA = Study on the Influence of Air Pollution on Lung ; LUR = land use regression; E/E' = ratio of peak early diastolic filling velocity and peak early diastolic mitral annulus velocity; LAVI = Left Atrial Volume Index; RV = right ventricle; EF = ejection fraction

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

6.4.3.2 Toxicology Studies of Impaired Heart Function

In the 2009 PM ISA there was one study (Lemos et al., 2006) that reported heart muscle hypertrophy for Balb/c mice exposed to PM_{10} for 4 months. Since the 2009 PM ISA, Aztatzi-Aguilar et al. (2015) reported that short-term $PM_{10-2.5}$ exposure in rats resulted in thickening of the coronary artery wall ($p < 0.05$). However, the authors did not report increases in expression of two genes typically associated with cardiac damage: Acta1 and Col3a. Nonetheless, there is limited evidence from animal toxicological studies for the potential for decreases in heart function following long-term $PM_{10-2.5}$ exposure. More information on this recently published study can be found in Table 6-65 below.

Table 6-65 Study specific details from toxicological studies of long-term $PM_{10-2.5}$ exposure and impaired heart function impaired heart function.

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Sprague-Dawley rats, M n = 4 per group)	Inhalation of 32 µg/m^3 $PM_{10-2.5}$ collected from a high traffic and industrial area north of Mexico City in early summer and exposed for 5 h/day, 4 days/week for 8 weeks	Coronary wall thickness Acta1 and Col3a gene expression

n = number, h = hour, d = day, week = week, M = male, f = female, Acta1 = skeletal alpha-actin, Col3a1 = collagen Type 3 alpha

6.4.4 Cerebrovascular Disease and Stroke

Cerebrovascular disease typically includes conditions such as hemorrhagic stroke, cerebral infarction (i.e., ischemic stroke) and occlusion of the pre-cerebral and cerebral arteries (Section 6.3.35). Only the WHI analysis reporting a positive association with stroke was available for inclusion in the 2009 PM ISA. Of the limited number of recent epidemiologic studies examining the relationship between $PM_{10-2.5}$ and stroke, there were some observations of positive associations (Table 6-66, Figure 6-35).

Table 6-66 Characteristics of the studies examining the association between long-term $PM_{10-2.5}$ exposures and stroke.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
Miller et al. (2007) 36 metro areas, U.S. Prospective cohort $PM_{10-2.5}$: 2000 Follow-up: 1994-1998	WHI observational cohort N = 65,893 Median follow-up: 6 yrs	Annual avg of closest monitor (2000) Most women within 10 km of monitor	NR	CVD event (MI, coronary revascularization, stroke, death from CHD, CBVD) Medical record review by physician adjudicators	Copollutant model: NR Copollutant correlations: NR
†(Hart et al., 2015b) U.S. (all contiguous states) Prospective cohort $PM_{10-2.5}$: 1989-2006 (sensitivity analyses restricting data to the years 2000-2006) Follow-up: 1988-2006	NHS N = 114,537 Follow-up: ~16 yrs	Annual avg, spatio-temporal model, $PM_{10-2.5}$ estimated by subtraction of monthly $PM_{2.5}$ from PM_{10}; time-varying exposure assigned based on residential address (C-V R^2 = 0.59, PM_{10} ; 0.76 and 0.77 pre- (limited $PM_{2.5}$ data) and post 1999, respectively)	Mean 1989-2006: 8.7 (SD 4.5) Mean 2000-2006: 7.3 (SD 4.1)	Self-reported physician diagnosed stroke	Copollutant model: NR Copollutant correlations: $PM_{2.5}$: r = 0.2; PM_{10}: r = 0.86
†(Puett et al., 2011) Northeast and Midwest, US (13 contiguous states) Prospective cohort $PM_{10-2.5}$: 1988-2002 Follow-up: 1989-Jan 2003	Health Professionals Follow-up Study N = 51,529 Avg follow-up NR	Annual avg estimated using spatio-temporal models for 2 time periods; C-V R^2 = 0.39, precision = 5.5 µg/m^3) see Yanosky et al. (2009) for details	Mean: 10.1 (SD: 3.3) IQR: 4.3	IS, HS ((medical record review)	Copollutant model: $PM_{2.5}$ Copollutant correlations: NR

Table 6-66 (Continued): Characteristics of the studies examining the association between long-term $PM_{10-2.5}$ exposures and stroke.

Study	Study Population	Exposure Assessment	Concentration $\mu g/m^3$	Outcome	Copollutants Examined
†(Stafoggia et al., 2014) 11 Cohorts Europe $PM_{10-2.5}$: 2008-2011 Outcome: 1992/2007–2010	ESCAPE N = 105,025	Annual exposure at residence using LUR fit to $PM_{10-2.5}$ estimated from the difference between PM_{10} and $PM_{2.5}$ model fit R^2 avg 0.68 (0.32-0.81), see (Eeftens et al., 2012)	6-17	Stroke incidence using hospital discharge data	Copollutant model: NR Copollutant correlations: NR
†(Hoffmann et al., 2015) Prospective cohort $PM_{10-2.5}$: 2008-2009 Outcome: 2000/03-2012	HNR study N = 4,433	Multi-year avg (baseline) using LUR fit to $PM_{10-2.5}$ estimated from the difference between PM_{10} and $PM_{2.5}$, residential address	9.99 (SD: 1.83)	Self-reported stroke with expert evaluation	Copollutant model: NR Copollutant correlations: NR

Avg = average, BRFSS = Behavioral Risk Factor Surveillance System, C-V = cross validation, ESCAPE = European Study of Air Pollution Exposure, HS = hemorrhagic Stroke, IS = Ischemic Stroke, HPFU = Health Professionals Follow-up Study, LUR = land use regression, NHS = Nurses' Health Study, N, n = number of subjects, NR = not reported, HNR = Heinz Nixdorf Recall study, SD = standard deviation

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

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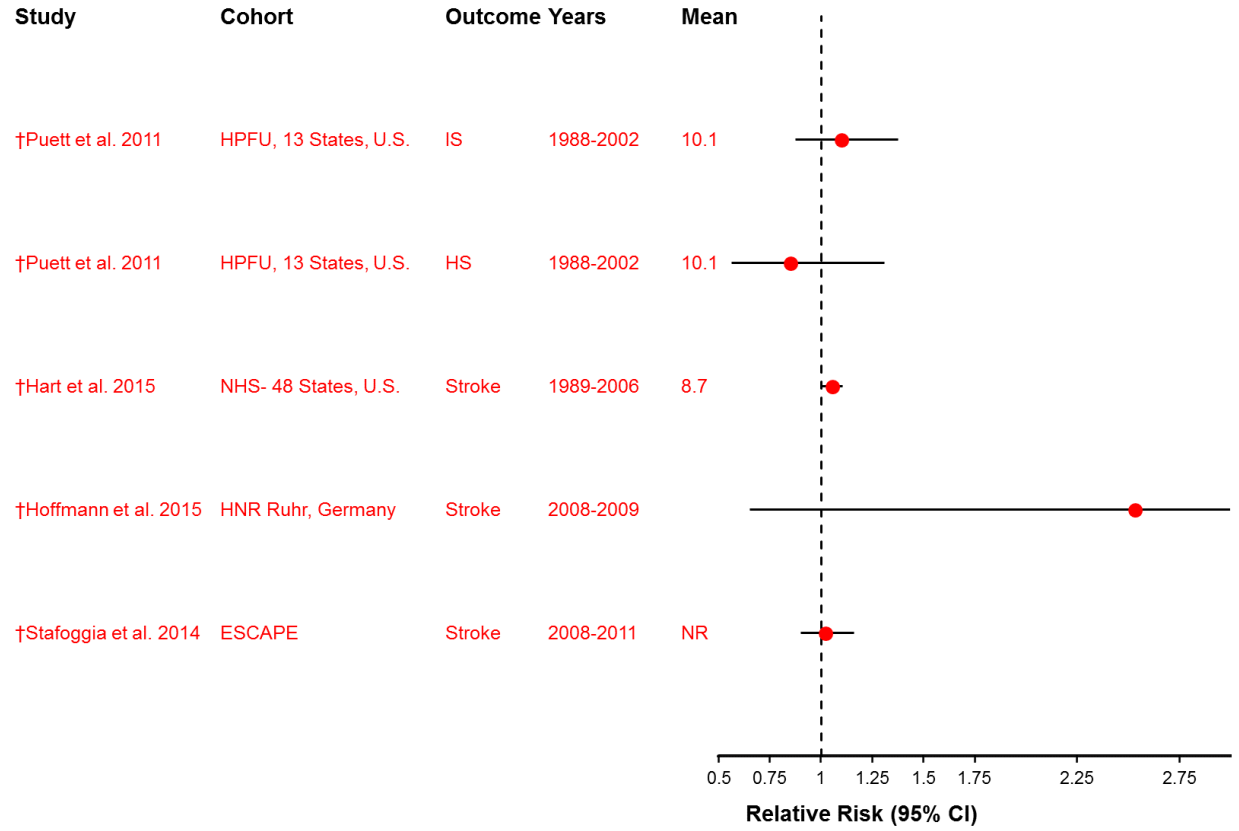
Hart et al. (2015b) examined data from women enrolled in the NHS and observed positive associations of $PM_{10-2.5}$ stroke [HR: 1.05 (95%CI: 1.00, 1.10)]. Larger associations between $PM_{10-2.5}$ and stroke [HR: 1.09 (95%CI: 1.00, 1.17)] were present among women with diabetes. Effect modification by diabetes persisted for stroke when analyses were restricted to the years with relatively complete exposure data. Larger associations of $PM_{10-2.5}$ with stroke were observed in the northeast compared to other regions, but not in the south. These strong associations in the northeast were even stronger in sensitivity analyses restricted to years with complete exposure data. Among male health professionals, Puett et al. (2011) reported an imprecise (n = 230 cases) increased risk for ischemic stroke [HR: 1.10 (95%CI: 0.88, 1.37and no association with hemorrhagic stroke [HR: 0.85 (95%CI: 0.56, 1.31)] in their basic model. A fully adjusted model that included comorbidities such as hypertension and diabetes returned similar results. The association between $PM_{10-2.5}$ and ischemic stroke strengthened after adjustment for $PM_{2.5}$ [HR: 1.31 (95%CI: 0.99, 1.72)]. Confidence intervals were wide due to small case numbers (N = 230 ischemic strokes), however.

No association of $PM_{10-2.5}$ was observed on incident stroke in the 11-cohort European Escape study [HR: 1.02 (95%CI: 0.90, 1.16)] (Stafoggia et al., 2014), although a separate analysis of one of the included cohorts (HNR) indicated a potential relationship between $PM_{10-2.5}$ and incident stroke. Although confidence intervals were wide Hoffmann et al. (2015), reported a strong positive association in this study [HR: 2.53 (95%CI: 0.65, 9.84)].

As shown in Figure 6-35, associations between $PM_{10-2.5}$ were not consistently observed in epidemiological of coronary events, CHD or stroke. Overall, the number of studies is limited and model performance is generally lower than the model performance for $PM_{2.5}$.



†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Mean concentrations in $\mu g/m^3$. Hazard Ratios are standardized to a 5- $\mu g/m^3$ increase in $PM_{2.5}$ concentrations. Corresponding quantitative results are reported in Supplemental Table 6S-25 (U.S. EPA, 2018). HS = hemorrhagic Stroke, IS = Ischemic Stroke, HPFU = Health Professionals Follow-up Study, NHS = Nurses' Health Study, NHR = Heinz Nixdorf Recall, ESCAPE = European Study of Air Pollution Exposure.

Figure 6-35 Associations between long-term exposure to $PM_{10-2.5}$ and stroke. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration.

6.4.5 Atherosclerosis

Atherosclerosis is the process of plaque buildup into lesions on the walls of the coronary arteries that can lead to narrowing of the vessel, reduced blood flow to the heart and IHD. The development of atherosclerosis is dependent on the interplay between plasma lipoproteins, inflammation, endothelial activation, and polymorphonucelar leukocyte attraction to the endothelium, extravasation, and lipid uptake. Additional information on atherosclerosis can be found in Section 6.2.4.

Increased cIMT is an indicator of atherosclerosis. An inverse cross-sectional association between long-term exposure to $PM_{10-2.5}$ and cIMT was observed in the ESCAPE study [-0.28% difference (95%CI: -1.16, 0.61)] (Perez et al., 2015) (Table 6-67).

Table 6-67 Characteristics of the studies examining the association between long-term $PM_{10-2.5}$ exposures and atherosclerosis.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
(Perez et al., 2015) Cross-sectional 4 European Cohorts: IMPROVE, HNR, KORA, REGICOR $PM_{10-2.5}$: 2008-2009 Outcome: 1997-2009	ESCAPE N = 9,183	Annual avg estimated using LUR (20 monitors) at residence Model fit R^2 = 0.71 (median, cross validation R^2 results 8-11% lower, see (Eeftens et al., 2012)	IMPROVE: Mean 7.1 (SD: 3.0), IQR: 3.0 HNR: Mean 10.0 (SD: 1.8), IQR: 1.9 KORA: Mean 6.2 (SD: 1.1), IQR: 1.2 REGICOR: Mean 15.6 (SD: 2.7), IQR: 3.7	cIMT	IMPROVE: $PM_{2.5}$ *r* = 0.62; $PM_{2.5}$abs *r* = 0.63; NO_2 *r* = 0.6; NO_X *r* = 0.55 HNR $PM_{2.5}$ *r* = 0.68; $PM_{2.5}$abs *r* = 0.72; NO_2 *r* = 0.46; NO_X *r* = 0.42 KORA: $PM_{2.5}$ *r* = 0.28; $PM_{2.5}$abs *r* = 0.83; NO_2 *r* = 0.79; NO_X *r* = 0.85 REGICOR: $PM_{2.5}$ *r* = 0.12; $PM_{2.5}$abs *r* = 0.11; NO_2 *r* = 0.09; NO_X *r* = 0.15

cIMT = carotid intima media thickness, ESCAPE = European Study of Cohorts for Air Pollution, HNR = Heinz Nixdorf Recall, IQR = interquartile range, KORA =, REGICOR =, LUR = land use regression

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

6.4.6 Blood Pressure and Hypertension

High blood pressure is typically defined as a systolic blood pressure above 140 mm hg or a diastolic blood pressure above 90 mm hg with the clinically relevant consequence of chronically high blood pressure defined as hypertension (Section 6.2.7). There were no studies of the effect of $PM_{10-2.5}$ on blood pressure, hypertension or related effects on the renal system reviewed in the 2009 PM ISA.

6.4.6.1 Epidemiologic Studies

A limited number studies examined the relationship between $PM_{10-2.5}$ and blood pressure or hypertension among adults. Fuks et al. (2014) reported null associations with use of blood pressure lowering medication [OR: 0.99 (95%CI: 0.93, 1.05)] and hypertension [OR: 1.00 (95%CI: 0.94, 1.06)] in the ESCAPE cohort. Both small (relative to the size of the confidence interval) decreases and small increases in SBP and DBP were also observed in ESCAPE providing little support for an effect on blood pressure. A study conducted in Taiwan where mean $PM_{10-2.5}$ concentration was 21.2 $\mu g/m^3$ showed no effect on SBP but reported elevated DBP and an increased risk of hypertension in association with $PM_{10-2.5}$ (Chen et al., 2015a).

6.4.6.2 Toxicology Studies of Changes in Blood Pressure (BP)

There were no studies in the 2009 PM ISA exploring the relationship between long-term inhalation exposure to $PM_{10-2.5}$ and changes in BP. Since the publication of that review, a toxicological study has reported no changes in mRNA levels of angiotensin or bradykinin related genes after long-term exposure to $PM_{10-2.5}$ (Aztatzi-Aguilar et al., 2015). However, the authors did report an increase in AT_1R protein levels following exposure ($p < 0.05$). Thus, there is limited evidence from this study that exposure to $PM_{10-2.5}$ may effect BP through changes in the renin-angiotensin system. More information on this recently published study can be found in Table 6-68 below.

Table 6-68 Study-specific details from toxicological studies of long-term $PM_{10-2.5}$ exposure and blood pressure (BP).

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult male Sprague-Dawley rats (n = 4 per group)	Inhalation of 32 μg/m^3 $PM_{10-2.5}$ for 5 h/day, 4 days/week, for 8 week	Angiotensin and bradykinin system gene and protein expression

m = male n = number, h = hour, d = day, week = week

1

6.4.7 Peripheral Vascular Disease (PVD), Venous Thromboembolism, Pulmonary Embolism

2 Pulmonary emboli (PE) are common subtypes of venous thromboembolism (VTE)
3 (Section 6.3.8). Pun et al. (2015) reported a positive association between long-term exposure to $PM_{10-2.5}$
4 and PE [HR: 1.09 (95%CI: 1.00, 1.19)] (Table 6-69). The association was stronger with idiopathic PE,
5 i.e., cases for which there was no underlying medical condition. Although confidence intervals were
6 wider, these associations were not substantially attenuated after adjustment for $PM_{2.5}$.

Table 6-69 Characteristics of the studies examining the association between long-term $PM_{10-2.5}$ exposures and other cardiovascular outcomes.

Study	Study Population	Exposure Assessment	Concentration μg/m^3	Outcome	Copollutants Examined
(Pun et al., 2015) 11 States, U.S. Follow-up 1992-2008 $PM_{10-2.5}$	NHS	Annual avg estimated using spatiotemporal model at residential address C-V R^2 = 0.63	Mean: 8.2 (SD: 4.2) IQR: 4.6	Self-reported diagnosis of PE confirmed by physician medical record review	Copollutant model: NR Copollutant correlations: NR

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Avg = average, IQR = interquartile range, N, n = number of subjects, NR = not reported, NHS = Nurses' Health Study, PE = pulmonary embolism.

6.4.8 Cardiovascular Mortality

7 In the 2009 PM ISA, there was limited evidence for an association between long-term $PM_{10-2.5}$
8 exposure and cardiovascular mortality for women, but not for men Chen et al. (2005). Several recent U.S.

cohort studies (Table 6-70) examined the association between long-term $PM_{10-2.5}$ exposure and cardiovascular mortality in occupational cohorts. Puett et al. (2009) examined the association between long-term $PM_{10-2.5}$ exposure and CHD mortality among a cohort of female nurses in the Nurses' Health Study from 13 states in the northeast and Midwest from 1992 through 2002. Spatio-temporal models were used to assign exposure to $PM_{2.5}$ and PM_{10} and the $PM_{10-2.5}$ concentrations were derived via subtraction. The authors observed positive associations with CHD mortality, though the associations were attenuated to below the null value in copollutant models that include $PM_{2.5}$. Using a design similar to that of the Nurses' Health Study, Puett et al. (2011) investigated the effect of long-term $PM_{10-2.5}$ (derived by subtraction of $PM_{2.5}$ from PM_{10}) exposure and mortality CHD among men enrolled in the Health Professionals cohort. Near null associations were observed for CHD mortality in this cohort.

A pooled-analysis of the European ESCAPE cohort combined data from 22 existing cohort studies and evaluated the association between long-term $PM_{10-2.5}$ exposure and cardiovascular mortality (Beelen et al., 2014). LUR models were used to assign exposure to $PM_{2.5}$ and PM_{10} and the $PM_{10-2.5}$ concentrations were derived via subtraction. The authors applied a common statistical protocol to data from each of the 22 cohorts, from 13 different European countries, in the first stage of the analysis and combined the cohort-specific effects in a second stage. The authors observed a near-null association between long-term $PM_{10-2.5}$ exposure and cardiovascular mortality (Beelen et al., 2014). The strongest association was observed for the subset of cardiovascular deaths attributable to cerebrovascular disease (HR: 1.17, 95% CI: 0.90, 1.52), though copollutant models with $PM_{2.5}$ were not reported for this comparison. Using the same exposure models used for the pooled cohort study, Dehbi et al. (2016) assigned $PM_{10-2.5}$ exposure to two British cohort studies that were pooled together to examine CVD mortality. The British cohorts included follow-up between 1989 and 2015, though $PM_{10-2.5}$ exposure estimates were available for 2010-2011. The authors observed a negative association when exposure was considered on the continuous scale, but positive associations for each quartile when exposure was categorized. However, the confidence intervals were wide and overlapping for all of the results, and the inconsistency may indicate generally null results, but instability in the model. In a separate European cohort, Bentayeb et al. (2015) used the CHIMERE chemical transport model to estimate PM_{10} and $PM_{2.5}$, and then subtracted to estimate long-term $PM_{10-2.5}$ exposure. The authors observed positive association with cardiovascular mortality.

While there are more studies available in this review that examine the association between long-term $PM_{10-2.5}$ exposure and cardiovascular mortality, the body of evidence remains limited, especially when compared to the body of evidence available for $PM_{2.5}$. In addition, to date all of the studies that have examined the relationship between long-term $PM_{10-2.5}$ exposure and mortality have used the difference method to derive concentrations for $PM_{10-2.5}$, contributing to the uncertainty associated with these effect estimates. Overall, there is no consistent pattern of associations for cardiovascular mortality (Table 11-8). In the instances where positive associations were observed for long-term $PM_{10-2.5}$ exposure and mortality, and $PM_{2.5}$ copollutant model results were reported, the $PM_{10-2.5}$ effect estimates were often attenuated but still positive after adjusting for $PM_{2.5}$.

Table 6-70 Epidemiologic studies of long-term exposure to $PM_{10-2.5}$ and cardiovascular mortality.

Study	Cohort (Location)	Mean $PM_{10-2.5}$ ($\mu g/m^3$)	Exposure Assessment	Single Pollutant Hazard Ratio[a] (95% CI)	Copollutant Examination
Chen et al. (2005)	AHSMOG (U.S.)	25.4	ZIP code average Subtraction method	CHD (men): 0.96 (0.81, 1.14) CHD (women): 1.17 (0.98, 1.40)	Correlation (*r*): NA Copollutant models with: NA
†Puett et al. (2009)	Nurses Health (U.S.)	7.7	Spatio-temporal models Subtraction method	CHD (women): 1.07 (0.85, 1.33)	Correlation (*r*): NA Copollutant models with: $PM_{2.5}$: CHD (women): 0.95 (0.75, 1.22)
†Puett et al. (2011)	Health Professionals (U.S.)	10.1	Spatio-temporal models Subtraction method	CHD (men): 1.03 (0.90, 1.18)	Correlation (*r*): NR Copollutant models with: $PM_{2.5}$: CHD (men): 1.05 (0.90, 1.22)
†Beelen et al. (2014)	ESCAPE (Europe)	4.0 – 20.7	LUR models Subtraction method	CVD: 1.02 (0.91, 1.13) IHD: 0.92 (0.77, 1.11) MI: 0.88 (0.71, 1.10) CBVD: 1.17 (0.90, 1.52)	Correlation (*r*): NR Copollutant models with: NR
†Dehbi et al. (2016)	Two British Cohorts	6.4	Same exposure as ESCAPE	CVD: 0.94 (0.56, 1.60)	Correlation (*r*): NR Copollutant models with: NR
†Bentayeb et al. (2015)	Gazel (France)	8.0	CHIMERE chemical transport model Subtraction Method	CVD: 1.32 (0.89, 1.91)	Correlation (*r*): NR Copollutant models with: NR

CHD=coronary heart disease, CVD=cardiovascular disease, ESCAPE = European Study of Air Pollution Exposure, LUR = land use regression, NR=not reported

†Studies published since the 2009 PM ISA.

6.4.9 Systemic Inflammation and Oxidative Stress

As discussed in Section 6.1.1 and Section 6.1.11, systemic inflammation and oxidative stress have been linked to a number of CVD related outcomes. Thus, this section discusses the evidence for markers of systemic inflammation and oxidative stress following long-term PM10-2.5 exposures.

6.4.9.1 Epidemiologic Studies

Increased levels of C-reactive protein (CRP) can indicate systemic inflammation (Section 6.3.12) and fibrinogen is a marker of coagulation (Section 6.3.13). (Lanki et al., 2015) provides little support for an association (% difference) between long-term exposure to $PM_{10-2.5}$ and CRP (3.0% [95%CI: -.7, 6.8]) or fibrinogen (1% [95%CI: -1.2, 0.9]).

6.4.9.2 Toxicology Studies

There were no studies in the 2009 PM ISA exploring the relationship between long-term inhalation exposure to $PM_{10-2.5}$ CAP and systemic inflammation/oxidative stress. Since the publication of the 2009 PM ISA, Aztatzi-Aguilar et al. (2015) reported that rats exposed to coarse PM had no change in IL-6 or HO-1 protein levels in the heart following long-term exposure to $PM_{10-2.5}$. More information on this recently published study can be found in Table 6-71 below.

Table 6-71 Study specific details from toxicological studies long-term $PM_{10-2.5}$ exposure and of systemic inflammation.

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult Sprague-Dawley rats, M, n = 4 per group	Inhalation of 32 μg/m^3 $PM_{10-2.5}$ for 5 h/day, 4 days/week, for 8 week	Markers of inflammation in heart tissue collected 24 h post-exposure

Note: n = number, M = male, h = hour, d = day, week = week

6.4.10 Summary and Causality Determination

In the 2009 PM ISA (U.S. EPA, 2009), the evidence describing the relationship between long-term exposure to $PM_{10-2.5}$ and cardiovascular effects was characterized as "inadequate to infer the presence or absence of a causal relationship." The limited number of epidemiologic studies reported contradictory results and animal toxicological evidence demonstrating an effect of $PM_{10-2.5}$ on the cardiovascular system was lacking. The literature base has expanded but remains limited although some

epidemiologic studies report positive associations of cardiovascular mortality and other outcomes with long-term exposure to $PM_{10-2.5}$. More recent evidence describing the relationship between long-term exposure to $PM_{10-2.5}$ and cardiovascular effects is discussed below and summarized in Table 6-72, using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015).

The evidence relating long-term exposure to $PM_{10-2.5}$ to cardiovascular mortality remains limited. Overall, there is no consistent pattern of associations for cardiovascular mortality (Table 6-70). In the instances where positive associations were observed for long-term $PM_{10-2.5}$ exposure and mortality, and $PM_{2.5}$ copollutant model results were reported, the $PM_{10-2.5}$ effect estimates were often attenuated but still positive after adjusting for $PM_{2.5}$. The epidemiologic studies examining the relationship between $PM_{10-2.5}$ and other cardiovascular outcomes including MI and stroke, atherosclerosis, VTE, and blood pressure has grown. Some studies report positive associations with these outcomes. Specifically, single pollutant associations of long-term exposure to $PM_{10-2.5}$ with IHD were observed in the NHS (Hart et al., 2015b), ESCAPE (Cesaroni et al., 2014), and MINAP (recurrent MI) (Tonne et al., 2015) while no association was observed in the HPFU after adjusting for $PM_{2.5}$ in copollutant models (Puett et al., 2011). After adjusting for noise, Hoffmann et al. (2015) reported an inverse association with IHD in the HNR study, which is one of the cohorts included in ESCAPE. Evidence of an association between long-term exposure to $PM_{10-2.5}$ and stroke was similarly inconsistent with a positive association observed in the NHS (Hart et al., 2015b) and little evidence of an effect in HPFU (Puett et al., 2011) or ESCAPE (Stafoggia et al., 2014). No evidence of an association with cIMT in the only available study, an ESCAPE meta-analysis, was reported(Perez et al., 2015). An association between long-term $PM_{2.5}$ exposure and pulmonary embolism was reported in the NHS (Pun et al., 2015). An inconsistent pattern of results relating to the effect of $PM_{10-2.5}$ on increased blood pressure and hypertension was reported in a limited number of studies (Chen et al., 2015a; Fuks et al., 2014). To date the studies that have examined the relationship between long-term $PM_{10-2.5}$ exposure and mortality have used the difference method to derive concentrations for $PM_{10-2.5}$, contributing to the uncertainty associated with these effect estimates.

The toxicological evidence related to long-term $PM_{10-2.5}$ exposures was overall lacking and represents a substantial data gap in the present collection of literature. There was a study demonstrating that short-term $PM_{10-2.5}$ exposure in rats resulted in thickening of the coronary artery wall (Section 6.4.3.2). The same study also reported limited evidence of altered protein expression related to renal function and blood pressure, (Section 6.4.6.2) and no evidence for changes in markers of systemic inflammation or oxidative stress (Section 6.4.9). In addition, as evidenced in Section 6.4.1, there are important gaps in biological plausibility in part, due to the overall lack of experimental evidence.

There are individual high-quality epidemiologic studies that report positive associations with cardiovascular morbidity and mortality outcomes, but the evidence in not entirely consistent. Associations are sometimes attenuated in copollutant models and there is uncertainty stemming from the use of the subtraction method to estimate exposure. Furthermore, evidence from experimental animal studies is of insufficient quantity to establish biological plausibility. Based largely on the observation of positive

associations in some high-quality epidemiologic studies, the **evidence is suggestive of, but not sufficient to infer, a causal relationship between long-term $PM_{10-2.5}$ exposure and cardiovascular effects.**

Table 6-72 Summary of evidence indicating that the evidence is suggestive of, but not sufficient to infer a causal relationship between long-term $PM_{10-2.5}$ exposure and cardiovascular effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Some epidemiologic studies report positive associations at relevant concentrations	Positive associations between long-term $PM_{10-2.5}$ exposure and cardiovascular mortality in some studies; however, lack of consistency across studies. Some high-quality studies report associations with IHD, stroke, or pulmonary embolism	Section 6.5.138 (Hart et al., 2015b) Cesaroni et al. (2014) Tonne et al. (2015) Pun et al. (2015) Miller et al. (2007)	8.7 7.3-31 8.2-8.6
Uncertainty regarding exposure measurement error	Studies rely on subtraction method to estimate exposure to $PM_{10-2.5}$ adding uncertainty to the interpretation of effect estimates	Section 3.5	
Uncertainty regarding the independent effect of $PM_{10-2.5}$	Limited number of epidemiologic studies evaluate copollutant confounding Null association with IHD after adjustment for $PM_{2.5}$ in HPFU Inverse association with IHD in HNR study after adjustment for noise	Puett et al. (2011) Hoffmann et al. (2015)	
Limited evidence of coherence across lines of evidence	A study reporting some indications of impaired heart function, and potentially changes in BP. No changes in markers of inflammation or oxidative stress were reported	(Aztatzi-Aguilar et al., 2015)	~30 $\mu g/m^3$
Biological plausibility	Overall, biological plausibility is extremely limited with important gaps in the potential pathways identified in Section 6.4.1.		

$PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than a nominal diameter of 2.5 µm

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the $PM_{10-2.5}$ concentrations with which the evidence is substantiated.

6.5 Short-Term UFP Exposure and Cardiovascular Effects

The 2009 ISA concluded the available evidence for short-term ultrafine particle (UFP) exposure and cardiovascular effects was "suggestive of a causal relationship." There was a relatively large body of evidence from controlled human exposure studies of fresh diesel exhaust (DE), which is typically dominated by UFPs, demonstrating effects of UFP on the cardiovascular system. In addition, cardiovascular effects were demonstrated by a limited number of laboratories in response to UF carbon black, urban traffic particles and CAPs. Responses included altered vasomotor function, increased systemic oxidative stress and HRV parameters. Studies using UF CAPs, as well as wood smoke and DE, provided some evidence of changes in markers of blood coagulation, but findings were not consistent. Toxicological studies conducted with UF TiO_2, CB, and DE demonstrated changes in vasomotor function as well as in HRV. Effects on systemic inflammation and blood coagulation were less consistent. PM-induced cardiac oxidative stress was noted following exposure to gasoline exhaust. Notably, the few epidemiologic studies of UFPs conducted did not provide strong support for an association of UFPs with effects on the cardiovascular system.

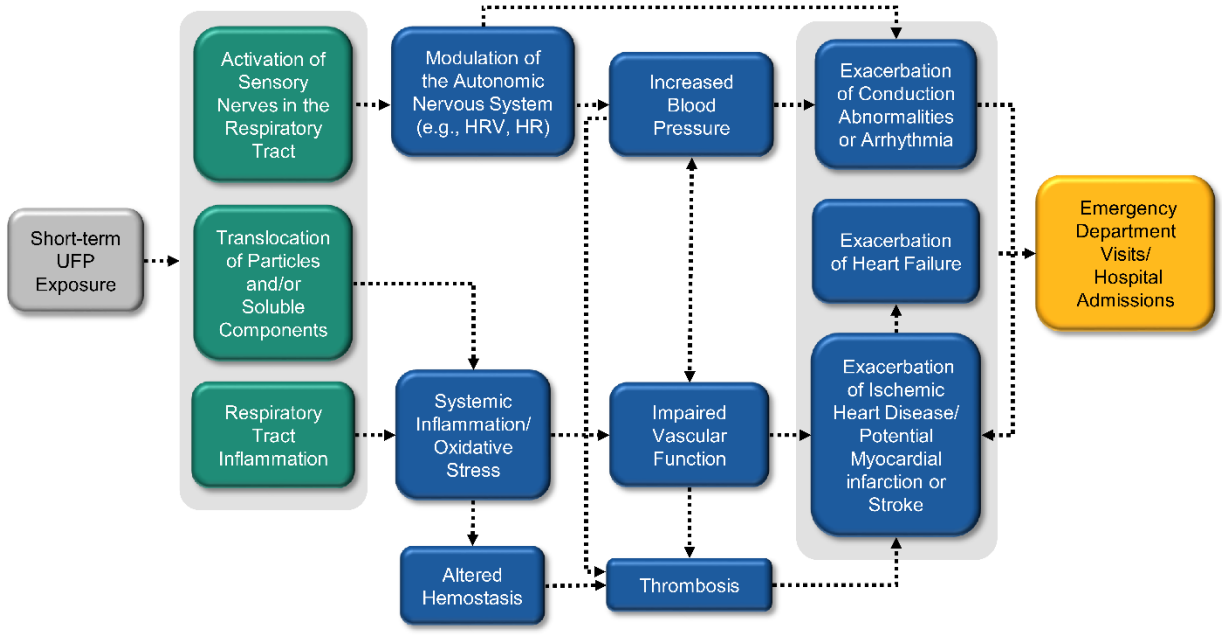
Recent evidence continues to be suggestive of a causal relationship between short-term exposures to UFPs and cardiovascular effects. Relatively speaking, the strongest evidence for cardiovascular-related effects following UFP exposure is for measures of HRV and coagulation. A small number of epidemiologic panel studies have reported associations between short-term exposure to UFPs and measures of HRV. This includes a well conducted epidemiologic panel study that found increases in SDNN with well-characterized 3 hour exposures. In addition, there was some evidence for positive associations between UFP exposure and markers of coagulation from epidemiologic panel studies, and evidence from a CHE study indicating decreases in the anticoagulant proteins plasminogen and thombomodulin in a subset of individuals with metabolic syndrome who express the GSTM1 null allele. In addition to changes in HRV and markers of coagulation, there was also limited evidence from CHE and epidemiologic panel studies for endothelial dysfunction, blood pressure, and systemic inflammation following UFP exposure.

The subsections below provide an evaluation of the most policy relevant scientific evidence relating-short-term UFP exposure to cardiovascular health effects. To clearly characterize and put this evidence into context, there is first a discussion of the biological plausibility of cardiovascular effects following short-term UFP exposure (Section 6.5.1). Following this discussion, the health evidence relating short-term UFP exposure and specific cardiovascular health outcomes is discussed in detail: ischemic heart disease and myocardial infarction (Section 6.5.2), heart failure and impaired heart function (Section 6.5.3) cardiac electrophysiology and arrhythmia (Section 6.5.4), cerebrovascular disease and stroke (Section 6.5.5), increased blood pressure and hypertension (Section 6.5.6), aggregated

cardiovascular outcomes (Section 6.5.7), and cardiovascular-related mortality (Section 6.5.8). The evidence for an effect of UFP exposures on endpoints such as changes in heart rate variability (HRV) and endothelial function are discussed (Section 6.5.9, Section 6.5.10, Section 6.5.11, and Section 6.5.12). Finally, considering the all of the information presented above, summary and causal determinations are presented (Section 6.5.13).

6.5.1 Biological Plausibility

This subsection describes the biological pathways that potentially underlie cardiovascular health effects resulting from short-term inhalation exposure to UFPs. Figure 6-36 graphically depicts these proposed pathways as a continuum of pathophysiological responses- connected by arrows- that may ultimately lead to the apical cardiovascular events observed in epidemiologic studies (i.e., ED visits and hospital admissions). This discussion of "how" short-term exposure to UFPs may lead to these cardiovascular events also provides at least some biological plausibility for the epidemiologic results reported later in Section 0. In addition, most studies cited in this subsection are discussed in greater detail throughout Section 0.



Note: the boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes.

Figure 6-36 Potential biological pathways for cardiovascular effects following short-term exposure to ultrafine particle (UFP).

When considering the available health evidence, plausible pathways connecting short-term exposure to UFPs to the apical events reported in epidemiologic studies are proposed in Figure 6-36. The first pathway begins as respiratory tract inflammation that leads to systemic inflammation[67]. The second pathway involves activation of sensory nerve pathways in the respiratory tract that leads to modulation of the autonomic nervous system. Once these pathways are initiated, there is evidence from experimental and observational studies that short-term exposure to UFPs may result in a series of pathophysiological responses that could lead to cardiovascular events such as ED visits and hospital admissions for IHD and HF.

Short-term inhalation exposure to UFPs may result in respiratory tract inflammation (CHAPTER 5). Inflammatory mediators such as cytokines produced in the respiratory tract have the potential to enter the circulatory system where they may cause distal pathophysiological responses that contribute to overt cardiovascular disease (see Section 6.1.1). There is limited evidence from CHE studies that following short-term UFP exposure, systemic inflammation (Liu et al., 2015a; Devlin et al., 2014) may occur. Importantly, systemic inflammation may result in altered hemostasis which may then increase the potential for thrombosis and possibly worsen IHD and HF. In addition, systemic inflammation may result in impaired vascular function that could potentially lead to rupture of existing plaques (Halvorsen et al., 2008). Dislodged plaques may then obstruct blood flow to the heart or stimulate intravascular clotting (Karoly et al., 2007), both of which could result in worsening of IHD and set the stage for HF. Thus, it is important to note that there is some evidence from CHE (Devlin et al., 2014) and epidemiologic panel studies (Wang et al., 2016; Rich et al., 2012; Hildebrandt et al., 2009; Peters et al., 2009) for altered hemostasis following short-term UFP exposure. Similarly, a CHE (Devlin et al., 2014) and an epidemiologic panel study (Ljungman et al., 2014) provide some evidence for impaired vascular function.

There is also evidence that short-term exposure to UFPs could potentially lead to these outcomes through activation of sensory nerves in the respiratory tract (CHAPTER 5). Once activated, autonomic nervous system modulation could exacerbate IHD and HF through proposed pathways that include increases in BP and/or exacerbation of conduction abnormalities or arrhythmia (Figure 6-36). Thus, it is important to note that CHE (Devlin et al., 2014; Samet et al., 2009) and epidemiologic panel studies (Hampel et al., 2014; Rich et al., 2012) report modulation of the autonomic nervous system (as evidenced by changes in HRV) following short-term UFP exposure. Similarly, evidence for increases in blood pressure can be found in epidemiologic panel studies (Chung et al., 2015; Kubesch et al., 2014; Liu et al., 2014b; Weichenthal et al., 2014a), while CHE (Devlin et al., 2014; Samet et al., 2009) and an additional

[67] It is also possible that UFP or soluble particle components can translocate directly into the circulatory system (Chapter 4) and lead to systemic inflammation, although the extent to which particle translocation occurs remains unclear.

epidemiologic panel (Link et al., 2013) study report conduction abnormalities or indicators of arrhythmia following short-term UFP exposure.

When considering the available evidence, there are potential pathways connecting short-term exposure to UFPs to cardiovascular health effects (Figure 6-36). More specifically, there exist potential pathways by which short-term exposure to UFPs may worsen IHD or HF, as well as contribute to the development of MI or stroke, potentially resulting in ED visits and hospital admissions. That said, the evidence supporting most of the individual events in these potential pathways is quite limited. This information will be used to inform a causal determination, which is discussed later in the chapter (Section 6.5.13).

6.5.2 Ischemic Heart Disease and Myocardial infarction

As noted above in Section 6.1.2, ischemic heart disease (IHD) is characterized by reduced blood flow to the heart. The majority of IHD cases are caused by atherosclerosis (Section 6.2.4), which can result in the blockage of the coronary arteries and restrict of blood flow to the heart muscle. A myocardial infarction (MI) or heart attack occurs as a consequence of IHD, resulting in insufficient blood flow to the heart that overwhelms myocardial repair mechanisms and leads to muscle tissue death.

There was no evidence in the 2009 PM ISA with respect to IHD, MI and short-term exposure to UFPs. In the current review, there are a few ED visit and hospital admission studies as well as a single epidemiologic panel study. Overall these studies do not suggest a relationship between short-term exposure to UFPs and IHD or MI.

6.5.2.1 Emergency Department Visits and Hospital Admissions

In Rome, Italy, Belleudi et al. (2010) considered nearly 23,000 ED visits for acute coronary syndrome and observed null associations with UFP exposure (particle number concentrations from a single, fixed-site monitor) at individual lags from 0 to 6 days. Gardner et al. (2014) also reported a null association between two subtypes of MI (ST segment elevation MI and non-ST segment elevation MI) and UFP (particle number concentration, 10-100 nm, from a fixed-site monitor) in a MI registry study in Rochester, NY. Conversely, in a MI registry study in Augsburg, Germany, Wolf et al. (2015a) observed a positive, albeit imprecise (i.e., wide 95% CI), association between same-day UFP exposure (particle number concentration, 10-2000 nm, from a fixed-site monitor) and MI. Additionally, Wolf et al. (2015a) observed a positive increase in recurrent MI events with UFP exposure averaged over a longer, multiday lag period (6.0%, 95% CI: 0.6%, 11.7%, lag 0-4 per 6,800 particles/cm^3 increase). Registry studies are advantageous because they are thought to lessen the degree of outcome misclassification generally seen in studies that rely on administrative data.

6.5.2.2 Panel Epidemiologic Studies of ST Segment Depression

There were no studies evaluating ST-segment depression available for the 2009 ISA and there is only a singly study in the recently published literature. Delfino et al. (2011) conducted a repeated measures study among older adults with coronary artery disease living in retirement communities in Los Angeles and did not find evidence for associations between average PNC of 1-hour up to 4-days and ST-segment depression.

6.5.3 Heart Failure and Impaired Heart Function

As first noted in Section 6.1.3, heart failure (HF) refers to a set of conditions including congestive heart failure (CHF) in which the heart's pumping action is weakened. With CHF the flow of blood from the heart slows, failing to meet the oxygen demands of the body, and returning blood can back up, causing swelling or edema in the lungs or other tissues.

There were no studies in the 2009 PM ISA with respect to short-term UFP exposure and heart function. In the current review, a hospital admission study showed a positive association that was lag dependent. However, relative to control animals, a toxicological study did not find an increase in markers consistent with cardiac damage following short-term exposure to $PM_{10-2.5}$.

6.5.3.1 Emergency Department Visits and Hospital Admissions

The 2009 PM ISA did not review any epidemiologic studies of ambient UFPs and ED visits and hospital admissions for heart failure. Recently, Belleudi et al. (2010) reported positive associations between ambient UFP exposure (particle number concentration from a single fixed-site monitor) and hospital admissions for heart failure in Rome, Italy. The authors examined individual lags from 0 to 6 days, and observed the highest magnitude associations at lag 0 (1.80% [95% CI: 0.39, 3.24%] per 9,392 particles/cm^3 increase) and lag 2 (1.65% [95% CI: 0.32, 3.00%]), with null associations at lags 5 and 6.

6.5.3.2 Toxicology Studies of Impaired Heart Function

There were no animal toxicological studies in the last review examining markers of potential heart failure following short-term UFP exposure. Since that document, Kurhanewicz et al. (2014) reported that short-term exposure to UFPs resulted in no appreciable change in LVDP or contractility. In addition, (Aztatzi-Aguilar et al., 2015) did not report statistically significant cardiac gene expression consistent with cardiac damage following short-term exposure to UFPs. More information on this recently published study can be found in Table 6-73 below.

Table 6-73 Study specific details from toxicological studies of short-term UFP exposure and impaired heart function.

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult male Sprague-Dawley rats (n = 4 per group)	Inhalation of UFP (107 $\mu g/m^3$) for 5 h/day, for 3 days	Acta1 and Col3a gene expression
(Kurhanewicz et al., 2014)	Adult, female C57BL/6 mice (10-12 week), n = 5-8/group	Inhalation of 138 $\mu g/m^3$ UFP for 4 h	LVDP and contractility (dP/dt) Tissue collected 24h post exposure.

Note: d = day, h = hour, n = number, f = female, M = male, LVDP = left ventricular developed pressure, Acta1 = skeletal alpha-actin, Col3a1 = collagen Type 3 alpha, post = post exposure

6.5.4 Cardiac Electrophysiology, Arrhythmia, and Cardiac Arrest

Electrical activity in the heart is measured using electrocardiography (ECG). The pattern of depolarization and repolarization in the heart can indicate various forms of arrhythmia and distinguish those arising in the ventricle from those arising in the atria. See Section 6.1.4 for more information on arrhythmia and measures of conduction abnormalities.

The 2009 PM ISA had a single epidemiologic study of ambient UFPs and arrhythmia-related ED visits and HA. In addition, there was a single CHE study that reported a shortening of the QT interval following short-term exposure to UFPs. Since the last review, one epidemiologic study reported a null association for arrhythmia related hospital admissions, but a CHE study did report conduction abnormalities by ECG that could indicate the potential for increased risk of arrhythmia following short-term UFP exposure.

With respect to OHCA, one study in the 2009 PM ISA that found a positive association between short-term UFP exposure and OHCA. Since the 2009 PM ISA, no new studies of OHCA have been reviewed.

6.5.4.1 Emergency Department Visits and Hospital Admissions for Arrhythmia and Out-of-Hospital Cardiac Arrest

A number of studies based on administrative databases have sought to evaluate the association between short-term fluctuations in ambient UFP concentrations and the risk of hospitalization for cardiac arrhythmias (also known as dysrhythmias). In these studies, a primary discharge diagnosis of ICD-9 427 has typically been used to identify hospitalized patients. ICD-9 427 includes a heterogeneous group of

arrhythmias including paroxysmal ventricular or supraventricular tachycardia, atrial fibrillation and flutter, ventricular fibrillation and flutter, cardiac arrest, premature beats, and sinoatrial node dysfunction.

The 2009 PM ISA did not review any epidemiologic studies of ambient UFPs and arrhythmia-related ED visits and HA. Recently, Anderson et al. (2010) examined the association between UFP exposure (particle number concentration, single fixed-site monitor) and atrial fibrillation in London, England. The authors reviewed records of implantable cardioverter defibrillators activations and reported a null association with UFP (OR: 1.00, 95% CI: 0.96, 1.05, per 1,000 particles/cm^3 increase, lag 0-5).

The majority of out-of-hospital cardiac arrests are due to cardiac arrhythmias. The 2009 PM ISA reviewed one study examining the association between UFP and OHCA. A study in Rome, Italy (Forastiere et al., 2005) reported positive associations between OHCA and UFPs. No studies published since the release of the 2009 PM ISA examined the association between UFP concentrations and OHCA.

6.5.4.2 Panel Epidemiologic Studies for Arrhythmia and Conduction Abnormalities

In the 2009 PM ISA, (Dockery et al., 2005b) reported a positive association for arrhythmias relative to 2-day averages of UFP. A handful of studies examined the relationship between short-term exposure to UFPs and changes in arrhythmia or cardiac conduction and generally reported null results. While Link et al. (2013) found a positive association between arrhythmia and 2-hour averages of NCs measured at the clinic site in a panel of adults with ICDs, null associations were reported for 24-hour averages. Positive associations for ventricular tachyarrhythmia with NCs in the prior 24-47 hours (0.5%; 95% CI: -0.1, 1.0; per 7,481/cm^3) were also reported by Bartell et al. (2013) in a study of ventricular tachyarrhythmia in older adults with coronary artery disease that used residential monitoring for NC (100-3,000nm); however, negative associations were reported with NCs in the prior 96-119 hours (-0.6%; 95% CI: -1.3, 0.1; per 7,481/cm^3) Hampel et al. (2010) and Rich et al. (2012) both examined QTc changes in relation to ambient NCs (10-100nm) among survivors of MI and cardiac rehabilitation patients, respectively. Hampel et al. (2010) used fixed site monitoring representative of urban background NCs in Dusseldorf, Germany. (Rich et al., 2012) conducted monitoring at the clinic site in Rochester, NY, located roughly 1,500 m from an interstate highway and within 19km of study participants. Neither study reported evidence of associations with 5-hour up to 5-day NC averages.

6.5.4.3 Controlled Human Exposure Studies for Arrhythmia and Conduction Abnormalities

In the 2009 ISA, a CHE study examined the relationship between ultrafine PM exposure and ventricular arrhythmia. Samet et al. (2009) reported a shortened QT interval. They also noted increased variance in the duration of QRS complexes under ultrafine CAP exposure in healthy, young individuals.

In the current ISA, an additional study examined the relationship between UFP CAP exposure and potential indicators of ventricular arrhythmia. Devlin et al. (2014) recently studied adults with metabolic syndrome, including a subgroup with the null allele for glutathione S-transferase (GSTM1- an important antioxidant gene). The GSTM1 null allele individuals had a small but significant increase in the QT interval one-hour post exposure ($p = 0.0070$) relative to FA, while a nonsignificant trend in increased QTc was reported for the entire study group. These GSTM1 null individuals also had an increased complexity of the QRS complex (possible indicator of increased risk of arrhythmia development) at both one-hour ($p = 0.025$) and 20 hours ($p = 0.008$) post exposure. More information on studies published since the 2009 ISA can be found in Table 6-74 below.

Table 6-74 Study-specific details from CHE studies of short-term UFP exposure and conduction abnormalities.

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Devlin et al., 2014)	Adults with metabolic syndrome n = 13 M; 21 F 27-70, average 15 of which carried the null allele for GSTM1	98 µg/m^3 UFPs (73% of which are <0.1 µm) 16,000–564,000 particles/cm^3 for 2 h at rest particles from Chapel Hill, NC	Measures of conduction abnormalities including QT interval: from continuously worn halter data

Note: SD = standard deviation, M = male, F = female, n = number, GSTM1 = Glutathione S-transferase Mu 1, ECG = electrocardiogram QT = time interval between from beginning of the Q-wave to end of the T-wave

6.5.4.4 Toxicological Studies for Arrhythmia and Conduction Abnormalities

In the 2009 ISA, there were no toxicological studies that examined the effect of UFP CAP exposure on indicators of arrhythmia or conduction abnormalities. In the current review, Kurhanewicz et al. (2014) reported that short-term exposure to UFPs resulted in no appreciable change in ECG measurements. More information on this recently published study can be found in Table 6-75 below.

Table 6-75 Study specific details from toxicological studies of short-term ultrafine particle (UFP) exposure and conduction abnormalities.

Study	Study Population	Exposure Details	Endpoints Examined
(Kurhanewicz et al., 2014)	Adult, female C57BL/6 mice (10-12 week), n = 5-8/group	Inhalation of 138 μg/m^3 UFP CAP for 4h.	QRS, QT interval, *P*-wave,

d = day, h = hour, n = number, f = female, M = male, ECG = electrocardiogram, QT = time interval between from beginning of the Q-wave, to end of the T-wave, c = corrected for heart rate

6.5.5 Cerebrovascular Disease and Stroke

Cerebrovascular disease typically includes conditions such as hemorrhagic stroke, cerebral infarction (i.e., ischemic stroke) and occlusion of the pre-cerebral and cerebral arteries. Ischemic stroke results from an obstruction within a blood vessel that supplies oxygen to the brain, potentially leading to infarction. Hemorrhagic stroke is less common but results to a disproportionate amount of fatalities.

There were no studies in the last review with respect to short-term UFP exposure and stroke. The current review has a single hospital admission study that generally found a positive association between short-term UFP exposure and stroke.

6.5.5.1 Emergency Department Visits and Hospital Admissions

The 2009 PM ISA did not review any epidemiologic studies of UFP concentrations and ED visits and hospital admissions for CBVD/stroke. Andersen et al. (2010) recently studied 7,485 incident hospital admissions for stroke in Copenhagen, Denmark from 1995 to 2003. Data from a national stroke registry allowed the authors to consider stroke type (ischemic vs. hemorrhagic), stroke severity (mild vs. severe), and ischemic stroke subtype (with atrial fibrillation vs. without atrial fibrillation) in relation to UFP exposure (particle number concentration (10-700 nm) measured by fixed-site monitors at two urban locations). Andersen et al. (2010) observed increases in odds of hospital admissions for ischemic stroke, mild stroke, ischemic stroke without atrial fibrillation, and mild ischemic stroke without atrial fibrillation over the previous five days (lag 0-4). The associations were generally imprecise (i.e., wide 95% CIs), especially for the subgroup analyses. The association with the highest magnitude was observed between UFP exposure and hospital admissions for mild ischemic stroke without atrial fibrillation (OR: 1.21, 95% CI: 1.04, 1.41, per 3,918 particles/cm^3 increase, lag 0-4). The observed association was robust to adjustment for PM_{10}, NO_X, and CO in copollutant models.

6.5.6 Blood Pressure and Hypertension

High blood pressure results in the increased force on the artery walls and can damage the blood vessels and increase risk for cardiovascular disease and stroke. Hypertension is characterized by persistently elevated blood pressure. Additional information on blood pressure and hypertension can be found in Section 6.1.6.

In the 2009 PM ISA, a handful of epidemiologic panels studies and a single CHE study reported that exposure to UFPs did not result in increases in BP. In the current review, an additional CHE studies also reported that exposure to UFPs did not result in increases in BP. However, panel epidemiologic studies in the current review do provide some evidence for increases in blood pressure following UFP exposure. Thus, across disciplines evidence is both limited and inconsistent.

6.5.6.1 Emergency Department Visits and Hospital Admissions

Hypertension, a medical condition characterized by persistently elevated blood pressure, is a leading risk factor for myocardial infarction, heart failure, and cerebrovascular diseases. The 2009 PM ISA did not review any epidemiologic studies of ambient UFPs and ED visits and hospital admissions for hypertension. In the only recent study available, Franck et al. (2011) observed positive associations between short-term UFP exposure (measured by particle number concentration, < 100 nm, single fixed-site monitor) and emergency calls for hypertensive crisis in Leipzig, Germany. The authors examined individual lags from 0 to 10 days, and observed positive associations at every lag except for 0, 1, and 10. The authors presented their results graphically; detailed effect estimates were not provided. Additionally, when using alternative exposure metrics based on surface area and volume concentrations, Franck et al. (2011) reported cardiovascular effects were not "significantly correlated" with UFP exposure (quantitative results not presented).

6.5.6.2 Panel Epidemiologic Studies of Changes in Blood Pressure (BP)

Limited evidence was available for the 2009 PM ISA (U.S. EPA, 2009) examining exposures to UFP and changes in BP, though several recently published studies are available. Weichenthal et al. (2014a), Kubesch et al. (2014), and Liu et al. (2014b) all conducted studies that were quasi-experimental in design and provide some evidence for associations between $PM_{2.5}$ and SBP and DBP. Weichenthal et al. (2014a) and Liu et al. (2014b) both used personal monitoring for NCs (10-100nm) with differential exposure scenarios (sites with high and low pollution). Weichenthal et al. (2014a) reported positive associations between 2-hour averages of NCs with SBP measurements taken 3 hours post-exposure, but associations with SBP were null. In contrast, Liu et al. (2014b) reported a decrease in DBP and NCs with a 1-day lag (-0.78 mm hg; 95% CI: -1.40, -0.16; per 10256/cm^3). Chung et al. (2015) and Kubesch et al.

(2014) both utilized differential exposures to traffic. Kubesch et al. (2014) measured SBP and DBP in participants following a 2 hour exposure to high or low traffic and found positive associations personal average NCs (100-1000nm) and SBP, but not DBP. Chung et al. (2015) also included participants with differential traffic exposures and reported positive associations between NC and SBP, but not DBP, though there is greater uncertainty in NCs in this study do to fixed-site monitoring. Rich et al. (2012) also examined associations between BP and exposures to UFPs in a panel of cardiac rehabilitation patients that lived within 19 km of the clinic where NCs (10-100 nm) were measured. Associations between NCs and DBP were positive across exposure periods ranging from 23-hours up to 4-days, though a decrease in DBP was associated with 5-day averages of NCs; positive associations were also observed for SBP with 1- to 5-day average NCs (Rich et al., 2012). Overall, these recent studies provide some evidence of a relationship between exposure UFPs and BP that is in contrast to evidence for exposures to $PM_{2.5}$, but the evidence base is still quite small for UFP exposures compared to $PM_{2.5}$.

6.5.6.3 Controlled Human Exposure Toxicology Studies of Changes in Blood Pressure (BP)

In studies from the 2009 ISA, BP was not found to be affected by exposure to UF carbon particles (Frampton, 2001), UF EC (Shah et al., 2008; Routledge et al., 2006), or UF ZnO (Beckett et al., 2005). In the current ISA, no changes in BP were reported by Devlin et al. (2014) in metabolic syndrome patients (including those with GSTM1 null allele) exposed to UFP CAPs. In addition, in healthy men, Mills et al. (2011) found an increase in BP following exposure to DE (Table 6-76), however the increase was not attenuated following exposure to particle-filtered DE. Thus, there is no evidence from CHE studies to suggest an effect of UFP exposure on BP. More information on studies published since the 2009 ISA can be found in Table 6-76 below.

Table 6-76 Study specific details from CHE studies of short-term ultrafine particle (UFP) exposure and blood pressure (BP).

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Devlin et al., 2014)	Adults with metabolic syndrome n = 13 M; 21 F 27-70, average 15 of which carried the null allele for GSTM1	98 µg/m^3 UF CAPs (73% of which are <0.1 µm) 16,000–564,000 particles/cm^3 for 2 h at rest particles from Chapel Hill, NC	BP: pre, during, 1 h post

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Mills et al., 2011)	Healthy M N = 16 18- 32 yr	300 µg/m^3 UFP Particles generated with diesel engine passed through 0.1 µm filter 15-minute rest and cycling intervals during exposure Particle filtered exposures had UFP removed	BP: 6 h post

Note: SD = standard deviation, M = male, F = female, n = number, h = hour, CAP = concentrated ambient particle, DE = diesel exhaust; GSTM1 = Glutathione S-transferase Mu 1, BP = blood pressure

6.5.6.4 Toxicological Studies of Changes in Blood Pressure (BP)

There were no animal toxicology studies in the 2009 PM ISA exploring the relationship between short-term exposure to UFP and the angiotensin system. Since the publication of that review, a study has reported that short-term exposure to UFP can result in statistically significant increases in Ace and B1r, but not At1r mRNA in rat heart tissue (Aztatzi-Aguilar et al., 2015). However, in mice Kurhanewicz et al. (2014) reported that short-term exposure to UFPs resulted in no appreciable change in Ace serum levels compared to filtered air exposure. More information on these studies can be found in Table 6-77 below.

Table 6-77 Study specific details from toxicological studies of short-term ultrafine particle (UFP) exposure and blood pressure (BP).

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult male Sprague-Dawley rats (n = 4 per group)	Inhalation of UFP 107 µg/m^3 for 5 h/day, for 3 days	Renin-angiotensin gene expression. Heart tissue harvested 24 h post exposure
(Kurhanewicz et al., 2014)	Adult, female C57BL/6 mice (10-12 weeks), n = 5-8/group	Inhalation of 138 µg/m^3 UFP for 4 h	ACE serum levels 24-h post exposure.

Note: d = day, h = hour, n = number, f = female, M = male, ACE = angiotensin converting enzyme

6.5.7 Emergency Department Visits and Hospital Admission Studies of Cardiovascular-Related Effects

Many epidemiologic studies consider the composite endpoint of ED visits and hospital admissions for all cardiovascular diseases, including diseases of the circulatory system. This endpoint generally encompasses ED visits and hospital admissions for ischemic heart disease, MI, PVD, heart failure, arrhythmia, CBVD and stroke, and diseases of pulmonary circulation. A smaller body of studies examine the endpoint of cardiac diseases, a subset of CVD that specifically excludes hospitalizations for cerebrovascular disease, peripheral vascular disease, and other circulatory diseases not involving the heart or coronary circulation. The 2009 PM ISA did not review any epidemiologic studies of ambient UFPs and ED visits and hospital admissions for CVD or cardiac disease. Several recent studies are available for review provide emerging evidence of an association between UFP concentrations and ED visits and hospital admissions for CVD.

In a study in London, England, Atkinson et al. (2010) reported that cardiovascular-related hospital admissions were positively associated with UFP exposure (particle number concentration measured at a single fixed-site monitor for lag 1 and lag 0-1; quantitative results not reported; results presented graphically). In another study in London, England using a single fixed-site monitor, Samoli et al. (2016) reported null associations for cardiovascular-related hospital admissions and UFP exposure (particle number count, upper size limit of 3,000 nm, lag 1). Samoli et al. (2016) also examined associations between UFPs exposure (source apportionment, particle number size distribution, particles < 600 nm). The authors reported positive, but imprecise, associations with UFP linked to urban background and traffic sources, though not for particles attributed to regional nucleation or secondary particle formation. Similarly, in a study of five cities in Central and Eastern Europe, Lanzinger et al. (2016b) reported null associations for UFP (number count, 100 nm; particle number concentration, 800nm) across individual lags (lag 0 to lag 7) and multi-day averaged lags. In city-specific analyses, results did not substantially differ based on the exposure metric used, and results for UFP (NC100nm) were robust to adjustment for $PM_{2.5}$ or NO_2 both in pooled and city-specific estimates. A delayed association was observed in Beijing, China (Liu et al., 2013). Liu et al. (2013) reported a 7.2% (95% CI: 1.1, 13.7%) increase in cardiovascular-related ED visits corresponding to a 9,040 particle/cm^3 increase in 11-day moving average of UFP concentrations (measured by number concentration, particles 3-100 nm, single fixed-site monitor). Liu et al. (2013) also reported attenuated associations with 2-day moving averages based on number concentration (1.1%, 95% CI: -3.0%, 5.3%; 10,340 particle/cm^3, particles 3-100 nm), particularly Aitken mode particles. In Prague, Czech Republic, Braniš et al. (2010) assessed associations between submicron particles (particles 14.6 to 487 nm) measured from a single fixed-site monitor and cardiovascular-related HA. The authors reported positive associations with nucleation (14.6 to 48.7 nm) and Aitken (48.7 to 205 nm) mode particles, but the highest magnitude associations were observed with accumulation (205 to 487 nm) mode particles (e.g., RR 1.093, 95% CI: 1.019, 1.174, at lag 2 per 1,000 particles/cm^3 increase).

Overall, the evidence provides limited support for the presence of a positive association between UFP exposure and cardiovascular-related ED visits and HA. Evidence for this relationship is provided by a limited number of single-city studies conducted in Europe and Asia. The observed associations tend to be for delayed lags, with weak or null associations with UFP concentrations on the same day, and increasing associations thereafter; however, these studies relied on a single monitor to estimate UFP exposure. As detailed in CHAPTER 2 (Section 2.5.1.1.5, Section 2.5.1.2.4, and Section 2.5.2.2.3), the use of a single monitor does not adequately account for the spatial and temporal variability in UFP concentrations as well as the change in the particle size distribution that changes with distance from source. The range in measures used to represent UFP exposures also complicates the overall interpretation of results. Furthermore, the studies did not examine the potential for copollutant confounding.

6.5.8 Epidemiologic Studies of Cardiovascular Mortality

In the 2009 PM ISA, a small number of studies examined associations between short-term UFP exposure and cardiovascular mortality, providing some initial evidence of a positive association. Although the number of studies has increased, the total body of evidence remains small, as detailed in CHAPTER 11 (Section 11.4.1). Across studies that examined the UFP – cardiovascular mortality relationship, there is inconsistency in the particle size distribution that was used to represent UFP exposures with some studies measuring total number concentration (NC), while other studies measured NC with the upper end of the size distribution ranging from 100 – 3,000 nm. This disparity in the measurement of UFPs between studies complicates the overall interpretation of results.

The assessment of the relationship between short-term UFP exposure and cardiovascular mortality is limited to studies conducted in Europe (Stafoggia et al., 2017; Lanzinger et al., 2016a; Samoli et al., 2016) and China (Breitner et al., 2011). Focusing on NC, Breitner et al. (2011) reported evidence of a positive association, but confidence intervals were wide, whereas, the other studies evaluated reported no evidence of an association. Additionally, of the studies evaluated, (Breitner et al., 2011) also examined alternative exposure metrics, surface area concentration (SC) and mass concentration (MC), and reported positive associations that were imprecise (SC: 0.24% [95% CI: -2.72, 3.29], lag 0-4 per 12,060 cm^{-3}; MC: 0.13% [95% CI: -2.87, 3.23], lag 0-4 per 14.0 $\mu g/m^{3)}$. Although there is some evidence of a positive association between short-term UFP exposure and cardiovascular mortality, within each study only a single monitor was used to estimate exposure to UFPs (Table 11-9, UFP studies in mortality chapter). As detailed in CHAPTER 2 (Section 2.5.1.1.5, Section 2.5.1.2.4, and Section 2.5.2.2.3), the use of a single monitor does not adequately account for the spatial and temporal variability in UFP concentrations as well as the change in the particle size distribution that changes with distance from source.

6.5.9 Heart Rate (HR) and Heart Rate Variability (HRV)

Measured by ECG, heart rate variability (HRV) represents the degree of difference in the inter-beat intervals of successive heartbeats, and is an indicator of the balance between the sympathetic and parasympathetic arms of the autonomic nervous system. Additional information on HRV and HR can be found in Section 6.1.10.

In the 2009 PM ISA, there were a handful of epidemiologic panel and CHE studies that reported changes in metrics of HRV following short-term UFP exposure. Since the last review, an additional CHE study reported changes in HRV following UFP exposure. In addition to the CHE studies, several epidemiologic panel studies examined potential associations between metrics of HRV and short-term UFP exposure. The results of these studies were inconsistent with some studies showing positive associations while others did not. In addition, a single toxicological study did not find an effect of UFP exposure on HRV measures. Taken together, there is some evidence for an effect of short-term UFP exposure on HRV, but overall the evidence remains inconsistent within and across disciplines.

With respect to heart rate, a CHE and toxicological study did not find that UFP exposure resulted in changes in heart rate.

6.5.9.1 Epidemiologic Panel Studies of Heart Rate (HR) and Heart Rate Variability (HRV)

Limited evidence was available for the 2009 ISA, though some evidence indicated decreases in HRV relative to increases in PNC. Several recently published studies are available that examine associations between UFP concentrations and HRV (Hampel et al., 2014; Weichenthal et al., 2014a; Bartell et al., 2013; Rich et al., 2012; Schneider et al., 2010). Rich et al. (2012) reported reduced rMSSD and SDNN with 5-hour and 23-hour lagged exposures to NCs (10-100nm) in a panel of adults in a cardiac rehabilitation program living within 19km of the clinic where monitoring was conducted. Weichenthal et al. (2014a) conducted a quasi-experimental study with personal monitoring for NCs (10-100nm) during ambient exposure periods at different sites and reported positive associations between 2-hour averages of NCs with SDNN measured 3 hours post-exposure, but associations with rMSSD were null. Bartell et al. (2013) also found positive associations between SDNN and 5-day averages of NCs in a study of community-dwelling seniors (71 years of age or older) using residential monitoring for particles 100-3,000 nm in size. In contrast, Schneider et al. (2010) did not find associations between rMSSD or HF with NCs measured at a site representing urban background (10-100nm) in a panel of older adults with coronary artery disease. Overall, these recent studies provide some evidence for an association between exposure to UFP and changes in HRV, particularly SDNN among older adults and individuals with a history of cardiovascular disease.

6.5.9.2 Controlled Human Exposure Studies of Heart Rate (HR) and Heart Rate Variability (HRV)

The 2009 PM ISA discussed two studies that examined HRV, but no studies reporting potential changes in HR. Samet et al. (2009) demonstrated that healthy adults exposed to UF CAPs had an increase in both HF and LF frequency domains, but not in time domains. In addition, Gong et al. (2008) reported a small and transient decrease in LF in healthy and asthmatic adults.

Since the 2009 PM ISA, Mills et al. (2011) reported no difference in HR following exposure to DE (Table 6-78), or particle-filtered DE in healthy men. With respect to HRV, Devlin et al. (2014) exposed metabolic syndrome patients, including a subset with the GSTM1 null allele, to UFP CAP or FA. In the subset of patients expressing the GSTM1 null allele, decreases in HF ($p < 0.05$) and an increase in both LF ($p < 0.05$) and the LF/HF ratio ($p < 0.05$) was reported. Taken together, the is limited evidence of an UFP effect on HRV, but not HR. More information on studies published since the 2009 ISA can be found in Table 6-78 below.

Table 6-78 Study specific details from controlled human exposure (CHE) studies of short-term ultrafine particle (UFP) exposure and changes in heart rate (HR) and heart rate variability (HRV).

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Devlin et al., 2014)	Adults with metabolic syndrome n = 13 M; 21 F 27-70, average 15 of which carried the null allele for GSTM1	98 µg/m^3 UF CAPs (73% of which are <0.1 µm) 16,000–564,000 particles/cm^3 for 2 h at rest particles from Chapel Hill, NC	HRV time parameters: collected over 24 h HRV frequency domains: pre, 1 h post, 20 h post
(Mills et al., 2011)	Healthy men N = 16 18- 32 yr	300 µg/m^3 UFP Particles generated with diesel engine passed through 0.1 µm filter 15-min rest and cycling intervals during exposure Particle filtered exposures had UFP removed	HR: 6 h post

Note: SD = standard deviation, M = male, F = female, n = number, h = hour, CAP = concentrated ambient particle, DE = diesel exhaust; IQR = interquartile range, HRV = heart rate variability, GSTM1 = Glutathione S-transferase Mu 1

6.5.9.3 Toxicology Studies of Heart Rate (HR) and Heart Rate Variability (HRV)

Since the publication of the 2009 ISA, Kurhanewicz et al. (2014) reported that short-term exposure to UFPs resulted in no appreciable change in HR, SDNN, rMSSD, or LF/HF in mice. More information on this recently published study can be found in Table 6-79 below.

Table 6-79 Study specific details from toxicological studies of short-term UFP exposure and heart rate (HR) and heart rate variability (HRV).

Study	Study Population	Exposure Details	Endpoints Examined
(Kurhanewicz et al., 2014)	Adult, F C57BL/6 mice (10-12 week), n = 5-8/group	Inhalation of 138 μg/m^3 UFP for 4h.	HR, HRV time and frequency domains

n = number, h = hour, d = day, M = male, F = female HR = heart rate, HRV = heart rate variability.

6.5.10 Systemic Inflammation and Oxidative Stress

As discussed in Section 6.1.1 and Section 6.1.11, inflammation has been linked to a number of CVD related outcomes. For example, circulating cytokines such as IL-6 can stimulate the liver to release inflammatory proteins and coagulation factors that can ultimately increase the risk of thrombosis and embolism. Similarly, oxidative stress can result in damage to healthy cells and blood vessels and a further increase in the inflammatory response. Thus, this section discusses the evidence for markers of systemic inflammation and oxidative stress following short-term UFP exposures.

6.5.10.1 Epidemiologic Panel Studies of Systemic Inflammation and Oxidative Stress

Several recently published panel studies add to the limited evidence available for the 2009 ISA that provide some evidence for increases in systemic inflammation relative to UFP counts. In a panel study including 31 young, healthy adults exposed to air pollution at 5 different sites with intermittent exercise, Steenhof et al. (2014) reported mixed results for associations between UFPs and WBC counts; while decreases were observed for eosinophils and lymphocytes with PNCs at 2 and 18 hours post-exposure, respectively, increases in monocytes were observed and no changes were reported for neutrophils or total WBC counts. In this same panel, no associations were observed for PNC and CRP (Strak et al., 2013a).

In nursing home residents in Los Angeles, CA with ischemic heart disease, Wittkopp et al. (2013) did not find associations for CRP or soluble receptor for IL-6 with up to 5-day averages of PNC. In addition, other studies in panels with pre-existing cardiovascular disease generally did not find evidence for associations. While Rich et al. (2012) and Croft et al. (2017) found a positive association between CRP and 24-47-hour averages of UFPs. Associations were not found for other averaging times or with WBC counts (Rich et al., 2012) and negative associations between 12-96-hour lags of UFPs and myeloperoxidase were observed (Croft et al., 2017). In elderly with ischemic heart disease, PNC was associated with higher IL-12 but not CRP, IL-6, IL1B, IL-8, and IFNγ in 52 participants in Kotka, Finland (Huttunen et al., 2012).

In Heinz Nixdorf Recall study including approximately 4,000 participants, particle number concentration (PNC) based on a chemical transport model with a resolution of 1 × 1 km was associated with higher CRP in averaging periods from 2 up to 28 days with the largest effect estimates reported for 21-day average [7.1% (95% CI 1.9, 12.6) per IQR (4,580 particles x 104/ml)] (Hertel et al., 2010). Similarly, Karottki et al. (2014) reported associations between 48-hour PNC and CRP; no associations were observed for changes in WBCs.

6.5.10.2 Controlled Human Exposure Studies of Short-Term UFP Exposure and Systemic Inflammation and Oxidative Stress

Controlled human exposure studies from the 2009 PM ISA reported no change in plasma CRP levels following a 2-hour exposure to UFPs, although one study looked at and reported a significant increase in IL-8 (Samet et al., 2009; Gong et al., 2008). No change in plasma CRP was reported.

In the current review, Liu et al. (2015a) studied the potential for UFP exposure and endotoxin to associate with the biomarkers for inflammation IL-6 and CRP-. no associations were found. Devlin et al. (2014) also found no differences in sICAM-1 or sVCAM-1 (as well as no differences in neutrophils, lymphocytes, monocytes, platelets) in patients with metabolic syndrome, including a subset with the GSTM1 null allele. However, 20 hour post exposure, CRP was elevated (30.4 ± 11.9%, $p = 0.016$), as was the acute phase inflammatory marker SAA (77.5 ± 37.2%, $p = 0.043$). With respect to filtered diesel exhaust, in healthy men Mills et al. (2011) reported no statistical difference in leukocytes, neutrophils, or lymphocytes following exposure to DE (Table 6-80) or particle-filtered DE. In total, there is limited evidence from one CHE study indicating a systemic inflammatory response in metabolic syndrome patients.

With respect to markers of oxidative stress, Liu et al. (2015a) examined the potential for UF CAP exposure to increase levels of the biomarker of lipid peroxidation MDA and the DNA oxidative damage biomarker 8-OHdG. Ultrafine CAP exposure did not result in an increase in blood or urine levels of MDA. However, urine sampling revealed increases in 8-OHdG (0.69 ng/mg creatinine; 95% CI: 0.09, 1.29) at one hour but not 21 hours post-exposure. Thus, there is only limited evidence to suggest that UFP

exposure effects markers of oxidative stress. More information on studies published since the 2009 ISA can be found in Table 6-80 below.

Table 6-80 Study specific details from controlled human exposure (CHE) studies of short-term UFP exposure and systemic inflammation.

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Devlin et al., 2014)	Adults with metabolic syndrome n = 13 M; 21 F 27-70, average 15 of which carried the null allele for GSTM1	98 µg/m^3 UF CAPs (73% of which are <0.1 µm) 16,000–564,000 particles/cm^3 for 2 h at rest particles from Chapel Hill, NC	Markers of systemic inflammation and pre,1 h post, 20 h post
(Liu et al., 2015a)	Healthy adults n = 50; 18-60 yrs 28 ± 9	135.8 ± 67.2 µg/m^3 ultrafine cap for 130 min from Toronto, Canada	Markers of inflammation and oxidative stress measured pre, 1 h, and 21 h post
(Mills et al., 2011)	Healthy men N = 16 18- 32 yr	300 µg/m^3 UFP Particles generated with diesel engine passed through 0.1 µm filter 15-min rest and cycling intervals during exposure Particle filtered exposures had UFP removed	Markers of coagulation

Note: SD = standard deviation, M = male, F = female, n = number, h = hour, GSTM1 = glutathione S-transferase Mu 1, CAP = concentrated ambient particle

6.5.10.3 Toxicological Studies of Short-Term Ultrafine Particle (UFP) Exposure and Systemic Inflammation and Oxidative Stress

In the 2009 PM ISA, there were no animal toxicological studies examining the effects of short-term UFP exposure on markers of systemic inflammation or oxidative stress. Since the publication of that document, Kurhanewicz et al. (2014) reported that short-term exposure to UFPs did not result in a change in CRP levels or potential markers of oxidative stress relative to FA control animals. More information on studies published since the 2009 ISA can be found in Table 6-81 below.

Table 6-81 Study specific details from controlled human exposure (CHE) studies of short-term UFP exposure and systemic inflammation.

Study	Study Population	Exposure Details	Endpoints Examined
(Kurhanewicz et al., 2014)	Adult, F C57BL/6 mice (10-12 week), n = 5-8/group	Inhalation of 138 μg/m^3 UFP for 4h.	CRP, markers of oxidative stress in serum 24h post -exposure

Note: n = number, h = hour, d = day, M = male, F = female CRP = c-reactive protein

6.5.11 Coagulation

Coagulation refers to the process by which blood changes from a liquid to a semi-solid state in order to form a clot. Increases in coagulation factors (e.g., fibrinogen) or decreases in anti-coagulation factors can promote clot formation, and thus, increase the potential for an embolism.

In the 2009 PM ISA, CHE studies examined whether exposure to UFPs could result in changes in markers of coagulation. In general, results from these studies were negative. Since the 2009 PM ISA, a couple of additional CHE studies have reported inconsistent results, with one study showing changes in markers of coagulation, while the other study did not. Similarly, results from epidemiologic panel studies also report limited evidence of an associations between UFP concentrations and changes in markers of coagulation.

6.5.11.1 Panel Epidemiologic Studies

In the 2009 PM ISA (U.S. EPA, 2009), no studies were available that examined associations between short-term exposure to UFPs and biomarkers of coagulation, though a handful of studies have been published since. Among the recently published studies is one that used a quasi-experimental study design, including personal monitoring at five different locations in Utrecht, the Netherlands allowing for increased exposure contrast and reduced correlations between PM characteristics. Results from this study demonstrate that NCs (7-3000 nm) measured at the five different exposure sites were not associated with platelet counts or fibrinogen (Strak et al., 2013a). However, average NCs for the five-hour exposure periods, particularly those from the outdoor sites, were associated with reduced lag time in FXII-mediated (intrinsic) thrombin generation in a single pollutant model and several two-pollutant models, including those with PM_{10}, $PM_{2.5}$, OC, NO_3-, and SO_4^{2}-. These measures indicated hypercoagulability via the intrinsic pathway, but there was little evidence to suggest changes in the extrinsic pathway (tissue-factor mediated) (Strak et al., 2013b).

Other panel studies have examined fibrinogen and a number of other biomarkers as well. Hildebrandt et al. (2009) conducted a study to examine blood markers in a panel of adults with chronic pulmonary disease and reported positive associations with 1- (2.5%; 95% CI: 0.2, 4.9) and 3-day (2.5%; 95% CI: 0.2, 4.9 and 3.3; 95% CI: 1.0, 5.6, respectively, per 3827/cm^3 increase) lagged NCs (10-100nm) as well as 5-day averages (3.1%; 95% CI: 0.2, 6.0; per 2918/cm^3 increase). However, other study results included a negative association between 3-day lagged NCs and fibrinogen, negative associations between vWF and D-dimer for a number of lags, and null associations for prothrombin fragment 1+2 (Hildebrandt et al., 2009). Fibrinogen was also positively associated with 24- to 47-hour average NCs (10-100nm) in cardiac rehabilitation patients in Rochester, NY (Wang et al., 2016; Rich et al., 2012) and with 12 up to 96 hour averages of NCs (10-100 nm) in adults with acute coronary syndrome (Croft et al., 2017). In contrast, associations with fibrinogen were not observed in a study of older adult participants with ischemic heart disease (Huttunen et al., 2012) or a panel of individuals with a history of MI (Peters et al., 2009), though exposure measurement, including NC size range, was not described in these studies. Brüske et al. (2011) examined associations between lipoprotein-associated phospholipase A2, which has recently been shown to be an independent predictor of coronary heart disease events, and NCs (<100nm; measured at a fixed-site representing urban background) and found negative associations at 0- to 2-day lags but positive associations for 4-5-day lags in a prospective panel study of MI survivors.

6.5.11.2 Controlled Human Exposure Studies

The 2009 PM ISA included a study of healthy and asthmatic adults exposed to UFP CAPs from CA(Gong et al., 2008). No significant changes were reported for D-dimer, vWF, PAI-1, factors VII and IX, fibrinogen, plasminogen, or TPA levels. In an additional study, healthy adults were exposed to UFPs from NC while alternating between 15-minute rest/exercise sessions. Increases in D-dimer concentration, but not in PAI-1, vWF, tPA, fibrinogen, plasminogen, or factors IX or VII, were found (Samet et al., 2009).

In the current review, Devlin et al. (2014) examined the effects of UFP exposure on markers of fibrinolysis in metabolic syndrome patients, including a subgroup (n = 15) carrying the null allele for GSTM1. The anticoagulant proteins plasminogen ($p = 0.022$) and thombomodulin ($p = 0.048$) had a statistically significant decrease when examining the entire study population at 20 hours but not one hour post exposure. There were no statistically significant changes in a number of other measured markers including tPA, D-dimer, and vWF. Moreover, in healthy men Mills et al. (2011) reported no difference in t-PA and PAI-1 antigen or activity or platelets following exposure to either DE or filtered-DE.

Taken together, there is some evidence from a single CHE study for changes in biomarker levels that would be indicative of increased risk of thrombosis and coagulation in patients with metabolic syndrome. More information on studies published since the 2009 ISA can be found in Table 6-82 below.

Table 6-82 Study specific details from controlled human exposure (CHE) studies of short-term UFP exposure and coagulation and thrombosis.

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Devlin et al., 2014)	Adults with metabolic syndrome n = 13 M; 21 F 27-70, average 15 of which carried the null allele for GSTM1	98 µg/m^3 UF CAPs (73% of which are <0.1 µm) 16,000–564,000 particles/cm^3 for 2 h at rest particles from Chapel Hill, NC	Markers of coagulation: pre,1 h post, 20 h post
(Mills et al., 2011)	Healthy men N = 16 18- 32 yr	300 µg/m^3 UFP Particles generated with diesel engine passed through 0.1 µm filter 15-min rest and cycling intervals during exposure Particle filtered exposures had UFP removed	Markers of coagulation

Note: SD = standard deviation, M = male, F = female, n = number, h = hour, GSTM1 = glutathione S-transferase Mu 1, CAP = concentrated ambient particle

6.5.12 Endothelial Dysfunction and Arterial Stiffness

Endothelial dysfunction is the physiological impairment of the inner lining of the blood vessels and is typically measured by FMD. Arterial stiffness is associated with a variety of cardiovascular risk factors and outcomes (Laurent et al., 2006) and is best measured by pulse wave velocity (PWV). More information on measures of endothelial dysfunction and arterial stiffness can be found in Section 6.1.13.

There were no studies in the 2009 PM ISA examining the relationship between exposure to UFPs and endothelial dysfunction or arterial stiffness. Since publication of the 2009 PM ISA, a single epidemiologic panel and a few CHE studies have examined the potential for UFP exposure to result in changes in measures in endothelial dysfunction. Taken together, these studies provide some evidence that exposure to UFPs can result in endothelial dysfunction.

6.5.12.1 Panel Epidemiologic Studies

There were no studies in the 2009 ISA examining associations between short-term exposures to UFPs and measures of endothelial dysfunction, and only a single study is available from the recently published literature. Ljungman et al. (2014) examined associations between UFPs and peripheral arterial tonometry, a measure of microvessel dilation, and pulse wave amplitude in the Framingham Heart Study and found positive associations for 1 to 7-day averages.

6.5.12.2 Controlled Human Exposure Studies

In the current review, BAD and FMD were both examined following UFP exposure in metabolic syndrome patients, including a subgroup with the GSTM1 null allele (Devlin et al., 2014). No effects of UFPs were observed following reactive hyperemia or nitroglycerin administration when compared to FA. In contrast, Mills et al. (2011) found that the vasodilation response to bradykinin ($p = 0.005$), acetylcholine ($p = 0.008$), and sodium nitroprusside ($p < 0.001$) were attenuated following exposure to DE (Table 6-83) relative to FA, but not following exposure to particle-filtered DE.

With respect to protein markers of endothelial dysfunction, Liu et al. (2015a) examined whether short-term exposure to UFPs increased levels of and ET-1 or VEGF. There were no increases in blood ET-1 or urine VEGF levels, but the authors did report a statistically significant ($p < 0.05$) increase in blood VEGF levels at 21 hours, but not one hour post exposure.

Taken together, the studies presented above provide some evidence of impaired vasomotor function following short-term exposure to UFPs present in diesel exhaust, but very little evidence following short-term exposure to UFP CAPs. More information on studies published since the 2009 ISA can be found in Table 6-83 below.

Table 6-83 Study specific details from controlled human exposure (CHE) studies of short-term UFP exposure and impaired vascular function.

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Devlin et al., 2014)	Adults with metabolic syndrome n = 13 M; 21 F 27-70, average 15 of which carried the null allele for GSTM1	98 µg/m^3 UF CAPs (73% of which are <0.1 µm) 16,000–564,000 particles/cm^3 for 2 h at rest particles from Chapel Hill, NC	Vascular function: pre, 1 h post, 20 h post

Table 6-83 (Continued): Study specific details from controlled human exposure (CHE) studies of short-term UFP exposure and impaired vascular function.

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Liu et al., 2015a)	Healthy adults n = 50; 18-60 yrs 28 ± 9	135.8 ± 67.2 μg/m^3 ultrafine cap for 130 min	Biomarkers of vascular function measured pre, 1 h, and 21 h post
(Mills et al., 2011)	Healthy men N = 16 18- 32 yr	300 μg/m^3 UFP Particles generated with diesel engine passed through 0.1 μm filter 15-min rest and cycling intervals during exposure Particle filtered exposures had UFP removed	Vascular function: 6-8 h post

Note: SD = standard deviation, M = male, F = female, n = number, h = hour, GSTM1 = glutathione S-transferase Mu 1, CAP = concentrated ambient particle

6.5.13 Summary and Causality Determination

In the 2009 PM ISA (U.S. EPA, 2009), the evidence from toxicological studies predominantly using DE exposures was suggestive of a causal relationship between short-term UFP exposure and cardiovascular effects. Cardiovascular effects included altered endothelial function, increased systemic oxidative stress, and altered HRV parameters. In addition, studies using UF CAPs, as well as wood smoke and DE, provided some evidence of changes in markers of blood coagulation, but results were not consistent across studies. The few epidemiologic studies of UFPs in the last review did not provide support for an association of UFPs with effects on the cardiovascular system. More recent evidence describing the relationship between short-term UFP exposure and cardiovascular effects is discussed below and summarized in Table 6-84, using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015).

Since the publication of the 2009 PM ISA, there have been a limited number of studies describing the relationship between short-term UFP exposure and cardiovascular effects. That being said, there is at least some evidence for cardiovascular effects following short-term exposure to UFPs. A small number of epidemiologic panel studies have observed positive associations between short-term exposure to UFPs and measures of HRV (Section 6.5.9.1) and markers of coagulation (Section 6.5.11.1), although there are also studies that did not report UFP-related effects. In addition, there is evidence from a single CHE study indicating decreases in the anticoagulant proteins plasminogen and thombomodulin in individuals with metabolic syndrome (Section 6.5.11.2). There was also inconsistent evidence from CHE and

epidemiologic panel studies for endothelial dysfunction, changes in blood pressure, and systemic inflammation following exposure to UFPs. Notably, there was little evidence of an effect when considering short-term UFP exposure on other cardiovascular endpoints or epidemiologic outcomes such as ED visits or hospital admissions. However, when considered as a whole, the evidence presented in Section 0 is **suggestive of, but not sufficient to infer, a causal relationship between short-term exposure to UFPs and cardiovascular effects.**

Table 6-84 Summary indicating that evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term UFP exposure and cardiovascular effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	UFP Concentrations Associated with Effects[c]
Evidence from a limited number of epidemiologic panel studies and a controlled human exposure study is generally supportive	Some evidence of positive associations in epidemiologic panel studies of HRV and coagulation A single CHE study indicating decreases in the anticoagulant proteins plasminogen and thombomodulin in individuals with metabolic syndrome.	Section 6.5.10 Section 6.5.11 Section 6.5.12 Section 6.5.13 Devlin et al. (2014)	See tables in identified sections
Limited and inconsistent epidemiologic evidence for ED visits and hospital admissions	Limited evidence does not support association with ED visits and hospital admissions for IHD Limited evidence supports association with ED visits and hospital admissions for aggregate CVD	Section 6.5.2.1 Section 6.5.7	
Uncertainty regarding potential confounding by copollutants	Single study provides limited evidence that UFP association is robust to PM_{10} and gaseous copollutants in study of stroke ED visits. Panel studies did not evaluate potential copollutant confounding	Andersen et al. (2010)	
Uncertainty regarding exposure metric and UFP size fraction	Inconsistency in the UFP metric used (i.e., NC, SC, and MC) and UFP size fraction examined complicating interpretation of results across studies.		
Uncertainty regarding exposure measurement error	Single study used personal UFP monitoring. Most studies relied on 1 monitor to measure UFPs, which is inadequate based on limited data demonstrating both that there is greater spatial variability in UFPs (i.e., NC) and that the particle size distribution changes with distance from source. Additionally, there is limited information on the temporal variability in UFP concentrations.	Hampel et al. (2014)	

Table 6-84 (Continued): Summary indicating that evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term UFP exposure and cardiovascular effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	UFP Concentrations Associated with Effects[c]
Little evidence from animal toxicological studies	The few animal toxicological studies that examined the relationship between UFP CAP exposure and CVD endpoints reported mostly negative results	(Aztatzi-Aguilar et al., 2015) Kurhanewicz et al. (2014)	
Limited evidence for biological plausibility of cardiovascular effects	There were very few studies on which to base biologically plausible pathways for the few epidemiologic studies reporting positive associations between UFP exposure and ED visits or hospital admissions	Section 6.5.1 Figure 6-36	

a = Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

b = Describes the key evidence and references, supporting or contradicting, contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

c = Describes the UFP concentrations and metric (i.e., number concentration [NC], surface area concentration [SC], mass concentration [MC]) with which the evidence is substantiated.

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6.6 Long-Term UFP Exposure and Cardiovascular Effects

The evidence pertaining to the effect of long-term exposure to ultrafine particles (UFPs) on the cardiovascular system reviewed in the 2009 PM ISA comprised a small number of toxicological studies that indicated the potential for long-term exposure UFP to lead to atherogenic changes. The evidence provided by these studies was characterized as "inadequate to infer the presence or absence of a causal relationship" (U.S. EPA, 2009).

The subsections below provide an evaluation of the most policy relevant scientific evidence relating-long-term UFP exposure to cardiovascular health effects. To clearly characterize and put this evidence into context, there is first a discussion of the biological plausibility of cardiovascular effects following long-term UFP exposure (Section 6.6.1). Following this discussion, the health evidence relating long-term UFP exposure and specific cardiovascular health outcomes is discussed in detail: atherosclerosis (Section 6.6.2) heart failure and impaired heart function (Section 6.6.3) increased blood pressure and hypertension (Section 6.6.4), and systemic inflammation and oxidative stress (Section 6.6.5). Considering all of the information presented above, summary and causal determinations are then presented (Section 6.6.6).

6.6.1 Biological Plausibility

There continues to be a lack of evidence for health effects following long-term exposure to UFPs. As a result, there is very little evidence for biological plausibility of health effects in humans, and thus, a biological plausibility figure was not constructed for this size fraction. However, as noted below, there is limited toxicological evidence for atherosclerosis (Li et al., 2013), impaired heart function (Aztatzi-Aguilar et al., 2015), systemic inflammation (Aztatzi-Aguilar et al., 2015) and changes in the renin-angiotensin system (Aztatzi-Aguilar et al., 2015).

6.6.2 Atherosclerosis

In the 2009 PM ISA, ultrafine CAPs derived from traffic were demonstrated to increase plaque size in ApoE$^{-/-}$ mice (Araujo et al., 2008). Since the 2009 PM ISA, Aguilera et al. (2016) reported a 2.1% increase (95%CI: 0.03, 4.10) per interdecile increase in PN and 2.3% increase (95% CI: 0.23, 4.4) per interdecile increase in Lung Deposited Surface Area (LDSA). NC (10-300 nm) concentration was measured directly with diffusion classifier for use in LUR model in this study. More information on this recently published study can be found in Table 6-85.

Table 6-85 Characteristics of the epidemiologic study examining the association of UFP with circulating markers of inflammation and coagulation.

Study	Study Population	Exposure Assessment	Concentration	Outcome	Copollutants Examined
†(Aguilera et al., 2016) 4 Cities, Switzerland Cross-sectional PNC: 2011/22 Outcome: 2010/2011	SAPALDIA N = 1,503	2 yr avg estimated at residence using LUR PNC Model R^2 = 0.85 miniature diffusion classifier (10-300 nm)	PNC Mean 11,184 (SD: 4,862) particles/cm^3	cIMT	PNC with $PM_{2.5}$ last yr r = 0.88, $PM_{2.5}$ 2001-2011 r = 0.86; $PM_{2.5}$ vehicular r = 0.86; $PM_{2.5}$ crustal 0.83

LDSA = Lung Deposited Surface Area, PNC = particle number concentration; SAPALDIA = Swiss study on Air Pollution and Lung Disease in adults; Hs-CRP = high sensitivity C-reactive Protein; cIMT = carotid intima media thickness; NR = Not reported

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

6.6.3 Heart Failure and Impaired Heart Function

Since the 2009 PM ISA, Aztatzi-Aguilar et al. (2015) reported that long-term UFP exposure in rats resulted in thickening of the coronary artery walls. These authors also found that long-term exposure to UFP resulted in a statistically significant increase in two genes typically associated with cardiac damage in heart tissue: Acta1 and Col3a. Thus, there is limited evidence from animal toxicological studies of potential decreases in heart function following long-term UFP exposure. More information on this study can be found in Table 6-86.

Table 6-86 Study-specific details from toxicological studies of long-term UFP exposure and impaired heart function.

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult male Sprague-Dawley rats (n = 4 per group)	Inhalation of ultrafine PM (107 µg/m^3) for 5 h/day, 4 days/week, for 8 weeks	Coronary wall thickness, Acta 1 and Col3a1 mRNA

Note: n = number, h = hour, d = day, week = week, M = male, f = female, Acta1 = skeletal alpha-actin, Col3a1 = collagen Type 3 alpha

6.6.4 Blood Pressure and Hypertension

There were no animal toxicology studies in the 2009 PM ISA exploring the relationship between long-term exposure to UFP and the angiotensin system. Since the publication of that review, long term exposure to UFP has been reported to significantly increase mRNA levels in the heart of At2R and At1R ($p < 0.05$), but not Ace, or b1R (Aztatzi-Aguilar et al., 2015). More information on this recently published study can be found in Table 6-87 below.

Table 6-87 Study-specific details from toxicological studies of long-term UFP exposure and blood pressure (BP).

Study	Population N, Sex; Age Mean ± SD	Exposure Details Concentration; Duration	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult male Sprague-Dawley rats (n = 4 per group)	Inhalation of 107 μg/m^3 ultrafine PM for 5 h/day, 4 days/week, for 8 weeks	Angiotensin and bradykinin system gene and protein expression

m = male n = number, h = hour, week = week

6.6.5 Systemic Inflammation and Oxidative Stress

As discussed in Section 6.1.1 and Section 6.1.11, inflammation has been linked to a number of CVD related outcomes. Similarly, oxidative stress can result in damage to healthy cells and blood vessels and a further increase in the inflammatory response. Thus, this section discusses the evidence for markers of systemic inflammation and oxidative stress following short-term UFP exposures.

6.6.5.1 Epidemiologic Studies

The epidemiologic evidence continues to be limited. In a recent study, Viehmann et al. (2015) observed small longitudinal changes in hs-CRP [3.8 -0.6, 8.4], fibrinogen [1.0 0.0, 2.0], WCC [1.0 -0.1, 2.1] and platelets [0.6 -0.4, 1.7] in association with an IQR increase in 365 day moving average PNC concentration among participants in the HNR study in Germany. The mean PNC concentration was 88,000 in this study.

6.6.5.2 Toxicology Studies

Since the 2009 PM ISA, Aztatzi-Aguilar et al. (2015) reported that rats exposed to UFP had increased ($p < 0.05$) IL-6 and decreased ($p < 0.05$) HO-1 protein levels in heart tissue. More information on this recently published study can be found in Table 6-88 below.

Table 6-88 Study-specific details from toxicological studies of long-term UFP exposure and systemic inflammation and oxidative stress.

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult male Sprague-Dawley rats (n = 4 per group)	Inhalation of 107 μg/m^3 ultrafine PM collected from a high traffic and industrial area north of Mexico City in early summer and exposed for 5 h/day, 4 days/week for 8 weeks	Markers of systemic inflammation and oxidative stress in heart tissue

Notes: m = male n = number, h = hour, d = day, week = week

6.6.6 Summary and Causality Determination

In the 2009 PM ISA, there was evidence from an animal toxicological study of increased atherosclerotic plaque size in mice following long-term exposure to UFPs. Since the publication of the 2009 PM ISA, a small number of epidemiologic studies reporting positive associations between long-term exposure to UFPs and cIMT and markers of inflammation and coagulation have become available. In addition, a single recent animal toxicological study reported evidence of impaired heart function (Section 6.6.3), as well as changes in markers associated with systemic inflammation, oxidative stress (Section 6.6.5.2), and the renin-angiotensin system following long-term UFP exposure (Section 6.6.4). However, the overall toxicological evidence base examining the effects of long-term UFP exposure on cardiovascular endpoints remains extremely limited, and thus, there is little biological plausibility for the effects observed in the epidemiologic studies mentioned above. Therefore, as in the previous review, the evidence characterizing the relationship between long-term UFP exposure and cardiovascular effects is **inadequate to infer the presence or absence of a causal relationship.** The evidence for the relationship between long-term exposure to UFPs and effects on the cardiovascular system is summarized in Table 6-89, using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015).

Table 6-89 Summary of evidence that is inadequate to infer the presence or absence of a causal relationship between long-term UFP exposure and cardiovascular effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	UFP PM Concentrations Associated with Effects[c]
Limited epidemiologic evidence	Long-term exposure to UFPs associated with Increase in cIMT and markers of inflammation and coagulation; Overall few epidemiologic studies of UFP health effects are conducted.	Aguilera et al. (2016) Viehmann et al. (2015)	Mean: 11,184 particles/cm^3 Mean: 88,000 particles/ml
Limited animal toxicological evidence	Long-term exposure to UFPs increased coronary artery wall thickness, markers of systemic inflammation, and some markers in the renin-angiotensin system.	Aztatzi-Aguilar et al. (2015)	
Uncertainty regarding potential confounding by copollutants	PNC strongly correlated with $PM_{2.5}$ concentrations (r = 0.88)	Aguilera et al. (2016)	
Uncertainty regarding exposure measurement error	Potentially uncharacterized spatial and temporal variation of UFP concentration limits interpretation of epidemiologic evidence		
Uncertainty regarding biological plausibility	Lack of evidence to characterize the biological plausibility of health effects following long-term PM 2.5 exposure.		

$PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than a nominal diameter of 2.5 µm; SO_2 = sulfur dioxide.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

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CHAPTER 7 METABOLIC EFFECTS

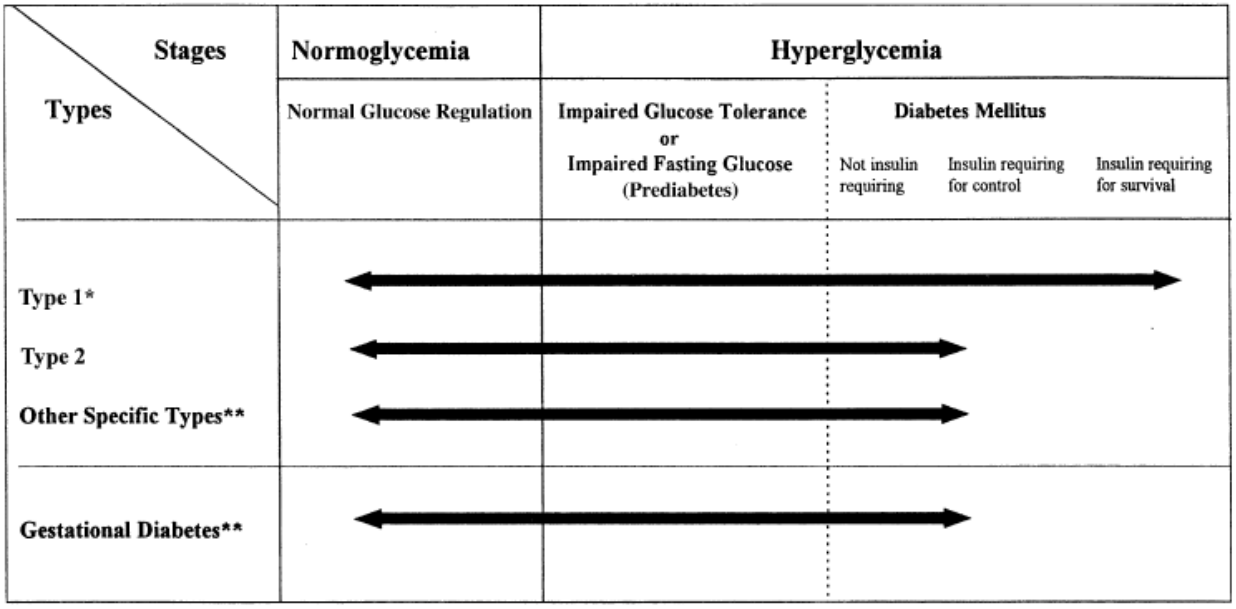
Summary of Causality Determinations for Short- and Long-Term Particulate Matter (PM) Exposure and Metabolic Effects

This chapter characterizes the scientific evidence that supports causality determinations for short- and long-term PM exposure and metabolic effects. The types of studies evaluated within this chapter are consistent with the overall scope of the ISA as detailed in the Preface (see Section P.3.1). In assessing the overall evidence, strengths and limitations of individual studies were evaluated based on scientific considerations detailed in the Appendix. More details on the causal framework used to reach these conclusions are included in the Preamble to the ISA (U.S. EPA, 2018).

Size Fraction	Causality Determination
Short-term exposure	
$PM_{2.5}$	Suggestive of, but not sufficient, to infer
$PM_{10-2.5}$	Suggestive of, but not sufficient, to infer
UFP	Inadequate
Long-term Exposure	
$PM_{2.5}$	Suggestive of, but not sufficient, to infer
$PM_{10-2.5}$	Suggestive of, but not sufficient, to infer
UFP	Inadequate

The evidence relevant to metabolic effects that was reviewed in the 2009 PM ISA included a small number of studies that examined the extent to which diabetes and metabolic syndrome-like phenotypes conferred susceptibility to PM-related health effects (U.S. EPA, 2009). Specifically, exaggerated insulin resistance, visceral adiposity and systemic inflammation in response to chronic exposure to CAPs was demonstrated in animals fed a high-fat diet. Epidemiologic studies reported some evidence for increased cardiovascular effects among people with diabetes or metabolic syndrome in association with PM_{10} exposure, providing preliminary evidence for pathophysiologic alterations experimentally demonstrated. There was no causal determination for metabolic effects in the 2009 ISA. The literature has expanded substantially with the bulk of evidence informing the relationship between long-term exposure to $PM_{2.5}$ and metabolic effects including glucose and insulin homeostasis and Type 2 diabetes (T2D).

The metabolic effects reviewed in this chapter include metabolic syndrome and its components (Table 7-1), diabetes (Table 7-2 and Figure 7-1), metabolic disease mortality as well as indicators of metabolic function that underlie metabolic and cardiovascular diseases. Studies that inform our understanding of whether people diagnosed with metabolic syndrome or diabetes are at increased risk of PM-related health effects are also discussed in CHAPTER 12, Section 12.3.2 (Populations and Lifestages Potentially at Increased Risk for PM Health Effects).



Note: *Even after presenting in ketoacidosis, these patients can briefly return to normoglycemia without requiring continuous therapy (i.e., "honeymoon" remission).

**In rare instances, patients in these categories (e.g., Vacor toxicity, Type 1 diabetes presenting in pregnancy) may require insulin for survival.

Source: Permission pending, ADA (2014).

Figure 7-1 Disorders of glycaemia: etiologic types and stages.

Metabolic syndrome is a term used to describe a collection of risk factors that include high blood pressure, dyslipidemia (elevated triglycerides and low levels of high density lipoprotein [HDL] cholesterol), obesity (particularly central obesity), and increased fasting blood glucose (FBG) (Table 7-1) (Alberti et al., 2009). The presence of these risk factors may predispose one to an increased risk of T2D and cardiovascular disease (see CHAPTER 6).

Table 7-1 Criteria for clinical diagnosis of Metabolic Syndrome

Risk Factor	Threshold
Waist circumference	≥89 cm in women and ≥102 cm in males
Triglycerides[a]	≥150 mg/dL (1.7 mmol/L)
HDL-C1	<40 mg/dL (1.0 mmol/L in males); <50 mg/dL (1.3 mmol) in females
Blood pressure[b]	Systolic ≥130 and/or diastolic ≥85 mm Hg
Fasting glucose[c]	≥100 mg/dL (5.6 mmol/L)

[a]A person taking drugs used to lower triglycerides or raise HDL-C is considered to exceed the threshold.
[b]A person taking blood pressure medication is considered to exceed the threshold.
[c]A person taking glucose regulating medication is considered to exceed the threshold.
Source: Permission pending, Adapted from Alberti et al. (2009).

Diabetes is characterized by a continuum of hyperglycemia (i.e., elevated glucose level) resulting from defects in insulin signaling, secretion or both (Figure 7-1). Several types of diabetes have been classified by the American Diabetes Association (ADA) (ADA, 2014). Type 1 diabetes (T1D) is caused by β-cell dysfunction or destruction that leads to insulin deficiency (Section 7.2.7), while T2D is characterized by defects in insulin secretion in an insulin resistant environment (Section 7.2.4). Gestational diabetes mellitus (GDM) is generally diagnosed during the 2nd or 3rd trimester of pregnancy (Section 7.2.6). The diagnostic testing criteria for diabetes are listed in Table 7-2. The A1C, which is also known as the hemoglobin A1C, HbA1C, or glycohemoglobin, is a blood test that provides information about a person's average blood glucose over the past 3 months by measuring the percentage of hemoglobin (i.e., a blood protein with a 3-month lifespan) modified by glucose. In controlled human exposure, animal toxicological, and epidemiologic studies the homeostasis model assessment (HOMA) model has been widely used for the quantification of insulin resistance (HOMA-IR) and pancreatic beta cell (HOMA-β) function and used to infer diabetes risk. The HOMA-IR index is given by the product of basal insulin and glucose levels divided by 22.5, whereas the HOMA-β index is derived from the product of 20 and basal insulin levels divided by glucose concentration minus 3.5 (Wallace et al., 2004; Matthews et al., 1985).

Table 7-2 Criteria for clinical diagnosis of diabetes.

Test	Criteria
A1C	A1C ≥6.5%[a]
	OR
Fasting Plasma Glucose (FPG)	FPG ≥126 mg/dL (7 mmol/L). Fasting is defined as no caloric intake for at least 8 h.[a]
	OR
Oral Glucose Tolerance Test (OGTT)	Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L during OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.[a.]
	OR
Random Glucose Test	In a person with classical symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

[a]In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.

Diabetes test criteria were extracted from American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37(Suppl. 1): S81–S90

Impaired insulin signaling is a pathophysiological effect leading to clinical outcomes including insulin resistance, increased blood glucose, and increased blood lipids. Specifically, insulin stimulates sensitive tissues to take up glucose, lipids, and amino acids. In muscle, insulin stimulates glucose oxidation or storage as glycogen and protein synthesis; in liver, insulin stimulates glycogen synthesis; and in adipose tissue, insulin stimulates lipid synthesis and storage. During a fast (overnight) plasma glucose (60–80 mg/dL) and insulin (3–8 μU/mL) levels are low; glucagon levels rise and lipids are mobilized from adipose tissue into the circulation; glycogenolysis and gluconeogenesis increase in the liver; and striated muscle metabolizes lipids and degrades proteins into amino acids (Boron and Boulpaep, 2017). When individuals do not respond properly to glucose and insulin levels (as in T2D mellitus), body fuels (glucose, lipid, and amino acid) are mobilized into the blood, putting a burden on liver, kidney, and vascular function. For example, lipid oversupply promotes hepatic steatosis, hepatic fibrosis, and atherosclerosis, which is a major contributor to cardiovascular disease (see Section 6.3.4).

7.1 Short-Term $PM_{2.5}$ Exposure and Metabolic Effects

There were no epidemiologic or toxicological studies of short-term exposure to $PM_{2.5}$ and metabolic syndrome or diabetes included in the 2009 PM ISA. In the present ISA, there are a limited

number of epidemiologic studies examining the effects of short-term $PM_{2.5}$ exposure on glucose tolerance, insulin sensitivity, and diabetes control (i.e., HbA1c levels). A small number of experimental animal studies that evaluate $PM_{2.5}$-mediated effects on glucose and insulin homeostasis are also available for review. A limited body of controlled human exposure and toxicological studies also provide some evidence that diet and genetic factors, as well as systemic and peripheral inflammation, may play a role in the $PM_{2.5}$ mediated metabolic disruption. Collectively, these studies indicate that short-term exposure to $PM_{2.5}$ may affect glucose and insulin homeostasis.

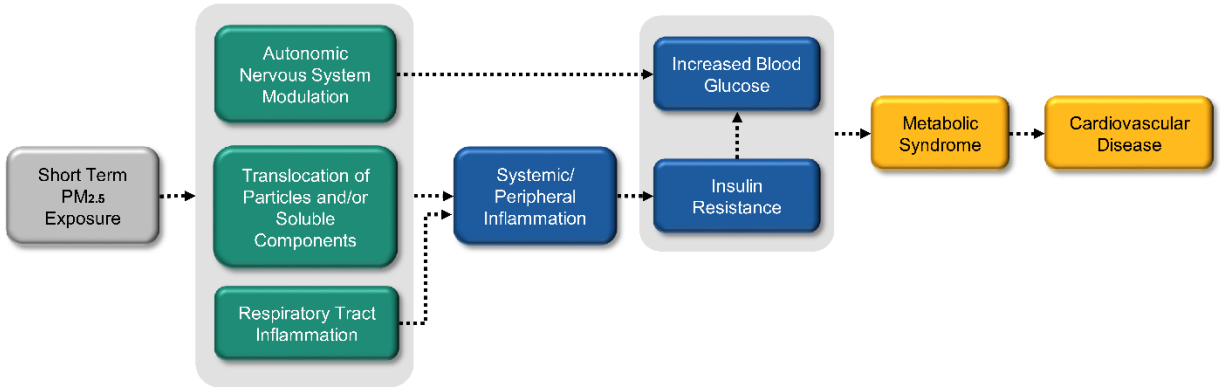
The discussion of short-term $PM_{2.5}$ exposure and metabolic effects opens with a discussion of biological plausibility (Section 7.1.1) that provides background for the subsequent sections in which groups of related endpoints are presented in the context of relevant disease pathways. These outcome groupings are glucose and insulin homeostasis (Section 7.1.2) and other indicators of metabolic function (Section 7.1.3). The collective body of evidence is integrated across and within scientific disciplines[68], and the rationale for the causality determination is outlined in Section 7.1.4.

7.1.1 Biological Plausibility

This section describes biological pathways that potentially underlie metabolic effects resulting from short-term exposure to $PM_{2.5}$. Figure 7-2 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" exposure to $PM_{2.5}$ may lead to metabolic health effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 7.1.

Progression from $PM_{2.5}$ exposure along the potential pathways depicted in Figure 7-2 are supported by experimental and observational evidence streams discussed below, as well as in other Chapters of the PM ISA including: dosimetry, respiratory, cardiovascular, and nervous system chapters (CHAPTER 4, CHAPTER 5, CHAPTER 6, and CHAPTER 8, respectively). CHAPTER 4 discusses the PM administered dose dependence on deposition, which is a function of particle size, intake, and physical chemistry as well as modifying factors such as lifestages and species. The available evidence for $PM_{2.5}$ is organized into potential pathways that include autonomic nervous system (ANS) modulation, translocation of soluble components and respiratory tract inflammation that converge upon systemic inflammation leading to insulin resistance and metabolic risk factors, metabolic syndrome, or comorbidities. Although the specific details underlying these proposed pathways are unclear, evidence from experimental and epidemiologic studies implicate relationships between short term $PM_{2.5}$ exposure and metabolic effects. Further, metabolic syndrome risk factors can lead to complications and comorbidities.

[68] As detailed in the Preface, risk estimates are for a 10 $\mu g/m^3$ increase in 24-hour avg $PM_{2.5}$ concentrations unless otherwise noted.



The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 7-2 Potential biological pathways for metabolic effects following short-term $PM_{2.5}$ exposure.

The central nervous system (CNS) and ANS pathways have the potential for activation due to stimulation of sensory nerves that are further described in CHAPTER 4 and CHAPTER 8. Soluble components of $PM_{2.5,}$ and poorly soluble particles that are part of the $PM_{2.5}$ fraction and smaller than approximately 200 nm, may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments (CHAPTER 4). The extent to which translocation into the systemic circulation occurs is currently uncertain. A study from the 2009 PM ISA (Campbell et al., 2005) described a proinflammatory response in the brain that was accompanied by increases in cytokines TNFα and IL-1α that functionally stimulate and enhance the inflammatory response (see CHAPTER 8). More recent evidence describes promotion of inflammatory gene expression (Section 8.1.3.2), and it is possible that these immune signaling molecules may initiate an innate immune response transmitted through the circulation to other organs tissues. Furthermore, Balasubramanian et al. (2013) found that $PM_{2.5}$ increased the neurotransmitter norepinephrine and the endocrine hormone corticotrophin releasing hormone (CRH) in the hypothalamus. Although Balasubramanian et al. (2013) measured norepinephrine hours after exposure, an increase in the neurotransmitter may mobilize the ANS. The ANS may activate a "flight or fight" response that not only increases vasoconstriction, heart rate and blood pressure, but also mobilizes glucose into the blood stream. Similarly, CRH release stimulates glucocorticoid synthesis marked by a stress response that leads to mobilization of energy stores (i.e., glucose and lipids) into the blood stream (Section 7.1.2.2).

Respiratory tract inflammation leading to inflammatory mediator diffusion from the lung is another potential part of a pathway leading to systemic inflammation (see CHAPTER 5 and CHAPTER

6), systemic oxidative stress, and peripheral inflammation, as indicated by Kim et al. (2015) from human liver function measures (Section 7.1.4) and Sun et al. (2013) from rodent adipose tissue. Once in the circulation inflammatory mediators (such as cytokines, damage associated molecular patterns [DAMPs], and oxidized lipids) may further stimulate the immune response by interacting with endothelium leading to coordination of immune signaling from the circulatory system into peripheral tissues. Short term $PM_{2.5}$ exposure reduced the antioxidant and anti-inflammatory capacity of HDL particles (CHAPTER 6) (Hazucha et al., 2013). These collective responses can stimulate the migratory capacity and increase infiltration of inflammatory cells as demonstrated by Xu et al. (2013) (Section 7.1.3.1), but also interfere with insulin signaling by stimulating the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκβ) pathway via toll-like receptor (TLR) activation (further discussed in Section 7.2.1). Of note, TLR activation interfered with insulin-mediated stimulation of the IRS/PI3K/Akt signaling pathway leading to impaired expression and/or function of insulin signaling components (de Luca and Olefsky, 2008). Further, Haberzettl et al. (2016) identified that short-term $PM_{2.5}$ exposure led to insulin resistance in aortas as measured by failure of insulin to stimulate Akt phosphorylation in mice. Collectively, these findings provide a potential pathway connecting systemic and peripheral inflammation to insulin resistance. Consistent with these experimental animal findings Brook et al. (2013b) reported an association of short-term exposure to $PM_{2.5}$ with increased glucose, insulin and HOMA-IR among healthy subjects and Zanobetti et al. (2014) reported a small increase in hospital admissions for diabetes in association with short-term exposure to $PM_{2.5}$.

As described here, there are proposed pathways by which short-term exposure to $PM_{2.5}$ could lead to metabolic health effects. One pathway involves CNS and ANS activation, translocation of soluble components, and pulmonary inflammation that may lead to systemic inflammation and inflammation of other peripheral organs that is linked to insulin resistance and metabolic syndrome comorbidities. ANS modulation that can also lead to activation of a "flight-or-fight" response increasing blood glucose that is linked to metabolic syndrome. While experimental studies involving animals contribute most of the evidence of upstream effects, epidemiologic studies found associations between short-term $PM_{2.5}$ exposure and both insulin resistance and cardiovascular disease endpoints. Together, these proposed pathways provide biological plausibility for epidemiologic results of metabolic health effects and will be used to support a causal determination, which is discussed later in the chapter (Section 7.1.4).

7.1.2 Glucose and Insulin Homeostasis

Insulin is secreted by β-cells within the pancreas in response to glucose levels. When glucose levels rise, depolarization of the pancreatic β-cells or modulation by other hormones stimulate insulin secretion. Thus, during feeding, blood insulin levels rise stimulating glucose uptake and replenishment of body fuel reserves in the form of triglycerides and glycogen. When insulin levels decrease (e.g., during fasting) fuels such as lipids from adipose tissue and amino acids from muscle are mobilized to the blood

stream where they are used by the liver to synthesize glucose (Section 7.1.1). Notably, the effects of short-term exposure to $PM_{2.5}$ on glucose and insulin homeostasis may be transient.

7.1.2.1 Epidemiologic Studies

Several epidemiologic studies examined the relationship of short-term exposure to $PM_{2.5}$ with indicators of glucose and insulin homeostasis (Table 7-3). Peng et al. (2016) found that short-term exposures (i.e., 1-, 7- and 28-day averages) were associated with increased FBG and a higher odds of impaired fasting glucose (IFG), defined as fasting blood glucose <100 mg/dL. These authors also reported that ICAM-1 promotor methylation mediated the association with 28-day average exposure to $PM_{2.5}$ and FBG. Brook et al. (2013b) reported increased glucose, insulin and HOMA-IR among healthy subjects exposed to $PM_{2.5}$ during 5-day exposure blocks. Lucht et al. (2018b) reported an increase in blood glucose level [0.80 mg/dL (95% CI: 0.33, 1.26)] in association with 28-day average $PM_{2.5}$ exposure among those without diabetes enrolled in the Heinz Nixdorf Recall (HNR) study. An association of HbA1c with 91-day average $PM_{2.5}$ exposure was also observed in this study (see Section 7.2.3). Results from a large retrospective cohort study in Israel did not report evidence to support associations of 24-hour or 7-day average $PM_{2.5}$ exposure with glucose level, glycated hemoglobin (HbA1c), or lipids, although a 3-month average exposure was associated with HbA1c and lipid level (Yitshak Sade et al., 2016) (see Section 7.2.3). Finally, Zanobetti et al. (2014) reported an increase in hospitalizations for diabetes in association with 2-day average concentrations of $PM_{2.5}$ (RR: 1.01 [95% CI: 1.00, 1.02]) most likely reflecting the risk of diabetes-related complications among those with diabetes. Overall, the small number of studies indicate that short-term exposure to $PM_{2.5}$ (1−7 days) may affect glucose and insulin levels among those without diabetes, and consequent increases in hospital admissions for conditions related to diabetes. None of these studies examined the extent to which confounding by copollutants may have influenced their findings.

Table 7-3 Epidemiologic studies of short-term exposure to $PM_{2.5}$ and effects on glucose and insulin homeostasis.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
†Peng et al. (2016) $PM_{2.5}$: 2000−2011	NAS N = 551 older men without diabetes	1-, 7-, 28-day avg preceding clinic visit, satellite derived AOD with LUR C-V R^2 = 0.81	1-day mean 10.92 (SD 5.42) 7-day mean 10.59 (3.48) 28-day mean 10.71 (2.62)	FBG IBG (FBG > 100 mg/dl)	Correlations (*r*): NR Copollutant models: NR
†Brook et al. (2013b) Dearborn, Michigan $PM_{2.5}$: June-Aug 2009/10	N = 25 healthy adults (18−50 yr) residing in rural location	5-day urban exposure	11.5 (SD: 4.8)	HOMA-IR Glucose, insulin, HRV, arterial stiffness	Correlations (*r*): NR Copollutant models: NR
†Lucht et al. (2018b) Ruhr area, Germany $PM_{2.5}$: 2000−2008	HNR study N = 4,176 Nondiabetic	EURAD model, 1 km grid cell *r* = 0.51−0.61, modeled and measured concentrations (Wurzler et al., 2004)	28-day mean = 17.4 IQR = 5.7	Blood glucose level	Correlations (*r*): *r* = 0.73 NO_2; *r* = 0.89 PM_{10} Copollutant models: NR
†Yitshak Sade et al. (2016) $PM_{2.5}$: 2003−2012	N = 73,117 Residents of southern Israel	24 h, 7 days, 3 mo concentration, satellite derived AOD, 1 × 1 km grid of residential address C-V R^2 = 0.72	24 h and 7-day concentrations NR	Glucose HbA1c Lipids	Correlations (*r*): NR Copollutant models: NR
†Zanobetti et al. (2014) 121 Communities, U.S. 1999−2010	Medicare >65 yr old	2-day avg for community, one or more monitors	NR (community specific only)	HAED visits for Diabetes (ICD9: 250)	Correlations (*r*): NR Copollutant models: NR

AOD = Aerosol Optical Density, avg = average, C-V = cross validated, EURAD = European Air Pollution Dispersion, FBG = Fasting Blood Glucose, HOMA-IR = Homeostatic Model Assessment Insulin Resistance, HbA1c = glycated hemoglobin, IBG = Impaired Blood Glucose, ICD = International Classification of Disease, IGT = impaired glucose tolerance, LUR = Land Use Regression, NR = Not Reported.

†Studies published since the 2009 PM ISA.

7.1.2.2 Toxicological Studies

Toxicological studies provided some evidence that $PM_{2.5}$ may impair the insulin signaling pathway leading to effects on glucose and insulin homeostasis (Table 7-4). Haberzettl et al. (2016) reported that insulin increased ($p < 0.05$) Akt phosphorylation, which is a marker of insulin sensitivity, in the aortas of mice breathing filtered air, whereas no insulin-stimulated phosphorylation of Akt was identified in short-term $PM_{2.5}$ CAPs exposed mice. This effect was also observed following long-term exposure to $PM_{2.5}$ (Section 7.2) and may precede changes in glucose tolerance or insulin resistance. When Haberzettl et al. (2016) treated mice with the insulin sensitizers metformin or rosiglitazone, aortic insulin signaling (also measured via Akt phosphorylation) was unaffected in exposed mice, whereas vascular insulin resistance and inflammation induced by $PM_{2.5}$ CAPs exposure were prevented (Section 7.1.3). Notably, treatment with or without the insulin sensitizers had no effect on blood glucose, plasma insulin levels, or the HOMA-IR or HOMA-β scores (Haberzettl et al., 2016). Liu et al. (2014b) reported insulin resistance (measured by HOMA-IR) at 1 and 3 weeks after $PM_{2.5}$ CAPs exposure. Balasubramanian et al. (2013) reported an acute increase ($p < 0.05$) in norepinephrine (NE) in the paraventricular nucleus and corticotrophin releasing hormone (CRH) in the median eminence of the hypothalamus of Lean Brown Norway rats 1 day, but not 3 days after $PM_{2.5}$ exposure. Norepinephrine increases suggest activation of the sympathetic nervous system, whereas increased CRH may activate the HPA stress axis leading to glucocorticoid release and mobilization of glucose, lipids, and amino acids to the blood stream (see CHAPTER 8).

Table 7-4 Study specific details from animal toxicology studies of metabolic homeostasis.

Study	Study Population	Exposure Details	Endpoints Examined
Balasubramanian et al. (2013)	Rat, male, adult Brown Norway or 4 or 8 mo. old JCR-LA (spontaneous obesity, hyperlipidemic, insulin resistant), n = 16	Grand Rapids, MI CAPs 519 μg/m^3 for 1 day and 595 μg/m^3 for 3 days; JCR/LA rats, Detroit, MI CAPs 291 μg/m^3 for 4 days; whole body inhalation.	Neurotransmitters (norepinephrine, corticotrophin releasing hormone, dopamine, and 5-hydroxy-indole acetic acid) levels in the paraventricular nucleus and median eminence of hypothalamus

Table 7-4 (Continued): Study specific details from animal toxicology studies of metabolic homeostasis.

Study	Study Population	Exposure Details	Endpoints Examined
Haberzettl et al. (2016)	Mouse, male, C57BL/6J, ND or HFD, 8−12 weeks, n = 4−8	Louisville, KY CAPs $PM_{2.5}$; 30−100 μg/m^3 Group 1: exposed for 6 h/day for 9 days. Group 2: treated with daily dose of water, metformin (50 mg/kg dose 2 days before, 100 mg/kg dose 1 day before and 300 mg/kg at the time of $PM_{2.5}$ exposure), or 1 mg/kg rosiglitazone 2 mg/kg 2 days before 9 days CAP exposure in drinking water.	Body weight, fasting blood glucose and insulin, HOMA-IR, organ weights, blood lipids, liver clinical chemistry, insulin signaling pathway, circulating bone marrow derived stem cells, Blood triglycerides, HDL, LDL, HDL/LDL
Ito et al. (2008)	Adult male Wistar Kyoto rats	Yokahama City, Japan CAPs collected during May 2004 (1.3 mg/m^3 ± 0.1), November 2004 (1.0 mg/m^3 ± 0.3), and September 2005 (1.9 mg/m^3 ± 0.4). Rats were exposed 4 days (4.5 h/day) or to FA for 3 days and CAPs for 1 day or to FA for 4 days	Blood pressure, HR and mRNA markers from heart tissue of HO-1, TBARS, ETA, cardiovascular disease (ET-1, ETA, ACE, ANP, BNP, Tnfα, Il-1B)
Seagrave et al. (2008)	Adult male Sprague-Dawley rats, 8−10 weeks old	Nose-only inhalation, $PM_{2.5}$ road dust from New York City, Los Angeles, and Atlanta at low (306 μg/m^3) and high (954 μg/m^3), one 6 h exposure	Heart tissue, oxidative stress, TBARS
Sun et al. (2013)	Rat, male, Sprague Dawley, ND or high fructose, 8 weeks, n = 7−8	Dearborn, MI CAPs $PM_{2.5}$; 356 μg/m^3; 8 h/day, 5 day/week for 9 days over 2 weeks, whole body inhalation	Body weight, inflammation, adipose tissue gene expression, iNOS, mitochondrial area
Wagner et al. (2014a)	Rat, male, Sprague Dawley, ND or high fructose, n = 7−8 per group	Dearborn, MI CAPs $PM_{2.5}$; 356 ± 87 μg/m^3, 441 ± 65 μg/m^3 for O_3 and $PM_{2.5}$ or O_3 alone. O_3 average was 0.485 ± 0.042 ppm for 8 h/day for 9 consecutive weekdays (Week 1 M-F, Week 2 M-Th)	Heart rate, heart rate variability, blood pressure
Wagner et al. (2014b)	Rat, male, SH (spontaneously hypertensive), 12−13 weeks, n = 8	Dearborn, MI CAPs $PM_{2.5}$; Study 1: 415 ± 99 μg/m^3 $PM_{2.5}$ Study 2: 642 ± 294 μg/m^3 $PM_{2.5}$ Study 3: 767 ± 256 μg/m^3 $PM_{2.5}$ Study 4: 364 ± 58 μg/m^3 $PM_{2.5}$ 8 h exposure repeated for 4 consecutive days	Distribution of major components, heart rate, lnSDNN, lnRMSSD, MAP, systolic, diastolic, associations between components and cardiac responses
Xu et al. (2013)	Mouse, male, C57BL//6, n = 6/group, 4 weeks old	Columbus, OH CAPs $PM_{2.5}$; (143.8 μg/m^3), 6 h/day, 5 days/week for 5, 14 or 21 days	Adipose gene expression, adipose inflammation, inflammatory cell migration capacity

7.1.2.3 Summary

A limited body of epidemiologic and experimental animal studies provide evidence that short-term exposure to $PM_{2.5}$ may affect glucose and insulin homeostasis. However, effects may be transient, so the upstream consequences are somewhat uncertain.

7.1.3 Other Indicators of Metabolic Function

7.1.3.1 Inflammation

Inflammation plays a critical role in the development of T2D and atherosclerosis leading to CHD (Section 7.1.1, CHAPTER 6). As outlined in the Section 7.1.1 (Biological Plausibility), systemic inflammation may promote a peripheral inflammatory response in organs and tissues, such as liver and adipose tissues. Consistent with the 2009 PM ISA, the evidence for systemic inflammation following short-term exposure to $PM_{2.5}$ is limited with some studies reporting changes in markers of inflammation such as the cytokine IL-6 and inflammatory proteins such as CRP while other studies do not show changes in these and other markers. Acute inflammation is transient in nature, inflammatory response is dynamic, and there is technical difficulty in measuring cytokine levels that may be at or below baseline levels, however (Angrish et al., 2016b).

Recent experimental and epidemiologic studies (Section 6.1.11) report at least some evidence of $PM_{2.5}$ mediated effects on systemic inflammation. For example, Behbod et al. (2013) reported that exposure to $PM_{2.5}$ CAP resulted in healthy adults having increased blood leukocytes and neutrophils at 24 hour, but not 3 hour post exposure. In an additional study, Urch et al. (2010) used two different $PM_{2.5}$ CAP exposure levels and reported a statistically significant increase ($p < 0.05$) in blood IL-6 levels following CAP exposure at 3-hour, but not immediately after or the day after exposure. In contrast, Liu et al. (2015) did not report a statistically significant change in Il-6 or CRP. Results from animal toxicology studies reported $PM_{2.5}$ mediated increases in ROS, suggesting oxidative stress (Ito et al., 2008; Seagrave et al., 2008). Evidence in support of systemic inflammation was also provided by a study in which mice exposed to $PM_{2.5}$ CAPs had increased ($p < 0.05$) monocyte chemoattractant protein 1 levels, while Tnf α, and Il 12 were not significantly altered (Xu et al., 2013). Epidemiologic panel studies were similar to CHE and animal toxicology studies in that some of these analyses showed increases in markers of systemic inflammation while others did not (Section 6.1.11.1). Although the above results are seemingly inconsistent, markers of systemic inflammation such as cytokines are often transiently expressed, thus making it difficult to consistently find changes across studies using a variety of methodological approaches (see Section 6.1).

Inflammation of peripheral organs and tissues were reported in animal toxicology studies. Xu et al. (2013) evaluated adipose inflammation concurrently with systemic inflammation in mice exposed to Columbus, OH $PM_{2.5}$ CAPs for 5, 14, or 21 days. The investigators found that the mRNA levels of visceral adipose tissue *Il-6* was increased ($p < 0.05$) at 5 days after exposure, while, no change in *Nos2*, *Tnfα*, *Arg-1*, or *Il-10* were detected (Xu et al., 2013). Furthermore, there was an increase in in the number of macrophages in the epididymal adipose tissue of $PM_{2.5}$ exposed mice at 5 days ($p < 0.05$) and 21 days ($p < 0.001$) post exposure compared to filtered air controls. A migratory cell assay evaluated and found that the migratory capacity of macrophages ($p < 0.0001$) and neutrophils ($p < 0.05$) was increased, suggesting that $PM_{2.5}$ altered the chemokine composition in visceral adipose tissue (Xu et al., 2013). Sun et al. (2013) provided evidence that $PM_{2.5}$ may exacerbate pre-existing conditions. Specifically, the authors identified increased monocyte/macrophage infiltration in rat epicardial and perirenal adipose tissue that was exacerbated by high fructose diet feeding for 8 weeks prior to exposure as well as oxidative stress (measured by iNOS immunofluorescence) (Sun et al., 2013).

Overall, some studies report increased markers of systemic inflammation following, or in association with, short-term exposure to $PM_{2.5}$. Inconsistency across short-term exposure studies may be related to several factors including the transient nature of the effects. For example, CHE studies examined responses from blood after several hours whereas animal toxicology studies examine responses from blood and other tissues after several days. A limited number of studies provide additional evidence that short-term exposure to $PM_{2.5}$ may result in inflammation of the visceral or perirenal adipose tissue, which is particularly relevant to metabolic function and a risk factor for metabolic syndrome.

7.1.3.2 Liver Function

The liver, which is strategically situated between the portal and systemic circulation, is the site for primary energy and xenobiotic metabolism (Boron and Boulpaep, 2017). Another important liver function is synthesis and degradation of proteins, carbohydrates, and lipids for distribution to extrahepatic tissues depending on energy needs. Finally, the liver regulates whole body cholesterol balance via biliary excretion of cholesterol, cholesterol conversion to bile acids, and by regulating cholesterol synthesis (Boron and Boulpaep, 2017). Consequently, the liver is an essential regulator of whole body metabolism and energy homeostasis.

Acute-phase liver proteins, such as CRP, can act as sensors of liver function and were discussed in more detail in CHAPTER 6, Section 6.2.11. Specifically, there were several epidemiologic studies that found associations between CRP, a protein produced by the liver in response to acute systemic inflammation. These proteins, in combination with other liver enzymes can give information about overall health, including liver function. In a panel study of older adults in Seoul Korea. Kim et al. (2015) reported increases (1−2%) in γ-glutamyl transpeptidase (γ-GTP, a marker of cholestatic function), aspartate aminotransferase (AST, a marker of acute inflammation, not necessarily liver specific) and alanine

aminotransferase (ALT, a marker of liver injury) in association with short-term $PM_{2.5}$ exposure (lag day 3). The mean concentration was 23.2 µg/m^3 during the study. In contrast, Haberzettl et al. (2016) found no change in the liver enzymes (including AST and ALT) in an animal model.

7.1.3.3 Blood Lipids

7.1.3.3.1 Epidemiologic Studies

Epidemiologic studies of short-term exposure to $PM_{2.5}$ and changes in blood lipids are limited in number. Chen et al. (2016) examined lagged exposure periods from 0−90 days, selecting the period with the best model fit using Akaike Information Criterion (AIC). Short-term (up to 14−day cumulative averages) were associated with changes in HDL to LDL cholesterol ratio, total cholesterol and LDL that were consistent with reduced metabolic function.

7.1.3.3.2 Toxicological Studies

Controlled human exposure studies of metabolic homeostasis are described in Table 7-5. Ramanathan et al. (2016) reported an increasing trend in the HDL oxidant index (HOI) that became significant ($p < 0.05$) when compared to the baseline HOI at 1 hour, but not 20 hours post exposure. These results suggested that PM reduced the antioxidant and anti-inflammatory capacity of HDL particles (Section 6.2.11). Hazucha et al. (2013) identified specific effects on blood lipids and reported a 4.5 and 4.1% decrease ($p < 0.05$) in blood HDL 3 and 22 hours after controlled chamber exposure to $PM_{2.5}$ CAPs in ex- and lifetime smokers. In contrast, short term animal toxicology studies reported no $PM_{2.5}$-mediated effects on blood triglycerides, HDL, LDL, or HDL/LDL ratio (Haberzettl et al., 2016).

Table 7-5 Study specific details from controlled human exposure studies of metabolic homeostasis.

Study	Study Population	Exposure Details	Endpoints Examined
Hazucha et al. (2013).	Current and ex-smokers; n = 11; 3 M, 8 F 35−74 yr	Chapel Hill, NC, 108.7 ± 24.8 µg/m^3 $PM_{2.5}$ for 2 h at rest	Blood HDL
Ramanathan et al. (2016).	Healthy adults n = 13 M, 17 F; 18−50 yr 28 ± 9	Toronto, Ontario. 148.5 ± 54.4 µg/m^3 $PM_{2.5}$ (652,259 ± 460,843 particles ≥ 0.3 µm, 2,987 ± 1,918 particles ≥ 2.0 µm) 2 h exposure at rest	HDL antioxidant index

7.1.3.4 Blood Pressure

Short-term $PM_{2.5}$ mediated effects on blood pressure are discussed in detail in the Cardiovascular Chapter (CHAPTER 6, Section 6.1.6). Positive associations between short-term $PM_{2.5}$ exposures and changes in SBP or DBP were not consistently reported in epidemiologic studies. A few CHE studies indicated that $PM_{2.5}$ CAPs may affect BP, however, there were also studies that found no $PM_{2.5}$-mediated effect. Similarly, the animal toxicology studies found little to no $PM_{2.5}$-mediated effects on BP in healthy animals, whereas BP was increased ($p < 0.05$) in the SH rat model (Wagner et al., 2014b), but decreased ($p < 0.05$) in a metabolic disease model (Wagner et al., 2014a). A similar PM exposure mediated an acute decrease ($p < 0.05$) in BP in corpulent JCR rats (Balasubramanian et al., 2013).

7.1.4 Summary and Causality Determination

There were no studies of the effect of short-term $PM_{2.5}$ exposure and metabolic effects reviewed in the 2009 PM ISA (U.S. EPA, 2009). Recent studies provide some evidence supporting effects on glucose and insulin homeostasis and other indicators of metabolic function. Evidence pertaining to the relationship between short-term exposure to $PM_{2.5}$ and metabolic effects is summarized in Table 7-6, using the framework for causality determination described in the Preamble to the ISAs (U.S. EPA, 2015).

Recent epidemiologic studies have demonstrated increased FBG, insulin, and HOMA-IR (Lucht et al., 2018a; Peng et al., 2016; Brook et al., 2013b) in association with short-term $PM_{2.5}$ exposure. Yitshak Sade et al. (2016) found no association with blood glucose or lipids and $PM_{2.5}$ exposure, although a positive association between $PM_{2.5}$ exposure (3-month average) and HbA1c, a measure of blood glucose control, was observed. An animal toxicological study provided some evidence for $PM_{2.5}$ impairment of the insulin signaling pathway (Haberzettl et al., 2016). Limited animal toxicology studies provided some evidence for inflammation in the visceral adipose tissue (Xu et al., 2013). Although the controlled human exposure evidence is inconsistent possibly due to the transient nature of inflammation (Section 7.1.3.1), there is epidemiologic evidence of an increase in inflammatory markers in the liver, i.e., γ-GTP, ALT, and AST (Kim et al., 2015). In summary, evidence for a relationship between short-term $PM_{2.5}$ exposure and metabolic effects is based on a small number of epidemiologic and toxicological studies reporting effects on glucose and insulin homeostasis and other indicators of metabolic function such as inflammation in the visceral adipose tissue and liver. **Overall, the collective evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{2.5}$ exposure and metabolic effects.**

Table 7-6 Summary of evidence indicating that the evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{2.5}$ exposure and metabolic effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Evidence of association from a limited number of high quality epidemiologic studies at relevant $PM_{2.5}$ concentrations.	Short term exposures were associated with increased fasting blood glucose, insulin, HOMA-IR and hospitalization for conditions related to diabetes.	†Peng et al. (2016) †Brook et al. (2013b)	1-day mean 10.9 5-day avg 11.5
No consideration of confounding by copollutants.	Epidemiologic studies did not present copollutant models.	Section 7.1.2.1	
Coherence across lines of evidence and related endpoints.	Small number of experimental studies report effects on glucose and insulin homeostasis providing evidence for direct effects on metabolism.	Section 7.1.2.2 Figure 7-2	
Limited biological plausibility.	Small number of studies demonstrating plausibility of pathways involving insulin resistance, systemic inflammation and peripheral inflammation.	Section 7.1.2.2 Section 7.1.3	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

7.2 Long-term $PM_{2.5}$ Exposure and Metabolic Effects

An animal toxicology study (Sun et al., 2009) that showed enhanced insulin resistance, visceral adiposity, and adipose inflammation in a diet-induced obesity mouse model was reviewed in the 2009 PM 1SA. In the present ISA, multiple epidemiologic and experimental studies of glucose and insulin homeostasis and diabetes, as well as other outcomes are available for review. Overall, there is evidence from some studies that long-term exposure to $PM_{2.5}$ can affect glucose and insulin homeostasis but prospective epidemiologic studies do not report consistent positive associations with the incidence of T2D.

The discussion of long-term $PM_{2.5}$ exposure and metabolic effects opens with a discussion of biological plausibility (Section 7.2.1) that provides background for the subsequent sections in which groups of related endpoints are presented in the context of relevant disease pathways. These outcome groupings are metabolic syndrome (Section 7.2.2), glucose and insulin homeostasis (Section 7.2.3), T2D

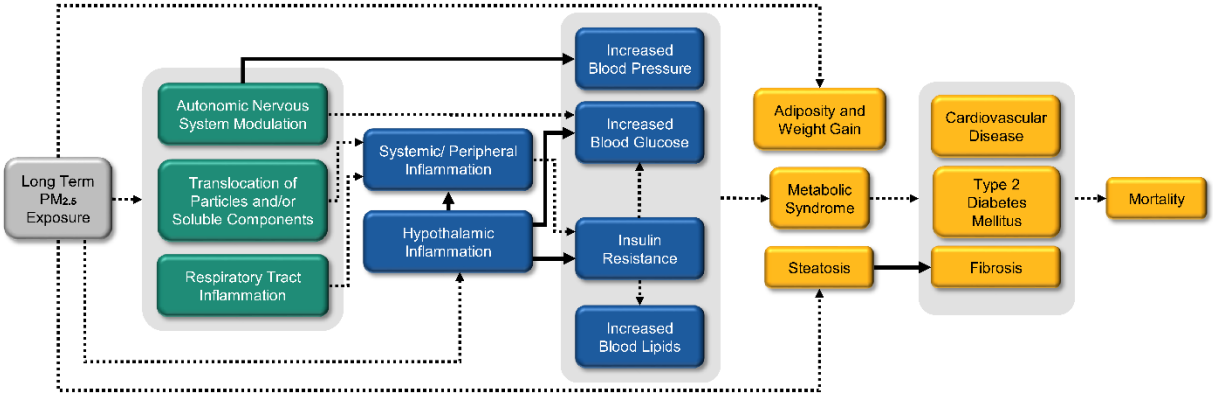
(Section 7.2.4), and other indicators of metabolic function (Section 7.2.5). Gestational diabetes and Type 1 diabetes are discussed in Section 7.2.6 and Section 7.2.7, respectively. Summary discussion for $PM_{2.5}$ components (Section 7.2.8), copollutant confounding (Section 7.2.9) and metabolic disease mortality (Section 7.2.10) follow. The collective body of evidence is integrated across and within scientific disciplines[69], and the rationale for the causality determination is outlined in Section 7.2.11.

7.2.1 Biological Plausibility

This section describes biological pathways that potentially underlie metabolic health effects resulting from long-term exposure to $PM_{2.5}$. Figure 7-3 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" exposure to $PM_{2.5}$ may lead to metabolic health effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 7.2.

The health sections below include numerous new long-term $PM_{2.5}$ exposure studies that further inform the potential pathways leading to metabolic effects. In the short-term $PM_{2.5}$ biological plausibility (Section 7.1.1) potential pathways were described that implicitly support proposed relationships between short term $PM_{2.5}$-mediated biological effects that collectively alter energy homeostasis to promote metabolic syndrome. New evidence gleaned from long-term $PM_{2.5}$ exposure studies expands the evidence pertaining to biological plausibility as well as our implicit understanding of the pathological continuum underlying metabolic disease development and progression. Specifically, the long-term exposure studies inform disease onset or longitudinal changes in measured endpoints that cannot be ascertained through the application of a short-term exposure study design. Furthermore, in some experimental studies, endpoints observed in short-term exposure studies are part of a long-term study and, therefore, do not include evidence gathered at animal sacrifice. Expansion of the pathways described in Section 7.1 are supported not only by the long-term exposure evidence described in this section, but also experimental and observational evidence described in the dosimetry, pulmonary, nervous system, and cardiovascular chapters (CHAPTER 4, CHAPTER 5, CHAPTER 6, and CHAPTER 8, respectively).

[69] As detailed in the Preface, risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations unless otherwise noted.



The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 7-3 Potential biological pathways for metabolic effects following long-term $PM_{2.5}$ exposure.

Inhalation of $PM_{2.5}$ may initiate pathways that include ANS activation, translocation of particles and/or soluble components, and respiratory tract inflammation that converge upon inflammation leading to insulin resistance (previously described in Section 7.1.1). The long-term exposure toxicological evidence from inhibitor studies in diabetic mouse models (Section 7.2.3.2) provide important evidence for connecting these initial pathways to metabolic syndrome risk factors and clinical outcomes. Aside from inflammatory mediator diffusion from the lung into the systemic circulation, inhibitor studies in a diabetic mouse model provide evidence that increased hypothalamic inflammation, mediated by the NFκβ signaling pathway, is sufficient to promote long term $PM_{2.5}$ mediated glucose intolerance, insulin resistance, increases in circulating inflammatory monocytes, and increases in inflammatory gene expression in peripheral tissues including liver, adipose, and heart (Zhao et al., 2015; Liu et al., 2014b) (CHAPTER 6 and CHAPTER 8). The convergence of these pathways on glucose and insulin disruption is notable since multiple studies, albeit from the same group of investigators evaluating $PM_{2.5}$ CAPs collected from the same Columbus, OH air shed, identified that long-term $PM_{2.5}$ exposure elicited insulin resistance and increased blood glucose/glucose intolerance in healthy mice (Section 7.2.3.2). Further molecular analysis of proteins involved in the NFκβ and insulin signaling pathways consistently showed that long-term $PM_{2.5}$ exposure decreased Akt phosphorylation in tissues including liver, adipose, heart, and skeletal muscle (Section 7.2.5.1), providing a potential connection between inflammatory mediator diffusion in the circulatory system leading to peripheral organ/tissue inflammation and insulin resistance. Zheng et al. (2013) indicated these effects were possibly mediated by activation of Toll-like receptor 4 (TLR4), c-Jun N-terminal kinase (JNK) and NFκβ, leading to suppression of the insulin-receptor substrate

1 (IRS-1) signaling and, consequently, decreased Akt phosphorylation leading to impaired insulin
2 signaling. These findings are consistent with the decreased Akt phosphorylation finding after short term
3 $PM_{2.5}$ exposure to CAPs collected from the Louisville, KY air shed (Haberzettl et al., 2016) and support a
4 continuum for $PM_{2.5}$ metabolic effects on insulin resistance.

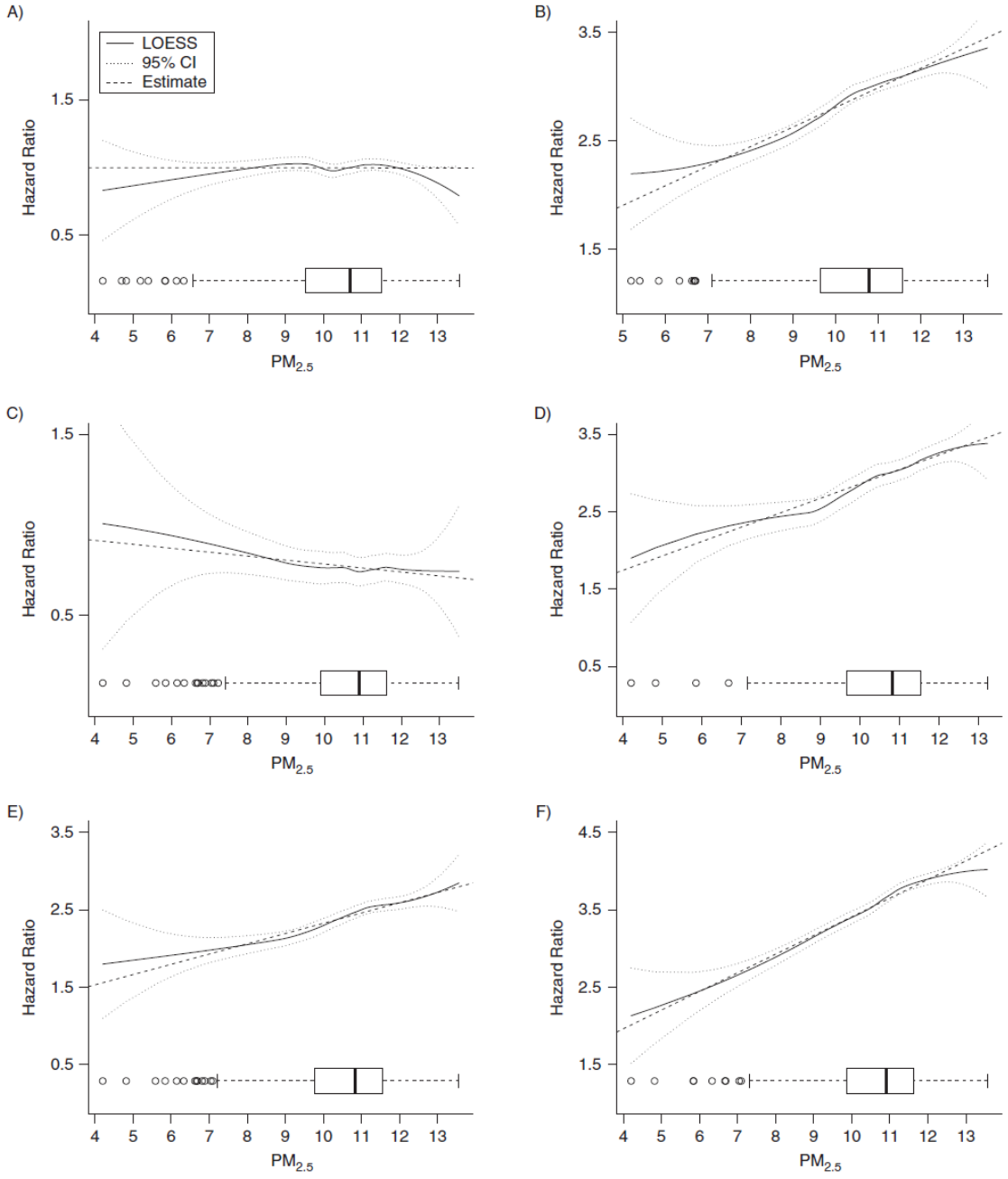
5 In addition to the immune activation and NFκβ signaling pathways discussed above, evidence
6 from genetic knockout models also supports roles for TLR4 and NADPH oxidase pathways leading to
7 monocyte recruitment and inflammation. Mice with nonfunctional neutrophil NADPH oxidase activity,
8 which is required for superoxide anion production, were protected from $PM_{2.5}$-induced increases in
9 superoxide production (Kampfrath et al., 2011), insulin resistance, increase in abdominal mass and
10 visceral adiposity, and fibrosis in mice (Zheng et al., 2015; Xu et al., 2010). Kampfrath et al. (2011)
11 found that genetic knockout of *Tlr4* protected mice from $PM_{2.5}$-mediated increases in circulating
12 monocytes and prevented phosphorylation of the $p47^{phox}$ subunit that is required for NADPH oxidase
13 activity and superoxide production. Yet, while superoxide was attenuated in *Tlr4* deficient mice, it
14 remained induced in monocytes, aorta, and perivascular fat (Kampfrath et al., 2011). Mice with a
15 nonfunctional CC-chemokine receptor 2 (CCR2), with a phenotype of defective monocyte requirement
16 during immune responses, were protected from $PM_{2.5}$ and high fat diet induction of hepatic steatosis,
17 insulin resistance, and systemic and peripheral inflammation (Liu et al., 2014c). Although no association
18 was found in a cross-sectional study between long-term $PM_{2.5}$ exposure and steatosis (Li et al., 2016),
19 hepatic steatosis and fibrosis were found in mice exposed long-term to $PM_{2.5}$ (Section 7.2.5.2).

20 As described here, there are proposed pathways by which long-term exposure to $PM_{2.5}$ could lead
21 to metabolic health effects. One pathway involves ANS modulation, translocation of particulates and/or
22 soluble components, and respiratory tract inflammation that may lead to systemic and peripheral
23 inflammation that is linked to insulin resistance and metabolic syndrome comorbidities. While
24 experimental studies involving animals contribute most of the evidence of upstream effects,
25 epidemiologic studies found associations of long-term $PM_{2.5}$ exposure with metabolic syndrome
26 (Section 7.2.2), insulin resistance and glucose tolerance (Section 7.2.3), T2D (Section 7.2.4),
27 cardiovascular disease (Chapter 6), and metabolic disease mortality (Section 7.2.10). The pathways
28 leading to these outcomes are not without gaps (e.g., the pathways to hypothalamic inflammation,
29 steatosis, adiposity and weight gain); however, they provide coherence and biological plausibility for the
30 evidence streams supporting metabolic health effects and will be used to support the causal determination,
31 which is discussed later in the chapter (Section 7.2.11).

7.2.2 Metabolic Syndrome

32 The criteria for a diagnosis of metabolic syndrome, which are summarized in Table 7-1, include
33 changes in glucose and insulin homeostasis, obesity, increased blood pressure, and increased triglyceride
34 levels. Although most available studies focus on individual components of metabolic syndrome, most

commonly glucose and insulin homeostasis (Section 7.2.3), the association of long-term exposure to $PM_{2.5}$ with a diagnosis of metabolic syndrome was examined in an epidemiologic study (Table 7-6). In this study, older adult, male, participants of the Normative Aging Study (NAS) were followed between 1993 and 2011. Associations with the incidence of newly diagnosed metabolic syndrome [HR: 3.30 (95% CI: 1.34, 8.11)] and several of its components including FBG ≥100 mg/dL [HR: 2.49 (95% CI: 1.16, 5.19)], blood pressure ≥130/85 mmHg [HR 2.49 (95% CI: 0.86, 7.34)], increased triglycerides ≥150 mg/dL [HR: 1.93 (95% CI: 1.00, 3.71)] were reported (Wallwork et al., 2017). Wallwork et al. (2017) also examined the C-R relationship between long-term $PM_{2.5}$ exposure and the hazard for metabolic syndrome and its components (Figure 7-4). No major departures from linearity were apparent and HRs remained significant and strengthened in a sensitivity analysis restricted to 1-year average $PM_{2.5}$ concentrations <12 $\mu g/m^3$.



(A) Abdominal Obesity; (B) high fasting blood glucose (C) low high-density lipoprotein cholesterol; (D) hypertension; (E) hypertriglyceridemia; (F) metabolic syndrome.

Source: Permission pending, Wallwork et al. (2017).

Figure 7-4 Locally weighted scatterplot smoothing (LOESS) regression of hazard ratios on $PM_{2.5}$ concentration. Composite diagnosis of metabolic syndrome and each individual component according to the level of exposure among older adult males in the Normative Aging Study.

7.2.3 Glucose and Insulin Homeostasis

As discussed in the introduction to the metabolic effects chapter (Section 7.1), insulin regulates glucose homeostasis. There was one animal toxicology study (Sun et al., 2009) that showed enhanced insulin resistance in a diet-induced obesity mouse model in the 2009 PM ISA. Several recent studies on this topic add to the overall evidence. Endpoints examined in these studies include FBG, HbA1c, and insulin resistance (e.g., the homeostatic model assessment of insulin-resistance [HOMA-IR]). Recent epidemiologic and experimental provide generally consistent evidence supporting the effect of long-term $PM_{2.5}$ exposure on glucose and insulin homeostasis.

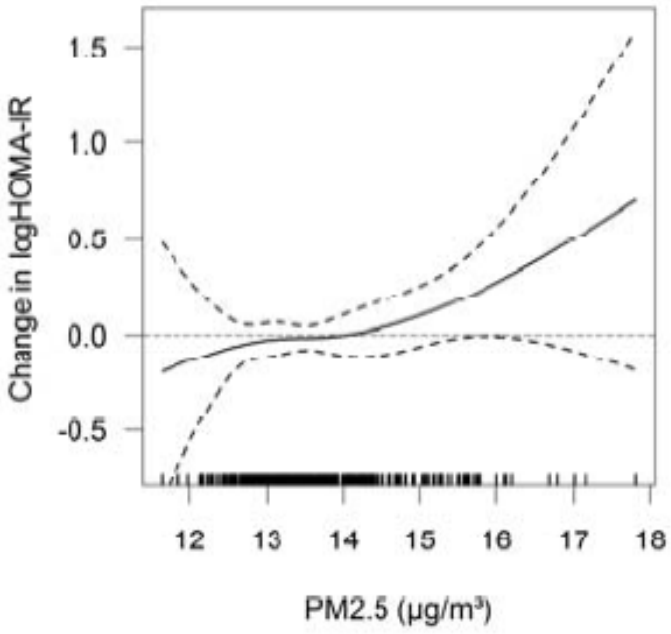
7.2.3.1 Epidemiologic Studies

The epidemiologic studies of the association between long-term $PM_{2.5}$ exposure and glucose and insulin homeostasis are described in Table 7-6. Lucht et al. (2018b) conducted a longitudinal analysis of nondiabetic participants of the HNR reporting an association of 91-day average exposure to $PM_{2.5}$ with increased HbA1c. In this study $PM_{2.5}$ exposure was associated with 0.09% increase in HbA1c (95% CI: 0.05, 0.13) in the main model, which was adjusted for an array of covariates including BMI, physical activity, smoking, neighborhood-level unemployment.

Several cross-sectional epidemiologic studies of glucose and insulin homeostasis provide support for the findings from this longitudinal study. Chen et al. (2016) analyzed the effect of both short- (0−90-day lags) and long-term exposure to $PM_{2.5}$ on glucose homeostasis in Mexican American women with a history of gestational diabetes (GMD) and their family members (BetaGene study). Subjects with a FBG level <7 mmol/L were assessed using detailed measurements of insulin sensitivity and secretion from a frequently sampled intra-venous glucose tolerance test (FSIGT). Cumulative exposure to $PM_{2.5}$ (lags up to 60 days) and annual average $PM_{2.5}$ were associated with several measures of insulin resistance, higher fasting blood glucose and indicators of dyslipidemia in this study. Associations with $PM_{2.5}$ persisted after adjustment for NO_2.

Wolf et al. (2016) reported increases, although CIs were wide, in HOMA-IR [17.32% (95% CI: −2.32, 39.11)], glucose [2.86% (95% CI; 0.00, 5.89)], insulin [14.82% (95% CI: −3.57, 35.00)], as well as Leptin and CRP in association with long-term exposure to $PM_{2.5}$ in a cross-sectional analysis of a German cohort (KORA). HOMA IR was log-transformed in the analysis due to a deviation from linearity (Figure 7-5). In another study, Yitshak Sade et al. (2016) examined short-term (Section 7.1.2) and 3-month average exposures to serum glucose, HbA1c, and lipids, reporting an association between 3-month average $PM_{2.5}$ exposure and HbA1c, an indicator of diabetes control, among those with diabetes [2.09% (95% CI: 0.25, 3.99)]. Chuang et al. (2011) reported associations of 1-year average $PM_{2.5}$ concentration with blood lipid and glucose levels in a cross-sectional study in Taiwan. Liu et al. (2016) found cross-sectional positive associations of long-term $PM_{2.5}$ concentration with FBG [0.03 nmol/L

(95% CI: 0.02, 0.04)] and HbA1c (0.01% 95% CI: 0.01, 0.01) in a study of retired adults in China [Note: these results have been standardized to 5 µg/m^3 but were originally presented per IQR (41.1 µg/m^3) increase in $PM_{2.5}$ concentration.].

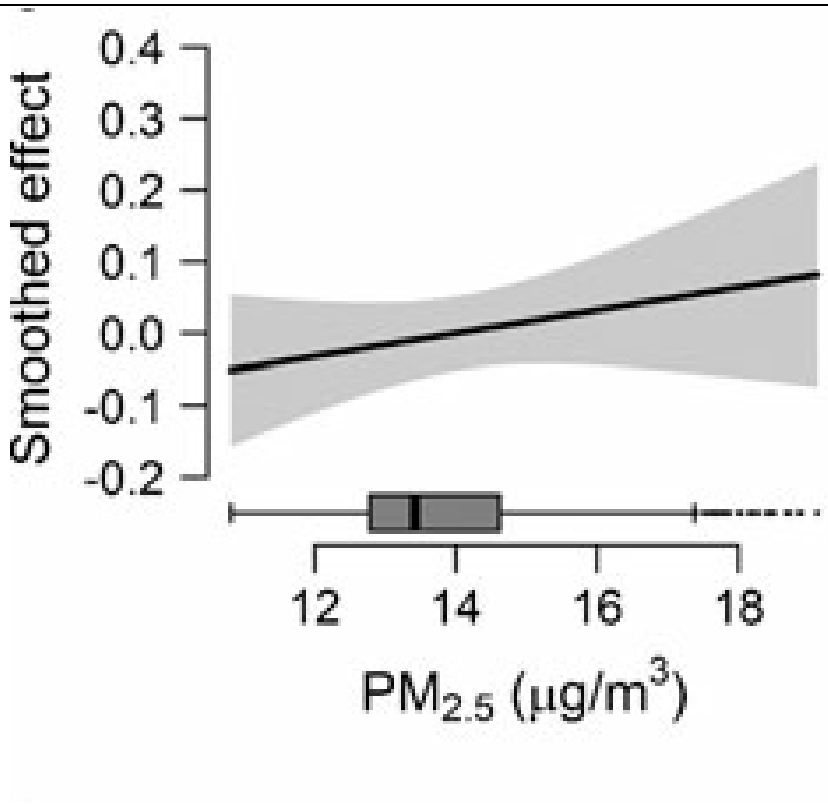


Source Wolf et al. (2016).

Figure 7-5 Concentration response function for $PM_{2.5}$ using restricted cubic spline with three degrees of freedom (adjusted for age, sex, body mass index (BMI), waist-hip ratio, smoking status, and month of blood draw).

Effects on glucose homeostasis in children are also observed in epidemiologic studies. Toledo-Corral et al. (2018) enrolled obese and overweight African-American and Latino children between 8 and 18 years of age to study the effect of long-term exposure to $PM_{2.5}$ on measures of glucose metabolism. $PM_{2.5}$ concentrations were associated with a metabolic profile that indicates an increased risk of developing T2D (i.e., fasting insulin, lower insulin sensitivity, higher acute insulin response to glucose and increased FBG) in this cross-sectional analysis. Thiering et al. (2013) reported an association between $PM_{2.5}$ concentration estimated at the residence using LUR and an increase in HOMA-IR at age 10, among participants in the GINIplus and LISAplus birth cohorts [27.7% (95% CI: −3.5, 66.2)]. In a subsequent analysis of a larger sample of children at age 15 years old (Thiering et al., 2016), a comparable increase in HOMA-IR was observed [16.59% (95% CI: −2.84, 39.32)]; however, the effect was attenuated in

copollutant models that adjusted for NO_2 [4.43% (−14.77, 27.50)]. The authors also examined the C-R relationship (Figure 7-6) reporting no statistical evidence that the relationship between long-term $PM_{2.5}$ exposure and HOMA-IR deviated from linearity.



Note: Box plots on the *x*-axis show the distribution of $PM_{2.5}$ concentration.
Source: Permission pending, Thiering et al. (2013).

Figure 7-6 Smoothed associations between insulin resistance and long-term $PM_{2.5}$ exposure assessed using generalized additive models adjusted for sex, age and body mass index (BMI).

7.2.3.2 Toxicological Studies

The effects of long-term $PM_{2.5}$ on glucose homeostasis (e.g., glucose tolerance test, insulin tolerance test, fasting glucose and insulin, blood glucose and insulin levels, and the HOMA-IR) were demonstrated in several studies of experimental animals (Table 7-7). Increased ($p < 0.05$) blood glucose levels and/or glucose intolerance and increased HOMA-IR in wild-type animals eating a normal chow diet and exposed (long-term, ≥30 days) to $PM_{2.5}$ compared to controls, was shown in studies from two laboratories [Figure 7-7 (Liu et al., 2014c; Liu et al., 2014a; Zheng et al., 2013; Xu et al., 2011a; Xu et al., 2010)]. In contrast, Haberzettl et al. (2016) showed no increased in glucose levels in mice and Yan et al.

(2014) found no HOMA-IR effects in rats after $PM_{2.5}$ exposure. The molecular evidence consistently suggested that long-term $PM_{2.5}$ exposure disrupted the insulin signaling pathway by inhibition of IRS1 signaling leading to decreased ($p < 0.05$) peripheral Akt phosphorylation in the liver (Liu et al., 2014a; Zheng et al., 2013; Xu et al., 2011a) and aorta (Haberzettl et al., 2016) of mice (see Section 7.2.5.1).

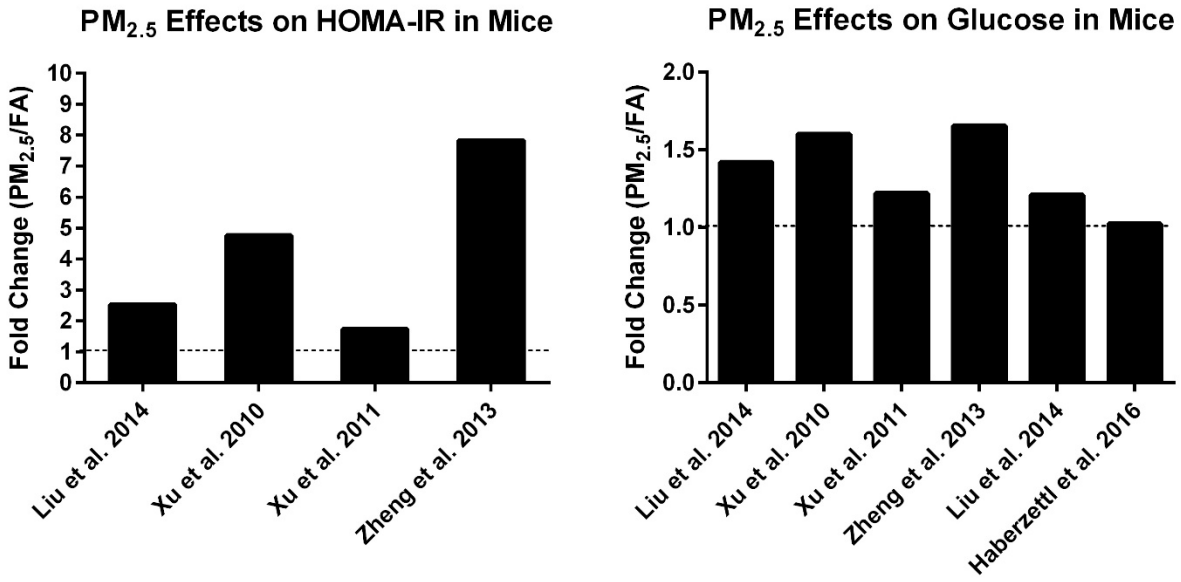


Figure 7-7 $PM_{2.5}$ effects on insulin resistance and glucose tolerance in mice exposed to 19.6−139 µg/m³ $PM_{2.5}$ for 30 days to 17 weeks.

Stages of diabetes progression include prediabetes, which is characterized by impaired glucose tolerance and/or decreased insulin sensitivity, an initial phase (Phase 1) in which pancreatic beta cells become dysfunctional, and a second phase (Phase 2), which is characterized by fasting hyperglycemia and beta cell atrophy. In the end stage (Phase 3) of the disease, the pancreatic cells no longer release insulin.

Table 7-7 Epidemiologic studies of long-term exposure to $PM_{2.5}$ and glucose and insulin homeostasis.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
†Wallwork et al. (2017) Boston, MA Longitudinal $PM_{2.5}$: 2000−2011 Outcome: 1993−2011	NAS N = 587 Older adult males	Annual avg prior to clinic visit, spatio-temporal model incorporating LUR and satellite derived AOD (10 × 10 km and 1 × 1 km grids), C-V R^2 = 0.81 and 0.87 depending on resolution	Mean: 10.5 (SD: 1.4) Range: 4.2−13.6	Metabolic syndrome and its components (Table 7-1)	Correlations (*r*): NR Copollutant models: NR
Lucht et al. (2018b) Ruhr area, Germany Longitudinal $PM_{2.5}$ Outcome: 2000−2008	HNR study N = 4,176 Nondiabetic	EURAD model, 1 km grid cell *r* = 0.51−0.61, modeled and measured concentrations (Wurzler et al., 2004)	Mean = 17.6 IQR = 4	Blood glucose level	Correlations (*r*): *r* = 0.82 NO_2; *r* = 0.47 PN_{AM} Copollutant models: NR
†Chen et al. (2016) Southern CA Cross-sectional $PM_{2.5}$: 2002−2008 Outcome: 2002−2008	BetaGene study N = 1,023 Mexican-American women with history of GDM	Spatial interpolation (inverse distance weighted, IDW) of monitor concentrations within 50 km	Mean(SD): 16.8 (5.5)	Insulin sensitivity and secretion using FSIGT, oGTT, blood lipids (see Section 7.1.3.3)	Correlations (*r*): NO_2 *r* = 0.56, Ozone *r* = −0.07 copollutant model: positive after adjustment for NO_2
†Wolf et al. (2016) Augsburg and two adjacent rural counties, Germany Cross-sectional $PM_{2.5}$: 2008−2009 2006−2008	KORA N = 2,944 Mean age: 56.2 yr	Annual avg, LUR, at residence (ESCAPE protocol)	Mean (SD) 13.5−13.6 (0.8−0.9)	HOMA-IR, Glucose, Insulin, HbA1c, Leptin, hs-CRP	Correlations (*r*): $PM_{10-2.5}$ *r* = 0.32, NO_2 *r* = 0.45 copollutant models: NR
†Yitshak Sade et al. (2016) Retrospective cohort $PM_{2.5}$: 2003−2012 Outcome: 2003−2012	N = 73,117	3-mo avg, satellite derived AOD with LUR, C-V R^2 0.72	Mean 22.3	HbA1c LDL HDL Triglycerides	Correlations (*r*): NR Copollutant models: NR

Table 7-7 (Continued): Epidemiologic studies of long-term exposure to $PM_{2.5}$ and glucose and insulin homeostasis.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
†Chuang et al. (2011) Taiwan Cross-sectional $PM_{2.5}$: 2000	Biomarkers of Aging Study N = 1,023	Annual avg (2000)	Mean (SD): 35.31 (15.9) IQR 20.42	FBG, HbA1c (lipids, BP)	Correlations (*r*): NR Copollutant models: NR
†Liu et al. (2016) China Cross-sectional $PM_{2.5}$/Outcome: June 2011−Mar 2012	Retirement Longitudinal study N = 11,847	Avg (2011−2012) at residence, satellite derived AOD and monitors (10 × 10 km)	Mean 72.6 (SD:27.3) IQR: 41.1	FBG HbA1c	Correlations (*r*): NR Copollutant models: NR
†Toledo-Corral et al. (2018) Los Angeles, CA Cross-sectional 2001−2012	N = 429 overweight and obese children 8−18	1−12 mo exposure prior to clinic visit at geocoded address	Mean (SD): 17.8 (5.2)	Glucose metabolism: FBG, fasting insulin, HOMA-IR, insulin sensitivity, acute insulin response	Correlations (*r*): NR Copollutant models: NR
†Thiering et al. (2013) Munich, Wesel, and South Germany Cross-sectional $PM_{2.5}$: 2008−2009	GINIplus and LISAplus N = 397 Children, age 10 yr	Annual avg at residence, LUR (Eeftens et al., 2012)	Mean 14 (SD: 1.9)	HOMA-IR	Correlations (*r*): NR Copollutant models: NR
†Thiering et al. (2016) Munich, Wesel, and South Germany Cross-sectional $PM_{2.5}$: 2008−2009	GINIplus and LISAplus N = 837 Adolescents, 15 yr	Annual avg at residence, LUR [see (Eeftens et al., 2012)]	Mean 15.1 (SD: 2.2)	HOMA-IR	copollutant model: attenuated after adjustment by NO_2

AOD = Aerosol Optical Density; Avg = average; EURAD = European Air Pollution Dispersion; FBG = fasting blood glucose; FSIGT = frequently sampled intra-venous glucose tolerance; GDM = gestational diabetes mellitus; GINIplus = German Infant Study on the Influence of Nutrition Intervention plus Environmental and Genetic Influences on Allergy Development; HbA1c = Glycated Hemoglobin; HOMA-IR = homeostasis model assessment of insulin resistance; LISAplus = Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics; LUR = land use regression; oGTT = oral glucose tolerance test; NR = not reported; KORA = Cooperative Health Research I the Region of Augsburg; C-V = Cross Validation.

†Studies published since the 2009 PM ISA.

1

There are several animal models available to evaluate diabetes progression including those that rely on diet to recapitulate prediabetes and diabetes-like phenotypes, KK-Ay mouse models of Phase 1 to 3 diabetes, and a streptozotocin-induced diabetic model, which selectively destroys the pancreatic islet β-cells resulting in a pathology like T1D in humans. Mouse models may present with varying degrees of obesity.

Recent studies of diabetes progression support the findings in animal toxicological studies of glucose homeostasis in wild-type animals fed normal chow (Table 7-8). In the diet-induced mouse models of diabetes Xu et al. (2010) and Liu et al. (2014c) found impaired ($p < 0.05$) glucose tolerance and/or insulin sensitivity independent of diet in mice exposed to $PM_{2.5}$ exposure for 10 and 17 weeks. Haberzettl et al. (2016) similarly fed animals a high fat diet, but found that 30-day exposure to $PM_{2.5}$ did not affect insulin resistance or glucose homeostasis. In contrast to the dietary models, the KK-Ay mouse model (for Phase 1−3 diabetes) developed hyperglycemia ($p < 0.05$) as soon as 5 weeks after $PM_{2.5}$ exposure, and the effects persisted 8-weeks after exposure, whereas insulin resistance (measured by HOMA-IR) was identified at 1, 3, and 8 weeks after CAPs exposure (Liu et al., 2014b). However, in a similar study Liu et al. (2014a) found glucose intolerance and insulin resistance 5 weeks after $PM_{2.5}$ exposure, but not 8 weeks after exposure. There was evidence from both models indicating that $PM_{2.5}$ caused inflammation (Section 7.2.5.1). Specifically, although $PM_{2.5}$ exposure and high fat diet did not interact to affect glucose tolerance or insulin resistance (discussed above), inflammation was worsened ($p < 0.05$) by high fat diets (Xu et al., 2010). In the KK-Ay mouse study Liu et al. (2014b) investigated the role of hypothalamic inflammation in T2DM. In two separate experiments Liu et al. (2014b) administered either a TNFα or IKKβ inhibitor into the intra-cerebroventricular region of KK-Ay mice. TNFα is an inflammatory cytokine and IKKβ binds cytosolic NF-κβ preventing NF-κβ translocation to the nucleus and regulation of inflammatory gene expression. TNFα inhibition had no effect on glucose tolerance or insulin sensitivity, however IKKβ inhibition ameliorated PM effects on GTT and ITT ($p < 0.05$). These results indicate a role for nervous system effects, specifically hypothalamic NF-κβ signaling, in regulating inflammation and energy homeostasis and are further discussed in the chapter on Nervous System Effects (Chapter 8).

Table 7-8 Study specific details from animal toxicology studies of glucose and insulin homeostasis.

Study	Study Population	Exposure Details	Endpoints Examined
Haberzettl et al. (2016)	Mouse, male, C57BL/6J, ND or HFD, 8–12 weeks, n = 4–8	Columbus, OH CAPs, $PM_{2.5}$; 30−100 µg/m^3 Group 1: exposed for 6 h/day for 9 or 30 days. Group 2: treated with daily dose of water, metformin 50 mg/kg dose 2 days before, 100 mg/kg dose 1 day before and 300 mg/kg at the time of, or 1 mg/kg rosiglitazone 2 mg/kg two days before 9 days CAP exposure in drinking water.	Body weight, fasting blood glucose and insulin, HOMA-IR, organ weights, blood lipids, liver clinical chemistry, insulin signaling pathway, circulating bone marrow derived stem cells.
Liu et al. (2014c)	Mouse, male, C57BL/6 and Ccr2$^{-/-}$ (inflammation model), ND or HFD, 18 weeks, WT-FA (n = 8), WT-PM (n = 9), CCR2-FA (n = 9), CCR2-PM (n = 8)	Columbus, OH CAPs, $PM_{2.5}$; 116.9 µg/m^3; 6 h/day, 5 days/week for 17 weeks, whole body inhalation.	Body weight, glucose tolerance test, HOMA-IR, inflammation, liver and plasma lipids, vasorelaxation, macrophage infiltration, intra-vital leukocyte-endothelial interactions in adipose and muscle.
Liu et al. (2014a)	Mouse, male, KK-Ay, 5 weeks old	Columbus, OH CAPs, $PM_{2.5}$; 100 µg/m^3, 6 h/day, 5 days/week, 5 weeks or 8 weeks	Body weight, oxygen consumption, CO_2 production, thermogenesis, spleen mass, blood cytokine, hepatic Akt phosphorylation, glucose homeostasis, adiponectin and leptin, adipose tissue p38 and ERK phosphorylation.
Liu et al. (2014b)	Mouse, KK-Ay (develop diabetes and overweightness), 5 or 7 weeks old, sex not reported Exposure 1 (n = 7−8/group), Exposure 2 (n = 6/group), Exposure 3 IMD-0354 group n = 8, infliximab group n = 6	Columbus, OH CAPs, $PM_{2.5}$ Exposure 1: 116.9 µg/m^3 for 6 h/day, 5 days/week, 5 weeks or 8 weeks Exposure 2: 139.5 µg/m^3 + infliximab (TNFα antibody) or artificial CSF for 6 h/day, 5 days/week, 5 weeks Exposure 3: CAPs $PM_{2.5}$ 73.6 µg/m^3 + IMD-0354 (IKKB inhibitor) or DMSO for 6 h/day, 5 days/week, 4 weeks	Exposure 1: Fasting blood glucose, HOMA-IR, hypothalamus TNFα, IL-6 and IKKB mRNA levels, oxidized PAPC. Exposure 2: Hypothalamic TNFα antagonism, GTT, ITT, thermogenesis, body weight. Exposure 3: IKKB inhibition IKK-NFkB pathway upregulation normalized PM effects on GTT and ITT, circulating monocytes (p = 0.0616), and visceral adipose monocytes (p < 0.05) compared to PM controls. Body weight, food intake, glucose tolerance test, insulin levels, HOMA-IR, oxygen consumption, heat production, inflammation, inhibition of the cerebroventricular NFκβ pathway, insulin signaling pathway.
Xu et al. (2010)	Mouse, male, ND or high fat (HFD), wild-type or *p47$^{phox-/-}$* ND, 3 weeks, n = 16/group	Columbus, OH CAPs, $PM_{2.5}$; diet study: 111.0 µg/m^3; 6 h/day, 5 days/week for 10 weeks, whole body inhalation	Glucose tolerance test, HOMA-IR, inflammatory markers and inflammation, adiposity, and vasomotor responses

Table 7-8 (Continued): Study specific details from animal toxicology studies of glucose and insulin homeostasis.

Study	Study Population	Exposure Details	Endpoints Examined
Xu et al. (2011a)	Mouse, male, C57BL/6, ND, 4 weeks, n = 11 FA, n = 9 $PM_{2.5}$	Columbus, OH CAPs, $PM_{2.5}$; 94.4 μg/m^3; 6 h/day, 5 days/week for 10 mo, whole body inhalation.	Body and adipose depot weights, glucose tolerance test, HOMA-IR, systemic inflammation, adipokines, mitochondrial size and number, gene expression, superoxide production/oxidative stress/Nrf2 signaling, insulin signaling pathway.
Yan et al. (2014)	Rat, male, Sprague Dawley T1D (streptozotocin induced), 14 weeks, n = 8	Taipei Air Pollution Exposure System for Health Effects (TAPES) filtered for $PM_{2.5}$; 13.3 μg/m^3, 24 h/day, 7 days/week, for 16 weeks, whole body inhalation.	Glucose/insulin/serum lipids, HOMA-IR, inflammatory and renal function blood biomarkers, urinary protein excretion, histopathology (heart, aorta, and kidney).
Yan et al. (2014)	Rat, male, Sprague Dawley T1D (streptozotocin induced), 14 weeks, n = 8	Taipei Air Pollution Exposure System for Health Effects (TAPES) filtered for $PM_{2.5}$; 13.3 μg/m^3, 24 h/day, 7 days/week, for 16 weeks, whole body inhalation.	Glucose/insulin/serum lipids, HOMA-IR, inflammatory and renal function blood biomarkers, urinary protein excretion, histopathology (heart, aorta, and kidney).

7.2.3.3 Summary

A longitudinal study of older adults in the Boston-area that reported associations of long-term $PM_{2.5}$ with metabolic syndrome and several of its components and another longitudinal study reported an effect on HbA1c among those without diabetes. Multiple cross-sectional epidemiologic studies supported these findings but epidemiologic studies generally did not consider confounding by copollutants. Coherence with the epidemiologic findings was provided by findings from some animal toxicological studies that demonstrated increased blood glucose levels, glucose intolerance and increased HOMA-IR in wild-type animals eating a normal chow diet following long-term exposure to $PM_{2.5}$ compared to controls (Figure 7-7). Limited support for these findings was provided by studies of animal models of diabetes progression.

7.2.4 Type 2 Diabetes Mellitus

Type 2 Diabetes (T2D) Mellitus is an endocrine disorder characterized by high blood glucose levels (i.e., fasting blood glucose ≥126 mg per dL) and insulin resistance. There were no studies of long-term $PM_{2.5}$ exposure and diabetes reviewed in the 2009 PM ISA (U.S. EPA, 2009). Multiple recent studies examine the association of long-term exposure to $PM_{2.5}$ with diabetes in adult populations. Most of the epidemiologic studies are longitudinal in design and have been conducted in well-established cohorts in the U.S. (e.g., Multi-Ethnic Study of Atherosclerosis [MESA] Air, Black Women's Health Study [BWHS], Nurses' Health Study [NHS], and Health Professional Follow-up Study [HPFS]). The

collective epidemiologic and toxicological evidence described below provide a basis for long-term $PM_{2.5}$ exposures leading to impaired glucose and insulin homeostasis and diabetes. Although findings across epidemiologic studies were not consistent, some high quality, longitudinal studies reported positive associations between long-term exposure to $PM_{2.5}$ and the incidence of diabetes. In addition, there is toxicological evidence that found PM exacerbated glucose tolerance in mouse models of diabetes.

7.2.4.1 Epidemiologic Studies of Type 2 Diabetes Mellitus

Prospective studies do not consistently report positive associations between long-term $PM_{2.5}$ exposure and incident diabetes (Table 7-6, Table 7-9).

Studies used a variety of outcome ascertainment methods ranging from self-reported diabetes to confirmed FBG level. Although some studies did not explicitly distinguish between T1D and T2D, most studies focused on incident cases among adults, which are generally cases of T2D. Park et al. (2015) examined the association of long-term $PM_{2.5}$ exposure and diabetes in MESA Air participants (n = 5,135) who were free of the disease at their baseline exam. These investigators observed a positive but imprecise (i.e., wide confidence intervals) association with diabetes [HR: 1.11 (95% CI: 0.75, 1.61)]. Stratified analyses showed that the association between $PM_{2.5}$ and diabetes was present among women [HR: 1.22 (95% CI: 0.72, 2.03)] but not among men [HR: 1.00 (95% CI: 0.55, 1.77)]. Adjustment for covariates, including neighborhood-level SES and site, increased the magnitude of the effect estimates observed in this study. Unlike in the MESA cohort, sex-specific estimates for the association with incident diabetes were similar among female nurses and male health professionals in the study by Puett et al. (2011) where a positive but imprecise association was observed in the population overall [HR: 1.04 (95% CI: 0.95, 1.13)]. The association with $PM_{2.5}$ was unchanged after adjustment for neighborhood level SES (quantitative results not presented) but diminished in copollutant models adjusting for $PM_{10-2.5}$ (Puett et al., 2011).

In an analysis of Los Angeles residents in black women's health study (BWHS) who were followed from 1995 through 2005, Coogan et al. (2012) observed a positive association [HR: 1.28 (95% CI: 0.88, 1.85)] with a wide CI. In an extended analysis of the full BWHS cohort that included women residing in 56 metropolitan areas, followed from 2005 through 2011, Coogan et al. (2016) reported no association [HR: 0.98 (95% CI: 0.83, 1.16)], however. The preliminary analysis of Coogan et al. (2012) reported substantial attenuation in the association of $PM_{2.5}$ with diabetes after adjustment for NO_X (copollutant confounding was not evaluated in the 2016 study because a null association with $PM_{2.5}$ was observed). In a sensitivity analysis of Los Angeles residents followed through 2011 that allowed comparison to the previous findings, the HR was positive but attenuated and the CI was relatively wide (Coogan et al., 2016).

Table 7-9 Epidemiologic studies of long-term exposure to $PM_{2.5}$ and diabetes.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Park et al. (2015) Longitudinal cohort $PM_{2.5}$: 2000 Outcome: 2000−2012	MESA N = 5,135	Annual avg at residence, spatio-temporal model [see Sampson et al. (2011)]	Mean 17.3 (SD 3.1) in people with diabetes (baseline) Mean 16.7 (SD: 2.8) in people without diabetes	Use of diabetes medication or fasting glucose ≥126 mg/dL	Correlation (*r*), NO_X = 0.69 Copollutant model: NR
†Puett et al. (2011) Longitudinal cohort U.S. $PM_{2.5}$: 12 mo prior to diagnosis Outcome NHS: 1976−2009 Outcome HPFS: 1986−2009	NHS (N = 74,412) and HPFS (N = 15,048) N = 3,784 cases	Annual avg at geocoded residential address, spatiotemporal models C-V R2 = 0.77 (post-1999) and R^2 = 0.69 (pre-1999)	Mean NHS: 18.3 (SD: 3.1) Mean HPFS: 17.5 (SD 2.7) IQR: 4	DM self-reported doctor diagnosed with confirmation of a subset of cases by medical record review: elevated plasma glucose or ≥1 DM symptoms (e.g., weight loss, thirst, polyuria) or use of hypoglycemic medication	Correlation (*r*): NR Copollutant models: $PM_{10-2.5}$
†Coogan et al. (2016) Longitudinal cohort 56 Metro areas, U.S. $PM_{2.5}$: 1999−2008 Outcome: 1995−2011	BWHS N = 33,771	Overall mean (1999−2008), LUR and BME hybrid model, C-V R^2 = 0.79	Mean: 13.9 (SD: 2.3) Range: 3.1−24.2 IQR: 2.9	Self-reported doctor diagnosed T2DM at age ≥30. Confirmation of 96% of cases in validation study using medical records.	Correlation (*r*): NR copollutant model: NR
†Coogan et al. (2012) Los Angeles, CA Longitudinal cohort $PM_{2.5}$: 2,000 Outcome: 1995−2005	BWHS N = 183 cases N = 3,992 black women (age 21−69 at baseline)	Annual avg, at residential zip code, kriging interpolation (10 × 10 km)	Mean 20.7 IQR: 20.3−21.6	Self-reported doctor diagnosed Type 2 diabetes mellitus at age ≥30	Copollutant model: NO_X

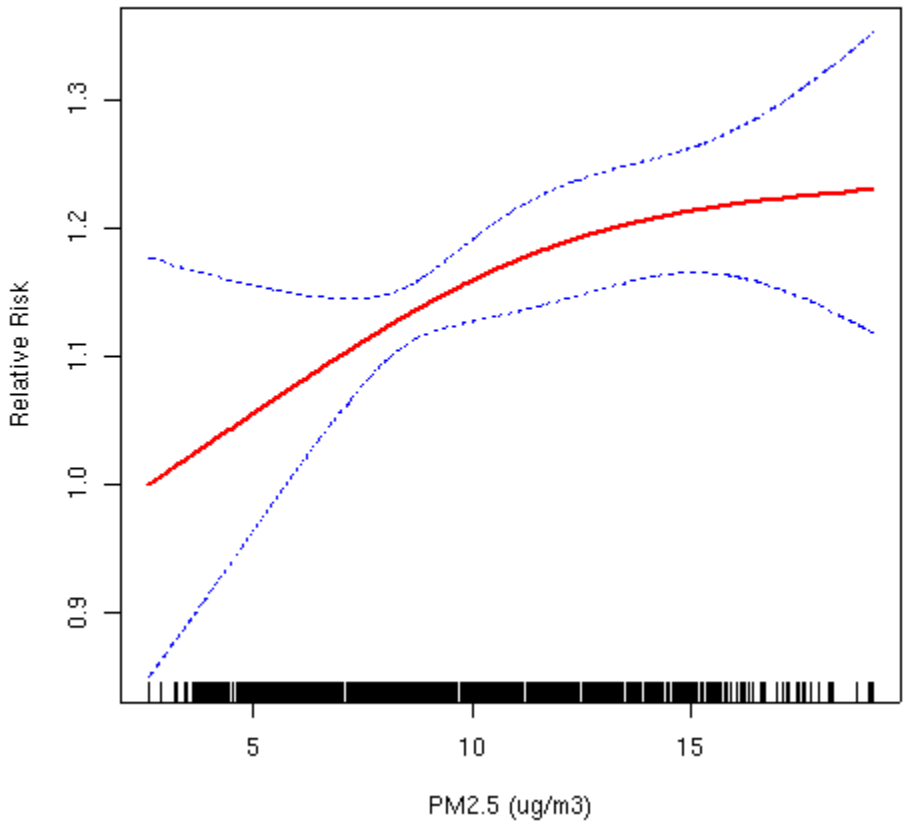
Table 7-9 (Continued): Epidemiologic studies of long-term exposure to $PM_{2.5}$ and diabetes.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Chen et al. (2013) Ontario, Canada Longitudinal cohort $PM_{2.5}$: 2001−2006 Outcome: 1996/2005−2010	Ontario, Diabetes Database n = 62,012 n = 6,310 cases	6 yr avg, at postal code, satellite derived AOD (10 × 10 km) Correlation between long-term avg from monitors and satellite based estimate, *r* = 0.77	Mean 10.6 (range: 2.6−19.1)	Incident diabetes administrative database (ICD9: 250 or ICD10: E10-E14)	Correlations (*r*): NR copollutant model: NR
†Hansen et al. (2016) Longitudinal cohort $PM_{2.5}$: 1990−2013 Outcome: 1993/99−2013	Danish Nurse Cohort n = 28,731 controls n = 1,137 cases	5 yr average at residence since 1990, 5 yr running average calculated from annual dispersion model [see Jensen et al. (2001)]. Model fit for PM NR.	Mean 18.1 (SD: 2.8)	National Diabetes Register of cases: hospital discharge (ICD-10:E10-14, DH36.0, DO24), chiropody as a diabetic patient, 5 blood-glucose measures within 1 year, or two blood glucose measures per year in 5 years, 2nd purchase of insulin or oral antidiabetic drugs within 6 mo. Note: T2D and T1D not distinguished	Correlations (*r*): NR copollutant models: NO_2
†Weinmayr et al. (2015) Longitudinal cohort Ruhr area, Germany $PM_{2.5}$: 2002−2003 Outcome: 2000/03−2005/08	HNR N = 3,607	Annual avg, dispersion model (1 × 1 km) Model fit for $PM_{2.5}$ NR (PM_{10} *r* > 0.80 for measured and modelled data)	Mean 16.8 (SD1.5)	Self-reported doctor diagnosed DM or use of diabetes medication or FBG ≥126 mg/dL at follow-up (random subset of respondents). Note: T2D and T1D not distinguished.	Correlations (*r*): NR copollutant model: NR

AOD = Aerosol Optical Density, avg = average, BME = Bayesian Maximum Entropy, BWHS = Black Women's Health Study, C-V = cross-validation, DM = diabetes mellitus, ICD = International Classification of Disease, HPFU = Health Professionals Follow-up Study, IGM = Impaired Glucose Metabolism; LUR = Land Use Regression; HNR = Heinz Nixdorf Recall study, MESA = Multiethnic Study of Atherosclerosis, NHS = Nurses' Health Study, NR = not reported; km = kilometer, T1D = Type 1 diabetes, T2D = Type 2 diabetes, yr = years.

†Studies published since the 2009 PM ISA.

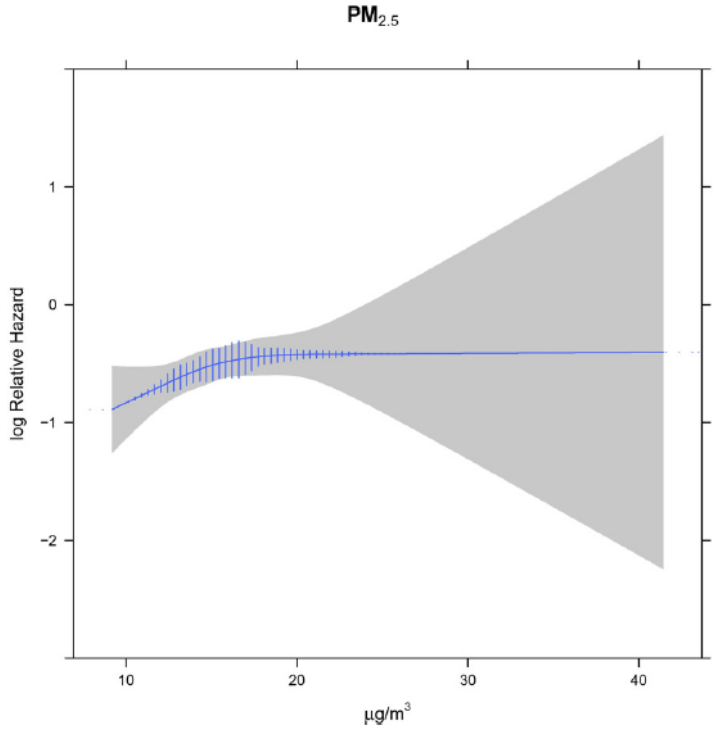
Several additional studies examining the effect of long-term $PM_{2.5}$ on the development of diabetes were conducted in Canada and Europe. Chen et al. (2013) combined several population-based surveys to establish a large cohort of men and women without diabetes living in Ontario, Canada (n = 62,012). This study found a positive association of long-term $PM_{2.5}$ exposures with incident diabetes [HR: 1.05 (95% CI: 1.01, 1.10)] after adjustment for covariates including individual and neighborhood indicators of SES and comorbidities. Chen et al. (2013) examined the shape of the concentration-response relationship using a natural cubic spline with two degrees of freedom and reported no statistical evidence of departure from linearity (Figure 7-8).



Source: Permission pending, Chen et al. (2013).

Figure 7-8 Concentration-response relationship between the concentration of $PM_{2.5}$ and incident diabetes among the cohort, depicted using a natural cubic spline function with two degrees of freedom. The hazard ratios were estimated by comparing to 2.6 µg/m³.

In a study of Danish nurses, Hansen et al. (2016) reported relatively precise risk of diabetes in association with long-term exposure to $PM_{2.5}$ [HR: 1.18 (95% CI: 1.03, 1.38)]. In addition, the association with $PM_{2.5}$ persisted in the copollutant model adjusted for NO_2. An association of a similar magnitude but with a wider confidence interval was observed among participants in the HNR study [HR: 1.18 (95% CI: 0.78, 1.74)] (Weinmayr et al., 2015). Metrics derived to estimate $PM_{2.5}$ from traffic were also associated with incident diabetes in this study. The log relative hazard for the Danish Nurses Cohort is pictured in Figure 7-9 (Hansen et al., 2016). The curve is attenuated and the hazard estimate becomes less precise beginning above approximately 20 µg/m^3 but there was no statistical evidence of deviation from linearity.

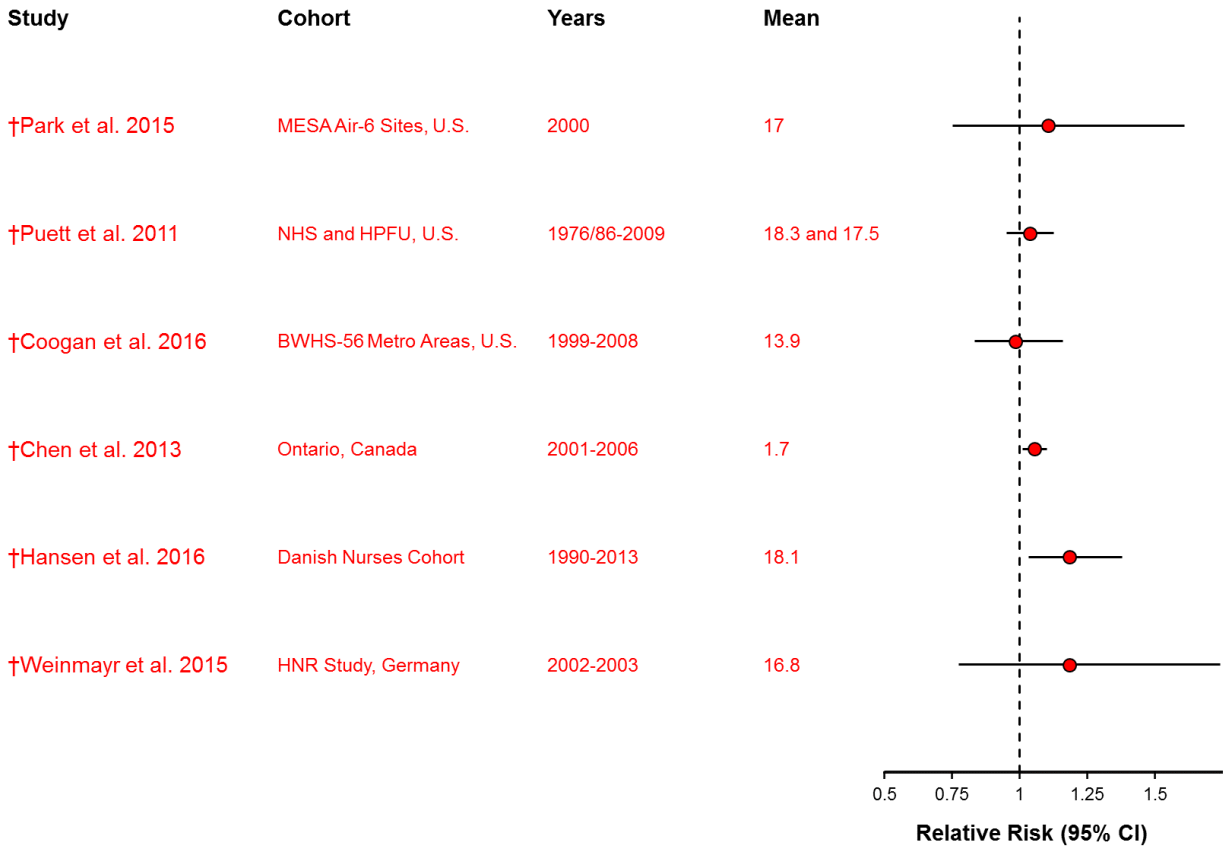


Source: Permission pending, Hansen et al. (2016).

Figure 7-9 Association (log relative hazard) between 5-year running average level at residence and incident diabetes in the Danish Nurses Study. Adjusted for age, calendar time, smoking, physical activity alcohol, fatty meat consumption, fruit and vegetable consumption, hypertension, myocardial infarction (MI), employment status, marital status and body mass index (BMI).

7.2.4.2 Summary

The risk of incident diabetes associated with long-term exposure $PM_{2.5}$ was increased in some, but not all, of the studies that were reviewed. With a few exceptions (Hansen et al., 2016; Chen et al., 2013), confidence intervals for the observed positive associations included the null. There were also differences regarding effect modification by sex (i.e., the effect size was larger in women enrolled in MESA but similar in women enrolled in NHS compared to men enrolled in HPFS). Note that Eze et al. (2015) reported a meta-analyzed pooled estimate for males [RR: 1.02 (95% CI: 0.96, 1.08)] and females [RR: 1.05 (95% CI: 1.01, 1.09)]. This pooled estimate, however, did not include the relatively recent MESA study or the extended analysis of the BWHS cohort, which reported no association. Based on a limited number of studies, associations with $PM_{2.5}$ were attenuated after adjustment for $PM_{10-2.5}$ with inconsistent findings in models adjusted NO_X or NO_2.



Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Mean concentrations in $\mu g/m^3$. Relative risks are standardized to a 5 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations.

BWHS = Black Women's Health Study, CI = Confidence Interval, HPFU = Health Professionals Follow-up Study, HNR = Heinz Nixdorf Recall, MESA = Multi-Ethnic Study of Atherosclerosis, NHS = Nurses' Health Study.

†Studies published since the 2009 PM ISA.

Corresponding quantitative results are reported in Supplemental Table S7-1 (U.S. EPA, 2018).

Figure 7-10 Associations between long-term exposure to $PM_{2.5}$ and incident diabetes in longitudinal epidemiologic studies. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration.

7.2.5 Other Indicators of Metabolic Function

7.2.5.1 Inflammation

Experimental, epidemiologic, and controlled human exposure evidence link inflammation to the development of metabolic disease and comorbidities (Chapter 6 and Section 7.1.1 and Section 7.2.1).

Furthermore, it is widely believed that inflammation plays a critical role in the development of T2D and atherosclerosis, further complicating heart disease. Metabolic tissues, such as liver and adipose tissue, are essentially cocultures of metabolic (hepatocytes and adipocytes) and immune cells (i.e., Kupffer cells and macrophages) (Boron and Boulpaep, 2017). Furthermore, metabolic and immune responses (i.e., toll-like receptor and NFκβ) are coordinately regulated by inflammatory and endocrine signaling between organs and cells in response to environmental stimuli such as nutrients and pathogens. Therefore, the discussion below integrates inflammatory evidence from the cardiovascular, respiratory, and nervous system health effects chapters below with a specific focus on peripheral inflammation (Table 7-10).

Table 7-10 Study specific details from animal toxicology studies of inflammation and other indicators of metabolic function.

Study	Species, Sex, Strain, Sex, Diet, Age	Exposure Details (Pollutant, Concentration, Duration, Route)	Endpoints Evaluated
Haberzettl et al. (2016)	Mouse, male, C57BL/6J, ND or HFD, 8–12 weeks, n = 4–8	Columbus, OH CAPs, $PM_{2.5}$; 30−100 μg/m^3 Group 1: exposed for 6 h/day for 9 or 30 days. Group 2: treated with daily dose of water, metformin (50 mg/kg dose 2 days before, 100 mg/kg dose 1 day before and 300 mg/kg at the time of), or 1 mg/kg rosiglitazone 2 mg/kg two days before 9 days CAP exposure in drinking water.	Body weight, fasting blood glucose and insulin, HOMA-IR, organ weights, blood lipids, liver clinical chemistry, insulin signaling pathway, circulating bone marrow derived stem cells.
Kampfrath et al. (2011)	Mouse, male, C57BL/6, $NOX2^{-/-}$ (C57BL/6 background) Balb/c (TLR4wt), Tlr4Lps-d (TLRd, BALB/cAnPt background), c-fmsYFP (FVB/N background)	CAPs $PM_{2.5}$; 6 h/day, 5 days/week for: TLR4wt, TLRd, $NOX2$wt, and $NOX2^{-/-}$ for 20 weeks; c-fmsYFP for 23 weeks.	PM increases monocyte adherence and infiltration in cremaster muscle and mesenteric adipose tissue.
Liu et al. (2014c)	Mouse, male, C57BL/6 and $Ccr2^{-/-}$ (inflammation model), ND or HFD, 18 weeks, WT-FA (n = 8), WT-PM (n = 9), CCR2-FA (n = 9), CCR2-PM (n = 8)	Columbus, OH CAPs $PM_{2.5}$; 116.9 μg/m^3; 6 h/day, 5 days/week for 17 weeks, whole body inhalation	Body weight, glucose tolerance test, HOMA-IR, inflammation, liver and plasma lipids, vasorelaxation, macrophage infiltration, intra-vital leukocyte-endothelial interactions in adipose and muscle.

Table 7-10 (Continued): Study specific details from animal toxicology studies of inflammation underlying metabolic disease.

Study	Species, Sex, Strain, Sex, Diet, Age	Exposure Details (Pollutant, Concentration, Duration, Route)	Endpoints Evaluated
Liu et al. (2014a)	Mouse, male, KK-Ay, 5 weeks old, n = 7−8/group	Columbus, OH CAPs $PM_{2.5}$; 102.9 ± 19.16 μg/m^3, 6 h/day, 5 days/week, 5 weeks or 8 weeks December 28, 2011—February 28, 2012, OASIS exposure system	IPGTT or ITT, blood glucose, adiponectin, and leptin, bone marrow, spleen, epididymal white adipose tissue, stromal vasculature cells were stained for inflammation (F4/80 + anti-CD11c + cells) and flow cytometry, aortic ring, O_2 consumption, CO_2 production, heat production, body weight, hepatic Akt, p38 and ERK phosphorylation
Liu et al. (2014b)	Mouse, KK-Ay (develop diabetes and overweightness), 5 or 7 weeks old, sex and genotype not reported, Exposure 1 (n = 7−8/group), Exposure 2 (n = 6/group), Exposure 3 (n = 8/group) IMD 0354 group n = 8, infliximab group n = 6	Columbus, OH CAPs $PM_{2.5}$ Exposure 1: 116.9 μg/m^3 for 6 h/day, 5 days/week, 5 weeks or 8 weeks Exposure 2: 139.5 μg/m^3 + infliximab (TNFα antibody) or artificial CSF for 6 h/day, 5 days/week, 5 weeks Exposure 3: 73.6 μg/m^3 + IMD-0354 (IKKB inhibitor) or DMSO for 6 h/day, 5 days/week, 4 weeks	Exposure 1: fasting blood glucose, HOMA-IR, hypothalamus TNFα, IL-6 and IKKB mRNA levels, oxidized PAPC Exposure 2: hypothalamic TNFα antagonism did not alter GTT, ITT, thermogenesis, body weight Exposure 3: IKKB inhibition IKK-NFkB pathway upregulation normalized PM effects on GTT and ITT, circulating monocytes (p = 0.0616), and visceral adipose monocytes (p < 0.05) compared to PM controls Body weight, food intake, glucose tolerance test, insulin levels, HOMA-IR, oxygen consumption, heat production, inflammation, inhibition of the cerebroventricular NFκβ pathway, insulin signaling pathway
Mendez et al. (2013)	Mouse, male, C57BL/6, normal diet (ND), 6 weeks, n = 4/group	Columbus, OH CAPs, $PM_{2.5}$; 94.4 μg/m^3; 6 h/day, 5 days/week for 10 mo, whole body inhalation	Inflammation, adipocyte size, ER stress markers
Wei et al. (2016)	Rat, pregnant females (12 weeks old) and male offspring, Sprague Dawley, ND or high fructose, gestation day 4—PND 3 or 8 weeks, filtered n = 8−10, unfiltered n = 6−10	Beijing, China air filtered for $PM_{2.5}$; 73.5 μg/m^3; continuous whole-body inhalation from gestation date 4 until PND 3 or 8 weeks	Body and organ weight, lung inflammation, LDL, TC, TG, malondialdehyde (MDA), GPL-1, chemoattractants, and anti-inflammatory cytokines

Table 7-10 (Continued): Study specific details from animal toxicology studies of inflammation underlying metabolic disease.

Study	Species, Sex, Strain, Sex, Diet, Age	Exposure Details (Pollutant, Concentration, Duration, Route)	Endpoints Evaluated
Xu et al. (2010)	Mouse, male, ND or high fat (HFD), wild-type or *p47*$^{phox-/-}$ ND, 3 weeks, n = 16/group	Columbus, OH CAPs, $PM_{2.5}$; diet study: 111.0 µg/m^3; 6 h/day, 5 days/week for 10 weeks, whole body inhalation	Glucose tolerance test, HOMA-IR, inflammatory markers and inflammation, adiposity, and vasomotor responses
Xu et al. (2011a)	Mouse, male, C57BL/6, ND, 4 weeks, n = 11 FA, n = 9 $PM_{2.5}$	Columbus, OH CAPs, $PM_{2.5}$; 94.4 µg/m^3; 6 h/day, 5 days/week for 10 mo, whole body inhalation	Body and adipose depot weights, glucose tolerance test, HOMA-IR, systemic inflammation, adipokines, mitochondrial size and number, gene expression, superoxide production/oxidative stress/Nrf2 signaling, insulin signaling pathway
Xu et al. (2011b)	Mouse, male, ApoE$^{-/-}$ (atherosclerosis), 4 weeks, n = 8/group	East Lansing, MI CAPs $PM_{2.5}$; 96.89 µg/m^3; 6 h/day, 5 days/week for 2 mo, whole body inhalation	Superoxide production, inflammatory response, WAT and BAT gene expression, mitochondrial number and size
Yan et al. (2014)	Rat, male, Sprague Dawley T1D (streptozotocin induced), 14 weeks, n = 8	Taipei Air Pollution Exposure System for Health Effects (TAPES) filtered for $PM_{2.5}$; 13.3 µg/m^3, 24 h/day, 7 days/week, for 16 weeks, whole body inhalation	Glucose/insulin/serum lipids, HOMA-IR, inflammatory and renal function blood biomarkers, urinary protein excretion, histopathology (heart, aorta, and kidney)
Zheng et al. (2013)	Mouse, male, C57BL/6, ND or high fat (HFD), 6 weeks, n = 4 FA, n = 5 CAPs exposed	Columbus, OH CAPs, $PM_{2.5}$; 74.6 µg/m^3; 6 h/day, 5 days/week for 3 or 10 weeks, whole body inhalation	Steatosis, steatohepatitis, glycogen storage, glucose tolerance test, fasting insulin and HOMA-IR, inflammatory pathway, liver and plasma lipids, gene expression, insulin signaling pathway
Zheng et al. (2015)	Mouse, male, C57BL/6, ND or high fat (HFD), 8 weeks; *p47*$^{phox-/-}$ (NADPH oxidase deficient, susceptible to infection and granulomatous inflammation), ND, 3 weeks, n = 8 per group	Columbus, OH CAPs, $PM_{2.5}$; 74.6 µg/m^3; 6 h/day, 5 days/week for 10 weeks, 111.0 µg/m^3; 6 h/day, 5 days/week for 9 mo, whole body inhalation	Liver steatosis, fibrosis and collagen production

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There is evidence for systemic inflammation following long-term exposure to $PM_{2.5}$ (also see Section 6.2.12). Studies with $ApoE^{-/-}$ mice that are prone to develop atherosclerosis demonstrated worsened inflammation in white adipose tissue accompanied by mitochondrial alterations and oxidative stress in brown adipose tissue (Xu et al., 2011b). Long term $PM_{2.5}$ exposure led to systemic increases in proinflammatory cytokines in experimental models and was also associated with blood biomarkers of inflammation such as CRP (Section 6.2.12). In experimental models, long term $PM_{2.5}$ CAPs exposures in wild type rodents fed a normal diet demonstrated increased blood TNF-α (<0.05) (Zheng et al., 2013; Xu et al., 2011b; Xu et al., 2011a; Xu et al., 2010), TGF-β1 ($p < 0.05$) (Zheng et al., 2015), monocyte counts (Kampfrath et al., 2011), CD4+ and CD8+ T lymphocytes (Deiuliis et al., 2012), IL-6 ($p < 0.01$) (Yan et al., 2014), and malondialdehyde ($p < 0.001$) (Wei et al., 2016).

Increases in blood inflammation markers and immune cells were consistent with the histological observation of liver and adipose inflammation. Specifically, nonalcoholic steatohepatitis and fibrosis were noted in $PM_{2.5}$ CAPs exposed mice (Zheng et al., 2015; Zheng et al., 2013) and increased monocyte/macrophage infiltration in visceral (Xu et al., 2010), epididymal (Mendez et al., 2013; Xu et al., 2011b) adipose tissue. Further molecular analysis demonstrated a clear and consistent decrease in Akt phosphorylation in liver, skeletal, adipose, and heart tissues (Liu et al., 2014c; Liu et al., 2014a; Zheng et al., 2013; Xu et al., 2011a) possibly mediated by activation of TLR/Iκκβ/JNK pathways leading to repression of the PI3K/Akt pathways (also discussed above in Section 7.2.3).

Genetic models highlight a critical role for innate immunity in metabolic disease outcomes. Specifically, long-term $PM_{2.5}$ exposure had reduced or no effect on hepatic inflammation, hepatic steatosis and fibrosis, and adipose inflammation in mice with a mutation in *p47phox* (a critical subunit of NADPH oxidase) or CC-chemokine receptor Type 2 (CCR2, a receptor for CCL2 chemokines). Furthermore, $PM_{2.5}$-mediated effects on insulin resistance (discussed above) were improved ($p < 0.05$) in these genetic mouse models (Zheng et al., 2015; Liu et al., 2014c; Xu et al., 2010). Similarly, $PM_{2.5}$ exposure and HFD feeding worsened hepatic fibrosis and reactive oxygen species generation, whereas these effects were rescued in a $p47^{phox-/-}$ mouse (nonfunctional NADPH oxidase activity) (Zheng et al., 2015). These results indicate that $PM_{2.5}$ impacts on inflammation and glucose levels are mediated by the innate immune system and potentially modified by dietary fat.

In a mouse model genetically predisposed to diabetes and obesity, long-term $PM_{2.5}$ exposure resulted in hyperglycemia ($p < 0.05$), insulin resistance ($p < 0.05$), and systemic inflammation (Liu et al., 2014a).

In summary, these phenotypic observations demonstrate that long-term $PM_{2.5}$ CAPs exposure in rodents causes increased incidence of peripheral and systemic inflammation, extending from the lung to peripheral vasculature and distal adipose and hepatic organs that are exacerbated by diet and genetic predisposition. The implication is that systemic inflammation may impact liver and adipose function, and consequently disrupt insulin signaling leading to a shift in glucose and lipid homeostasis (Section 7.2.3).

7.2.5.2 Liver Function

Hepatic steatosis in the absence of alcohol consumption (i.e., nonalcoholic fatty liver disease [NAFLD]) is a progressive chronic disease. The main pathological feature of NAFLD is excessive lipid accumulation (>5% and typically triglycerides) within the cytosol of hepatocytes. NAFLD is often asymptomatic, but if left untreated may progress to steatohepatitis (inflamed fatty liver) and progress to permanent liver injury including fibrosis and cirrhosis (Angrish et al., 2016a). NFALD is often associated with metabolic syndrome risk factors, including obesity, T2D, and cardiovascular disease, and is therefore considered the hepatic manifestation of metabolic syndrome.

7.2.5.2.1 Epidemiologic Studies

There were no studies of long-term exposure to $PM_{2.5}$ and liver function reviewed in the 2009 PM ISA. The evidence remains limited (Table 7-11) Li et al. (2016) conducted a study of participants in the Framingham Offspring and Third Generation cohorts to determine the association between long-term $PM_{2.5}$ exposure and hepatic steatosis. No associations with liver-to-phantom ratio (LPR) [$\beta = 0.00$ (95% CI: 0.00, 0.01)] or hepatic steatosis [OR: 0.86 (95% CI: 0.66, 1.19)] was observed. In a study in Augsburg, Germany, Markevych et al. (2013) reported increase in several liver enzymes that may indicate reduced liver function. In this study increases in gamma-glutamyltransferase (GGT) [9.21% (95% CI: 0.18, 18.77)] but not aspartate transaminase (AST) [1.26% (95% CI: −2.89, 5.42)] or alanine transaminase (ALT) [−1.81% (−7.94, 4.69)] were observed.

Table 7-11 Epidemiologic studies of long-term exposure to $PM_{2.5}$ and indicators of liver function.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
†Li et al. (2016) Cross-sectional $PM_{2.5}$: 2003 Outcome: 2002−2005	Framingham Offspring and Third Generation Study N = 2,513	Annual avg (2003), spatio-temporal model, 1 × 1 km resolution, satellite derived AOD, out of sample R^2 = 0.88	Mean 10.6 (IQR: 1.4)	LPR Hepatic Steatosis	Correlations (*r*): NR Copollutant model: NR
†Markevych et al. (2013) Augsburg, Germany $PM_{2.5}$: 2008−2009 Outcome: 2004−2008	KORA N = 5,892 (31−85 yr)	ESCAPE Protocol	Mean: NR 5th−95th: 2.77	GGT AST ALT	Correlations (*r*): NR Copollutant model: NR

AOD = Aerosol Optical Depth, GGT = gamma-glutamyltransferase, AST = aspartate transaminase, ALT = alanine transaminase, LPR = Liver-to-Phantom Ratio, KORA = Cooperative Health Research in the Region of Augsburg.

†Studies published since the 2009 PM ISA.

7.2.5.2.2 Toxicological Studies

There were no experimental studies of long-term exposure to $PM_{2.5}$ and liver function reviewed in the 2009 PM ISA. Several recent animal studies identified pathological fatty changes in the liver after exposure to $PM_{2.5}$ CAPs (Table 7-10). Specifically, histological phenotyping with H&E stain, Sirius-red, and Masson's trichrome staining identified hepatic steatosis, lobular and cellular inflammation, and perisinusoidal inflammation among mice exposed for 10 consecutive weeks to $PM_{2.5}$ CAPs (Zheng et al., 2013). Zheng also reported that $PM_{2.5}$ exposure reduced hepatic glycogen storage in the same animals. In a follow-up study Zheng et al. (2015) also found perisinusoidal fibrosis in mice exposed for 10 weeks or 9 months that was worsened by a high fat diet. However, there was no evidence of fibrosis in $p47^{phox-/-}$ mice (a mutation that inactivates NADPH oxidase (see Section 7.2.5.1) after 10 weeks of $PM_{2.5}$ CAPs exposure). Similarly, Liu et al. (2014c) identified steatosis marked by increased liver triglycerides ($p > 0.05$) and increased oil red O staining levels ($p > 0.05$) that were attenuated in $CCR2^{-/-}$ mice. Considered together, these results support that $PM_{2.5}$ exposure increases hepatic lipid levels and worsens progressive liver disease via innate immunity (see Section 7.2.5.1).

7.2.5.3 Endocrine Hormones

Body energy levels are maintained during feeding and fasting by many endocrine hormones secreted by organs and glands, e.g., the pancreas (insulin and glucagon), gastrointestinal tract (ghrelin), adipose tissue (adiponectin and leptin), neurons (i.e., epinephrine), and adrenal gland (glucocorticoids, i.e., cortisol). There are two recent studies reporting changes in adipose endocrine hormones. Xu et al. (2011a) identified decreased ($p < 0.05$) adiponectin and leptin blood levels in C57BL/6 mice exposed 6 hours/day, 5 days/week for 10 months compared to vehicle controls. Liu et al. (2014a) identified decreased plasma adiponectin and increased leptin levels ($p < 0.05$) in KK-Ay mice 5 weeks after $PM_{2.5}$ exposure compared to FA controls, whereas no differences were detected 8 weeks after exposure.

7.2.5.4 Adiposity and Weight Gain

Adiposity, particularly visceral adiposity, and weight gain are risk factors for metabolic syndrome, T2D and cardiovascular disease. Although most epidemiologic studies consider BMI as a potential confounder or modifier of the association between $PM_{2.5}$ and cardiovascular disease, there were no studies of the association of long-term exposure to $PM_{2.5}$ with adiposity or weight gain reviewed in the 2009 PM ISA.

7.2.5.4.1 Epidemiologic Studies

A limited number of epidemiologic studies of adiposity and weight gain (Table 7-12) are currently available for review. White et al. (2016) examined the associations of long-term exposure to $PM_{2.5}$ with weight gain among women in the BWHS. Overall, no evidence of an association between $PM_{2.5}$ was observed in this population.

Mao et al. (2017) reported increased risk of childhood overweight and obesity, comparing the highest to the lowest quartile of exposure, with exposure to $PM_{2.5}$ averaged over the first 2 years of life, as well as during each trimester of pregnancy. This study also indicated the highest risk among children of mothers who were overweight or obese prior to pregnancy and exposed to $PM_{2.5}$. There was a dose-response relationship between $PM_{2.5}$ and childhood obesity and overweight that was indicated after the median exposure (10.5−10.9 $\mu g/m^3$) for each of the exposure windows. Exposure during the second trimester showed a steeper C-R relationship.

Table 7-12 Epidemiologic studies of long-term exposure to $PM_{2.5}$, overweight and obesity.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
†White et al. (2016) 56 Metro areas, U.S. Prospective cohort $PM_{2.5}$: 1998−2008 Outcome: 1995−2011	BWHS N = 38,374 Follow-up 16 yr	Multiyear avg, LUR with BME (C-V R^2 = 0.79) for residential histories	Mean: 13.9	Weight change	Correlations (*r*): NR Copollutant model: NR
†Mao et al. (2017) Boston, MA Prospective cohort 2003−2012	BMC N = 1,446 mother-infant pairs	Closest monitor, preconception, 1st, 2nd, 3rd, 2 first 2 yr of life	NR	Childhood overweight and obesity	Correlations (*r*): NR Copollutant model: NR

BME = Bayesian Maximum Entropy; BMC = Boston Medical Center; HOMA-IR = Homeostatic Model Assessment of Insulin; Resistance; LUR = Land Use Regression; NR = not reported.

†Studies published since the 2009 PM ISA.

7.2.5.4.2 Toxicological Studies

Long-term $PM_{2.5}$ exposures had little to no effect on animal body weight. Long-term $PM_{2.5}$ exposure affected abdominal fat mass (measured by MRI) in one study ($p < 0.05$), although there was no interaction between high fat feeding and $PM_{2.5}$ on abdominal fat mass (Xu et al., 2010). Liu et al. (2014a) identified a trend ($p = 0.0578$) toward increased epididymal white adipose tissue 5 weeks after exposure, but found no difference between $PM_{2.5}$ and filtered air 8 weeks after exposure. Studies are detailed in Table 7-10.

7.2.5.5 Blood Lipids

7.2.5.5.1 Epidemiologic Studies

The previous PM ISA did not include any relevant epidemiologic studies describing associations between long-term exposure to $PM_{2.5}$ and blood lipid levels. The available literature includes ecological studies or studies conducted at relatively high concentration (>20) (Calderón-Garcidueñas et al., 2013; Chuang et al., 2011). In addition, Wallwork et al. (2017) examined blood lipids in the context of all the components of metabolic syndrome and observed increased triglycerides among older adult males in the NAS in association with annual average $PM_{2.5}$ concentration. Yitshak Sade et al. (2016) examined blood lipids, in addition to HbA1c and FBG, and reported associations of 3-month average $PM_{2.5}$ exposure with HDL and LDL in a retrospective study in Israel noting larger effect sizes among those with diabetes.

7.2.5.5.2 Toxicological Studies

In mice, long-term $PM_{2.5}$ CAPs exposures resulted in increased ($p < 0.05$) liver (Liu et al., 2014c), (116 μg/m^3 for 17 weeks), and blood (Zheng et al., 2013), (74 μg/m^3 for 9 months), triglycerides and blood cholesterol (Zheng et al., 2013) levels. It is important to note, however that rodent cholesterol dietary intake and plasma clearance is markedly higher than humans meaning that rodents, on average, have much lower plasma LDL levels (7 mg/dl) than humans (120 mg/dl). Study characteristics are detailed in Table 7-10.

7.2.5.6 Blood Pressure and Hypertension

Small increases in SBP, PP, and MAP were found in association with $PM_{2.5}$ in MESA and Sister Study but not in all the available studies (Section 6.3.7). A limited number of animal toxicological studies

demonstrate a relationship between long-term exposure to $PM_{2.5}$ and consistent increases in BP (Section 6.2.7.2). These results are in coherence with epidemiologic studies reporting positive associations between long-term exposure to $PM_{2.5}$ and hypertension (Section 6.2.18).

7.2.6 Gestational Diabetes

Several studies of gestational diabetes were conducted. Generally, the results of the studies were inconsistent, though several reported positive associations with gestational diabetes or impaired glucose tolerance with $PM_{2.5}$ exposures during the second trimester. While the evidence base for gestational diabetes is growing, it is still limited to a relatively small number of studies which report generally inconsistent results (see Section 9.2.1 on Reproductive and Developmental Effects for more details).

7.2.7 Type 1 Diabetes

Type 1 diabetes (T1D) mellitus, which typically affects children and young adults, is a chronic condition that results when the pancreas fails to produce the insulin needed for glucose homeostasis. There were no studies of T1D reviewed in the 2009 PM ISA.

7.2.7.1 Epidemiologic Studies

The evidence relating to the effect of long-term exposure to $PM_{2.5}$ on T1D is limited to a study examining the age of onset as opposed to development of the disease (Table 7-12). Beyerlein et al. (2015) analyzed data from the Bavaria, Germany registry of incident diabetes in children. $PM_{2.5}$ was associated with reduced age of onset of diabetes [10th percentile age of diagnosis −1.4 years (95% CI: −1.97, 0.77) per 2 SD increase] after adjustment for level of urbanization. Manifestation of T1D was not associated with PM_{10} in a larger study designed to replicate these findings (Rosenbauer et al., 2016). Ambient pollution concentrations were modelled at a lower spatial resolution in the Rosenbauer et al. (2016) study. In addition, Beyerlein et al. (2015) adjusted for individual-level SES (i.e., parental education) while Rosenbauer et al. (2016) adjusted for community-level SES (i.e., German Index of Multiple Deprivation).

Table 7-13 Epidemiologic studies of long-term exposure to $PM_{2.5}$ and age of onset for Type 1 diabetes.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
†Beyerlein et al. (2015) Cross-sectional Bavaria, Germany 2009−2013	Registry mean age = 9.3 yr N = 617	Annual avg (2001) Kriging interpolation and LUR (1 × 1 km grid), at residential address	NR	Age of onset T1D (islet antibody test)	Correlations (*r*): NR Copollutant models; NR
†Rosenbauer et al. (2016) Westphalia, Germany 2001−2006 PM_{10}: 2006−2014	Registry N = 6,807 (0−19)	REM-CALGRID model (8 × 8 km grid), at residential zip code	NR	Age of onset T1D	Correlations (*r*): NR Copollutant models; NR

Avg = average; km = kilometer; LUR = land use regression; N, n = sample size; NR = Not reported; REM-CALGRID = Regional Eulerian Model—California Grid Model; T1D = Type 1 Diabetes, yr = years.

†Studies published since the 2009 PM ISA.

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7.2.7.2 Toxicological Studies

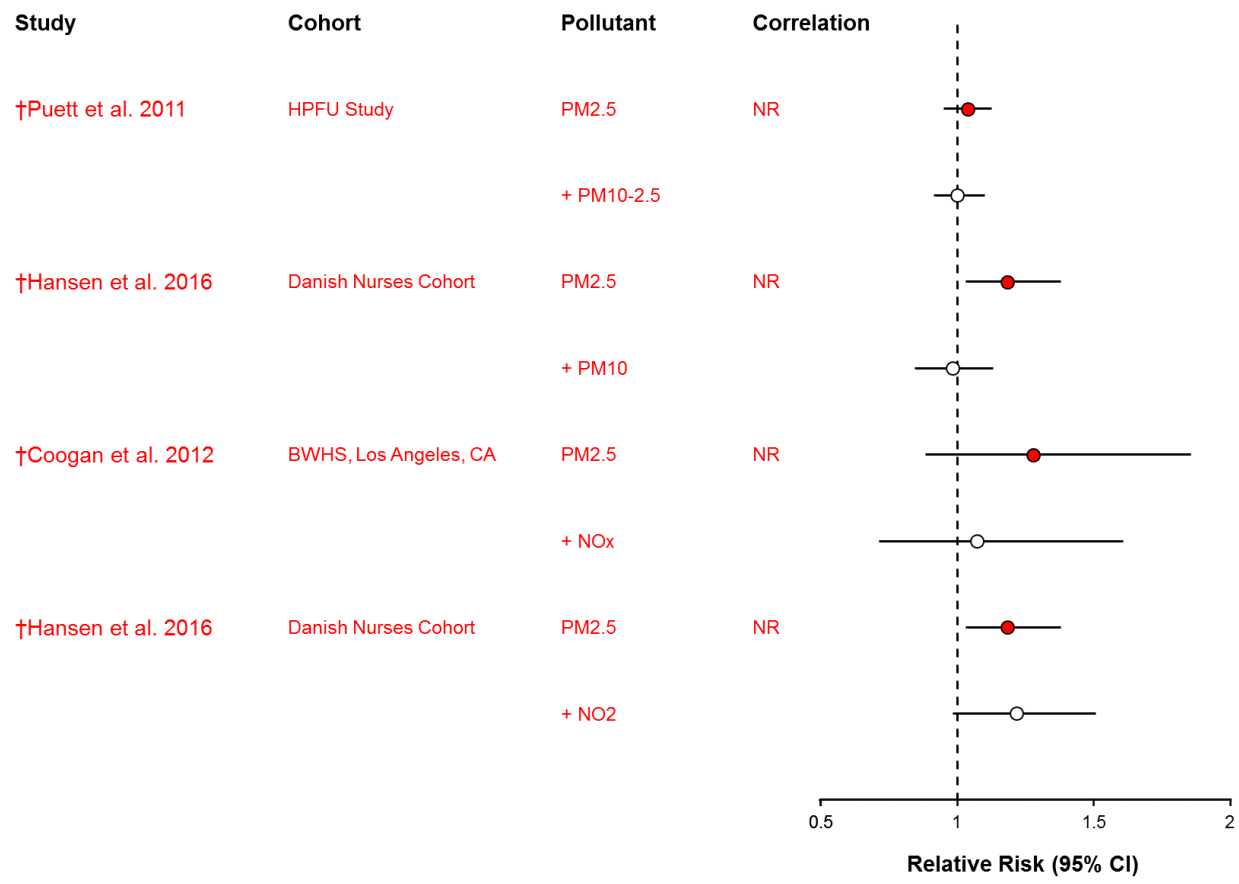
In a Type 1 diabetic rat model, $PM_{2.5}$ exposure had no effect on glucose homeostasis, insulin sensitivity, or blood lipid chemistry, however glycated hemoglobin (HbA1c, a marker of elevated glucose) was increased ($p < 0.05$) (Yan et al., 2014).

7.2.8 Associations between $PM_{2.5}$ Components and Sources and Metabolic Effects

There were no studies of the association of long-term $PM_{2.5}$ components or sources with metabolic effects reviewed in the 2009 PM ISA. The literature on this topic remains limited. Weinmayr et al. (2015) developed metrics to distinguish exposure to total $PM_{2.5}$ from $PM_{2.5}$ from traffic using data from the HNR Study in Germany. In this longitudinal analysis of T2D (mean follow-up 5.1 years), the authors reported similar hazards when standardized to an IQR increase [HR: 1.08 (95% CI: 0.89, 1.29) total $PM_{2.5}$ vs. HR: 1.1 (95% CI: 0.99, 1.23) traffic $PM_{2.5}$].

7.2.9 Copollutant Confounding

A limited number of studies are available that report results from copollutant models. Overall, estimates were not robust to adjustment for NO_2, NO_X or $PM_{10-2.5}$. Puett et al. (2011) reported that the weak association of long-term exposure to $PM_{2.5}$ with incident diabetes [HR: 1.04 (95% CI: 0.95, 1.13)] was null after adjustment for $PM_{10-2.5}$ [HR: 1.00 (95% CI: 0.91, 1.11)]. Note that the results for Coogan et al. (2012) included in the figure are for an interim analysis of women from Los Angeles, CA not the full cohort. No association between $PM_{2.5}$ and diabetes was observed in the later analysis of the entire cohort that included additional years of follow-up. The larger HR reported by Hansen et al. (2016) of 1.18 (95% CI: 1.03,1.38) among Danish nurses was null after adjustment for PM_{10} [HR: 0.98 (95% CI: 0.84, 1.13)] but persisted after adjustment for NO_2 [HR: 1.22 (95% CI: 0.98, 1.51)]. The decrease in HOMA-IR reported by Thiering et al. (2016) among children was also diminished after adjustment for NO_2 in a copollutant model (not presented in Figure 7-11). In this study, the 14.6% (95% CI −2.5, 34.6) increase in HOMA-IR was reduced 4.3% (95% CI: −14.8, 27.5) in the copollutant model.



Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Mean concentrations in $\mu g/m^3$. Hazard Ratios are standardized to a 5 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations.

BWHS = Black Women's Health Study, CI = Confidence Interval, HPFU = Health Professionals Follow-up Study, NO_2 = nitrogen dioxide, NO_X = Oxides of Nitrogen, NR = Not Reported.

†Studies published since the 2009 PM ISA.

Corresponding quantitative results are reported in Supplemental Table S7-2 (U.S. EPA, 2018).

Figure 7-11 Copollutant model results for studies of long-term exposure to $PM_{2.5}$ and incident diabetes. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration.

7.2.10 Metabolic Disease Mortality

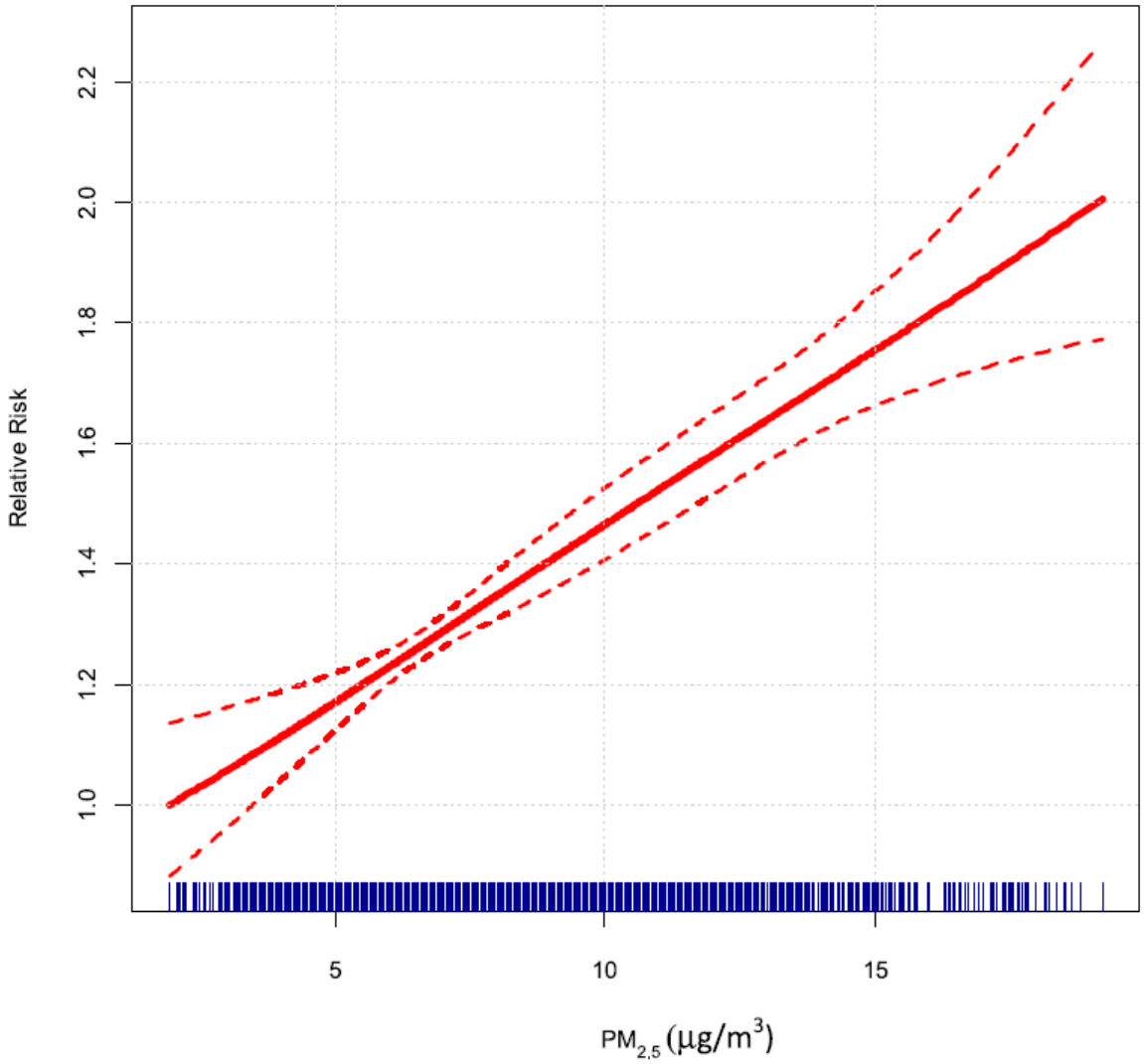
Studies that examine the association between long-term $PM_{2.5}$ exposure and cause-specific mortality outcomes, such as diabetes or other metabolic disease mortality, provide additional evidence for $PM_{2.5}$-related metabolic effects, specifically whether there is evidence of an overall continuum of effects. Evidence from studies of long-term $PM_{2.5}$ exposure and mortality are presented in detail in Section 11.2; no studies investigating metabolic disease mortality related to long-term $PM_{2.5}$ exposure were identified in

the 2009 PM ISA (U.S. EPA, 2009). Recent analyses from two well-established cohorts (the ACS and CanCHEC cohorts) have included this outcome and are summarized here to inform the effect of long-term $PM_{2.5}$ exposure on metabolic disease effects (Figure 7-12).

Pope et al. (2014), Turner et al. (2016) and Jerrett et al. (2016) all used the extended follow-up period of the ACS (1982−2004) to examine the associations between long-term $PM_{2.5}$ exposure and mortality due to diabetes. Pope et al. (2014) and Turner et al. (2016) assigned exposure using an LUR-BME model and observed positive associations with deaths due to diabetes. Jerrett et al. (2016) assigned $PM_{2.5}$ exposure using six different methods and observed positive associations with diabetes mortality for each one, though the precision of the association varied across exposure assessment methods. The most precise estimate was observed for the monitor-LUR hybrid model (HR: 1.09; 95% CI: 1.03, 1.17), and was similar in magnitude to the associations observed by Pope et al. (2014) and Turner et al. (2016).

A recent series of studies conducted in Canada linked census data with data from the Canadian Mortality Database to create the Canadian Census Health Environment Cohort (CanCHEC) and evaluated the relationship between long-term $PM_{2.5}$ exposure and metabolic disease mortality. These studies either examined deaths due to diabetes or the combination of circulatory disease and diabetes in their evaluation of metabolic disease. The authors observed positive associations between diabetes mortality and long-term $PM_{2.5}$ exposure, with similar estimates for satellite-derived estimates and ground monitor estimates (Crouse et al., 2016; Crouse et al., 2015; Brook et al., 2013a). The hazard ratios remained positive, but were less consistent in magnitude for circulatory disease and diabetes deaths combined (Weichenthal et al., 2016; Crouse et al., 2015). Pinault et al. (2016) linked a subset of participants from the CanCHEC cohort to the Canadian Community Health Survey, which allowed them to include an expanded set of individual-level covariates in their analyses. Among the nearly 300,000 participants included in the study, the authors observed positive associations with combined circulatory and diabetes mortality similar in magnitude to those observed for diabetes mortality in the larger cohort (Crouse et al., 2016; Crouse et al., 2015).

An important consideration in characterizing the association between long-term $PM_{2.5}$ exposure and mortality is whether the concentration-response relationship is linear across the full concentration range that is encountered, or if there are concentration ranges where there are departures from linearity. Brook et al. (2013a) conducted an analysis of the CanCHEC cohort to inform the shape of the C-R relationship for the association between long-term exposure to $PM_{2.5}$ and diabetes mortality, observing a linear, no-threshold relationship across the full range of concentrations measured during the study (Figure 7-12). C-R relationships for metabolic morbidity outcomes are described in Supplemental Table S7-4 (U.S. EPA, 2018).



Note: The association shown represents the results from the standard Cox survival model with a natural spline of $PM_{2.5}$ with two degrees of freedom. Tick marks on the *x*-axis represent the position of $PM_{2.5}$ concentration measured in µg/m^3. Dashed lines represent 95%confidence intervals (CIs).

Source: Permission pending, Brook et al. (2013a).

Figure 7-12 The relative risk of diabetes-related mortality in relation to long-term $PM_{2.5}$ exposure.

7.2.11 Summary and Causality Determination

There were no causal conclusions for metabolic effects in the 2009 PM ISA (U.S. EPA, 2009). The literature pertaining to the effect of long-term exposure to $PM_{2.5}$ and metabolic effects has expanded substantially since the 2009 PM ISA, with multiple epidemiologic and experimental studies currently available for review. Positive associations between long-term exposure to $PM_{2.5}$ and diabetes-related mortality were observed in well-established cohorts in the U.S. and Canada. The mortality findings are supported by epidemiologic and experimental studies reporting effects on glucose and insulin homeostasis, as well as other indicators of metabolic function (e.g., peripheral inflammation and liver function). Findings from epidemiologic studies of metabolic disease were not entirely consistent and consideration of copollutant confounding was limited; however, some well-conducted studies reported positive associations of long-term exposure to $PM_{2.5}$ with metabolic syndrome and its components (e.g., increased blood glucose, insulin resistance, and dyslipidemia) and the incidence of diabetes. The evidence characterizing the relationship between long-term exposure to $PM_{2.5}$ and metabolic effects is detailed below (Table 7-14), using the framework for causal determination described in the Preamble to the ISAs (U.S. EPA, 2015).

Several recent epidemiologic analyses of the ACS cohort found positive associations between long-term $PM_{2.5}$ exposure, which was estimated using a variety of exposure assessment methods, and mortality due to diabetes (Jerrett et al., 2016; Turner et al., 2016; Pope et al., 2014). Positive associations were also identified between long-term $PM_{2.5}$ exposure and diabetes in series of analyses from the large Canadian cohort, CanCHEC (Crouse et al., 2016; Crouse et al., 2015; Brook et al., 2013a). When the CanCHEC cohort was combined with Canadian Community Health Survey Pinault et al. (2016) observed positive associations with combined circulatory disease and diabetes mortality. Additionally, Brook et al. (2013a) observed a linear, no-threshold relationship across the full range of concentrations measured in this cohort.

Well-conducted studies from Canada and Denmark reported positive associations between long-term $PM_{2.5}$ exposure and the incidence of T2D (Hansen et al., 2016; Chen et al., 2013). A relationship between long-term $PM_{2.5}$ exposure and incident diabetes was not supported by analyses of data from well-established U.S. cohorts including MESA, NHS, HPFU, and BWHS, however (Coogan et al., 2016; Park et al., 2015; Puett et al., 2011). A longitudinal analysis of older adult male participants in the NAS (Wallwork et al., 2017), reported associations of long-term $PM_{2.5}$ with metabolic syndrome and several components including increased FBG and dyslipidemia. Another longitudinal epidemiologic study provided additional support, reporting an increase in blood glucose level in association with 28-day average $PM_{2.5}$ exposure (Lucht et al., 2018a). Several cross-sectional analyses also showed associations with measures of glucose and insulin homeostasis (Section 7.2.3.1). The limited number of epidemiologic studies that considered confounding by copollutants did not consistently report that the effect of $PM_{2.5}$ remained after adjustment for NO_2, NO_X or PM_{10}.

Experimental animal studies address some of the uncertainty in the epidemiologic evidence related to the independent effect of $PM_{2.5}$ exposure by providing evidence of direct effects on metabolic function. The animal toxicological studies provided evidence that long-term $PM_{2.5}$ exposure resulted in impaired insulin signaling, glucose tolerance, and insulin resistance (Section 7.2.3). In addition, these pathophysiological changes were often accompanied by increased inflammatory markers in the blood and peripheral inflammation in adipose, liver and heart tissues (Section 7.2.5). Most of the animal toxicology studies evaluating effects on glucose and insulin derived $PM_{2.5}$ CAPs from the same Columbus, OH air shed and were performed by the same group of investigators. Importantly, long-term $PM_{2.5}$ exposure effects were evaluated in animals fed a normal diet and animals models of metabolic syndrome-like phenotypes and provided evidence that long-term $PM_{2.5}$ exposure could lead to development or worsening of metabolic syndrome or its risk factors.

Epidemiologic studies report positive associations between long-term $PM_{2.5}$ exposure and diabetes-related mortality. Although results were not consistent across cohorts, some epidemiologic studies report positive associations with incident diabetes, metabolic syndrome, glucose and insulin homeostasis. Consideration of copollutant confounding was limited. Some support was provided by experimental studies demonstrating increased blood glucose, insulin resistance, and inflammation and visceral adiposity but the experimental evidence was not entirely consistent. **Overall, the collective evidence is suggestive of, but is not sufficient to infer, a causal relationship between long-term $PM_{2.5}$ exposure and metabolic effects.**

Table 7-14 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between long-term $PM_{2.5}$ exposure and metabolic effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Mortality			
Consistent findings in epidemiologic studies of diabetes-related mortality at relevant concentrations.	Epidemiologic studies in well-established U.S. and Canadian cohorts (ACS and CanCHEC) reported positive associations with deaths due to diabetes.	Section 7.2.10	Mean concentrations across studies: 6.3−12.6 μg/m^3

Table 7-14 (Continued): Summary of evidence indicating that the evidence is suggestive, but not sufficient to infer a causal relationship between long-term $PM_{2.5}$ exposure and metabolic effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Type 2 Diabetes			
Inconsistent findings from multiple epidemiologic studies of incidence of T2D; however, some high quality epidemiologic studies support a positive association.	Longitudinal studies conducted in Canada and in Denmark report positive associations. Prospective cohort studies (MESA, NHS and HPFU, BWHS) conducted in the U.S. reported null associations with T2D or associations with wide Cis.	Hansen et al. (2016) Chen et al. (2013)	Means 10.6−18.1 μg/m^3 Mean concentrations across studies 13.9−18.3 μg/m^3
Consistent associations in epidemiologic studies with metabolic syndrome and its components	Longitudinal analyses metabolic syndrome and its components. Support from cross-sectional analysis reporting positive associations with measure of glucose and insulin homeostasis.	Wallwork et al. (2017) Lucht et al. (2018a) Section 7.2.2 Section 7.2.3	Mean 10.5 Mean concentrations of cross-sectional studies 13.5−72.6 μg/m^3
Limited evidence from copollutant models in epidemiologic studies	Most studies do not consider potential confounding by copollutants in the analysis; the small number of studies that present copollutant models are inconsistent.	Section 7.2.9	
Uncertainty regarding exposure measurement error	Evidence base too limited to evaluate consistence within and across exposure assessment methods.		
Toxicological studies provide coherence for associations with metabolic syndrome and its components observed in the epidemiologic studies	Strong evidence for impaired insulin signaling, insulin resistance, increased blood glucose, systemic inflammation, and peripheral inflammation. Toxicological evidence demonstrating effects on insulin resistance is limited because multiple studies are from same air shed (Columbus, OH air shed). Finding of increased BP from a limited number of toxicological studies provide coherence for effects on metabolism.	Section 7.2.3.2,Section 7.2.5	513.3−139.5 μg/m^3 $PM_{2.5}$ CAPs exposure for 4−16 weeks

Table 7-14 (Continued): Summary of evidence indicating that the evidence is suggestive, but not sufficient to infer a causal relationship between long-term $PM_{2.5}$ exposure and metabolic effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Gestational Diabetes			
Findings from a limited number of epidemiologic studies were not consistent; support from other lines of evidence is lacking.	Although findings not entirely consistent, some studies reported associations with gestational diabetes or IGT with $PM_{2.5}$ exposures in the 2nd trimester.	Section 9.2.1	Mean concentrations across studies 9.7−11.9 µg/m^3
Other Indicators of Metabolic Function			
Biological plausibility derived from multiple lines of evidence	Multiple high quality epidemiologic studies finding positive associations between long-term $PM_{2.5}$ exposure and metabolic disease mortality, cardiovascular disease, diabetes, insulin resistance. Toxicological evidence provide coherence for potential pathways connecting $PM_{2.5}$ exposure to metabolic syndrome components, diabetes, and cardiovascular disease.	Section 7.2.1 Figure 7-2 Section 7.2.3, Section 7.2.4 and Section 7.2.10 Chapter 6	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

†Studies published since the 2009 PM ISA.

7.3 Short-term $PM_{10-2.5}$ Exposure and Metabolic Effects

There were no epidemiologic or experimental studies of short-term exposure to $PM_{10-2.5}$ and metabolic effects such as diabetes or glucose and insulin homeostasis reviewed in the 2009 PM ISA nor have recent studies become available. **The evidence is inadequate to infer the presence or absence of a causal relationship between short-term $PM_{10-2.5}$ exposure and metabolic effects.**

7.4 Long-Term $PM_{10-2.5}$ Exposure and Metabolic Effects

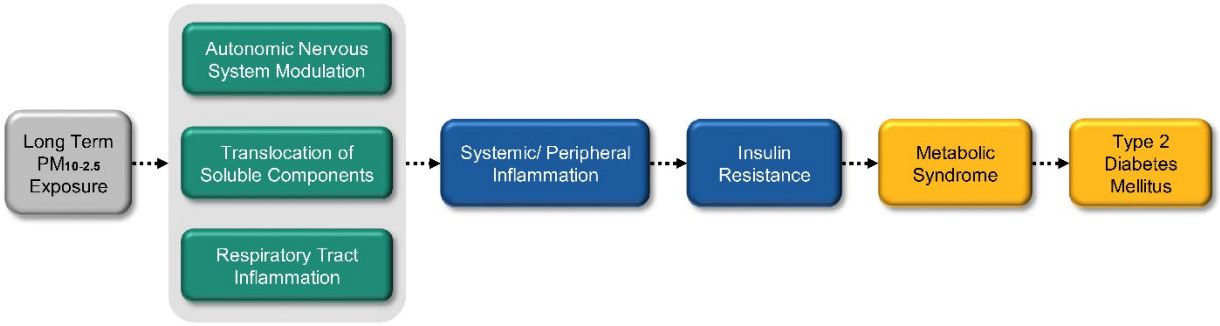
There were no studies of $PM_{10-2.5}$ and metabolic effects reviewed in the 2009 PM ISA. The discussion of the limited number of recent studies long-term $PM_{2.5}$ exposure and metabolic effects opens with a discussion of biological plausibility (Section 8.1.1) that provides background for the subsequent section in which the evidence related to T2D is presented. The collective body of evidence is integrated across and within scientific disciplines[70], and the rationale for the causality determination is outlined in Section 7.4.3.

7.4.1 Biological Plausibility

This section describes biological pathways that potentially underlie metabolic effects resulting from long-term exposure to $PM_{10-2.5}$. Figure 7-13 graphically depicts the potential pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" exposure to $PM_{10-2.5}$ may lead to metabolic health effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 7.4.

Soluble components of $PM_{10-2.5}$ may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments. The extent to which translocation into the systemic circulation occurs is currently uncertain (Chapter 4). Furthermore, the PM administered dose depends on deposition, which is a function of particle size, intake, and physical chemistry as well as modifying factors such as lifestages and species. It is possible that deposition of $PM_{10-2.5}$ may initiate pathways that include ANS modulation, translocation of soluble components, and respiratory tract inflammation that converge upon inflammation leading to insulin resistance. Therefore, implicit relationships between long-term $PM_{10-2.5}$ exposure and observed health effects that include diabetes can be drawn even though the evidence is limited. For example, Wolf et al. (2016) reported positive increases in CRP (a nonspecific marker of inflammation produced by the liver) supporting a pathway toward systemic and peripheral inflammation. Wolf et al. (2016) also reported a positive association with HOMA-IR, a measure of insulin resistance. These events and endpoints are on the pathway leading to T2D, an outcome that was positively associated with long-term exposure to $PM_{10-2.5}$ by Puett et al. (2011).

[70] As detailed in the Preface, risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{10-2.5}$ concentrations unless otherwise noted.



The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 7-13 Potential biological pathways for metabolic effects following long-term $PM_{10-2.5}$ exposure.

As described here, there are proposed pathways by which long-term exposure to $PM_{10-2.5}$ could lead to metabolic health effects. One pathway involves ANS modulation, translocation of soluble components, and respiratory tract inflammation that may lead to systemic and peripheral inflammation that is linked to insulin resistance and metabolic syndrome comorbidities. Together, these proposed pathways provide limited biological plausibility for epidemiologic results of metabolic health effects, highlight areas where further scientific understanding is needed, and will be used to support a causal determination, which is discussed later in the chapter (Section 7.4.3).

7.4.2 Type 2 Diabetes

Puett et al. (2011) observed a small increased hazard in association with long-term exposure to $PM_{10-2.5}$ [HR: 1.05 (95% CI: 0.98,1.13)] that remained after adjustment for $PM_{2.5}$ in the NHS. Cross-sectional studies provided supporting evidence that long-term $PM_{10-2.5}$ exposure is associated with IGM, diabetes, HOMA-IR, leptin and CRP (Wolf et al., 2016; Teichert et al., 2013). Overall, the number of epidemiologic studies (Table 7-14) is limited but findings are compatible with an effect of $PM_{10-2.5}$.

Table 7-15 Summary of studies examining the relationships for long-term exposure to $PM_{10-2.5}$ and diabetes.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Puett et al. (2011) Longitudinal cohort U.S. $PM_{10-2.5}$: 12 mo prior to diagnosis Outcome NHS: 1976−2009 Outcome HPFS: 1986−2009	NHS (N = 74,412) and HPFS (N = 15,048) N = 3,784 cases	Annual avg at geocoded residential address, spatiotemporal models C-V $PM_{2.5}$, R^2 = 0.77 (post-1999) and R^2 = 0.69 (pre-1999) C-V PM10 R^2 = 0.62 (Difference method)	Mean NHS: 18.3 (SD: 3.1) Mean HPFS: 17.5 (SD 2.7) IQR: 4	Incident diabetes (self-reported doctor diagnosed and confirmation by medical record review)	Correlations (*r*): NR Copollutant models Positive with $PM_{2.5}$
†Teichert et al. (2013) Cross-sectional Ruhr area, Germany PM_{10} and $PM_{2.5}$: 2008−2009 Outcome: 2008−2009	SALIA n = 363 (random sample of women 54−55)	LUR, back extrapolation to baseline examination (1984) to assign exposure at residence (difference method)	Mean 18.0 (1.4) Back extrapolated concentration: Mean 34.0 (3.2)	IGM = ≥100 mg/dl or previous diagnosis of diabetes	Correlations (*r*): NR Copollutant models: NR
†Wolf et al. (2016) Augsburg and two adjacent rural counties, Germany Cross-sectional $PM_{10-2.5}$: 2008−2009	KORA N = 2,944 Mean age: 56.2 yr	Annual avg, LUR, at residence (ESCAPE protocol)	Mean (SD) 6.2−6.3 (1.1)	HOMA-IR, Glucose, Insulin, HbA1c, Leptin, hs-CRP	Correlations (*r*): $PM_{2.5}$ *r* = 0.32, NO_2 *r* = 0.79 Copollutant models: NR

Avg = average, ESCAPE = European Study of Cohorts for Air Pollution Exposure, HbA1c = glycated hemoglobin, HOMA-IR = homeostatic model assessment of insulin resistance, HPFU = Health Professionals Follow-up Study, IGM = Impaired Glucose Metabolism, KORA = Cooperative health research in the Region of Augsburg, LUR = land use regression, N, n = number of subjects, NHS = Nurses' Health Study; SALIA = Study on the influence of air pollution on lung function, inflammation and aging, yr = years.

†Studies published since the 2009 Integrated PM ISA.

7.4.3 Summary and Causal Determination

There were no studies of $PM_{10-2.5}$ and metabolic effects in the 2009 PM ISA. A high quality epidemiologic study reporting an association between long-term $PM_{10-2.5}$ exposure and incident diabetes is now available (Puett et al., 2011). In addition, effects on glucose (Teichert et al., 2013) or insulin (Wolf et al., 2016) were observed in cross-sectional studies of glucose and insulin homeostasis conducted in European cohorts. Limited biological plausibility is derived from the potential for deposition of $PM_{10-2.5}$ to modulate the ANS, the immune system or disrupt glucose, lipid, and insulin homeostasis. The evidence relevant to the causal determination for long-term exposures to $PM_{10-2.5}$ is evaluated using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015). The key evidence, as it relates to the causal framework, is summarized in Table 7-15. **Overall, the evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10-2.5}$ exposure and metabolic effects.**

Table 7-16 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between long-term $PM_{10-2.5}$ exposure and metabolic effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Evidence at least one high quality epidemiologic study but studies limited in number, overall.	Positive association with incident T2D reported in NHS; Effects on glucose and insulin homeostasis observed in cross-sectional analyses of European cohorts.	Puett et al. (2011) Teichert et al. (2013) Wolf et al. (2016)	Mean concentrations across studies 6.2−34.0 μg/m^3
Uncertainty regarding epidemiologic evidence from copollutant models to support and independent $PM_{10-2.5}$ association	$PM_{10-2.5}$ association persisted after adjustment for $PM_{2.5}$ but evidence lacking, overall.	Puett et al. (2011)	
Uncertainty regarding exposure measurement error	$PM_{10-2.5}$ concentrations estimated using difference of monthly modelled concentrations of PM_{10} and $PM_{2.5}$ which has noted limitations.	Section 2.4.2	
	Potentially uncharacterized spatial variation adds additional uncertainty.	Section 2.5 and Section 3.3.1.1	
Limited biological plausibility	Some evidence that $PM_{10-2.5}$ may modulate the ANS following deposition, the immune system or disrupt glucose, lipid, and insulin homeostasis.	Section 7.4.1	

$PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm and greater than a nominal diameter of 2.5 μm.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the $PM_{10-2.5}$ concentrations with which the evidence is substantiated.

7.5 Short-Term UFP Exposure and Metabolic Effects

There are no experimental studies examining the effects short-term UFP exposure on metabolic function. A recent longitudinal analysis of the data from the HNR study found an association of 28-day

average accumulation mode UFP (NC) exposure with increased blood glucose [0.64 mg/dL (95% CI: 0.07, 1.21) per IQR increase] and increased HbA1c [0.03% (0.01, 0.05) per IQR increase] (Lucht et al., 2018a). Uncharacterized temporal and spatial variability in the exposure concentration is an uncertainty for this study because a 28-day average exposure was estimated for 1 km^2 grid cells, not the participants' residence (Section 3.4.5.1.1). **Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between short-term UFP exposure and metabolic effects.**

7.6 Long-Term UFP Exposure and Metabolic Effects

There were no studies of the effect of long-term UFP exposure and metabolic effects reviewed in the 2009 PM ISA. In a recent longitudinal epidemiologic study, Lucht et al. (2018a) reported an increase in FBG (0.67 mg/dL 0.10 1.24) and HbA1c [0.09% (0.07, 0.11) per IQR increase] in association with 91-day average exposure to accumulation mode UFP (NC). Uncharacterized spatial and temporal variability is an uncertainty in this study because UFP exposure was assigned to a 1 km^2 grid cell, not at the level of the participants' residence (Section 3.4.5.2). In addition, a toxicological study (Li et al., 2013) evaluated the effects of long-term UFP in mice (Table 7-16). This study investigated the effects of long-term UFP exposure in an *Ldlr*$^{-/-}$ mouse model fed a high fat diet in the presence or absence of an apolipoprotein A-I mimetic peptide (D-4F). This genetic mouse model has a mutation in the low-density lipoprotein receptor and are prone to very high blood cholesterol levels when fed a high fat diet. While the investigators identified UFP effects such as increased triglyceride, decreased HDL, reduced HDL antioxidant index, increased oxidized lipid metabolites (HETEs and HODEs), increased serum amyloid A (SAA) and TNFα, and increased area in atherosclerotic plaque lesions (all $p < 0.05$) that were improved by D-4F (a mimetic peptide of apolipoprotein A-I made of D-amino acids) administration, the authors did not include wild-type controls. Furthermore, there are inherent differences in cholesterol metabolism between mouse and human that render the mouse somewhat resistant to the development of atherosclerotic plaques. Specifically, mice lack cholesterol ester transfer protein that shuttles cholesterol from HDL to LDL for reverse cholesterol transport; therefore, mice carry most of their cholesterol on HDL particles rather than, like human, on LDL particles (Getz and Reardon, 2012). The available studies continue to be limited. **Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between long-term UFP exposure and metabolic effects.**

Table 7-17 Study specific details from animal toxicology studies of metabolic homeostasis.

Study	Study Population	Exposure Details	Endpoints Examined
Li et al. (2013)	*Ldlr*$^{-/-}$ mouse on C57Bl/6 background, male, 90 days old	Whole body inhalation of UFP collected in urban regions of Los Angeles, CA. Animals were exposed to 360 μg/m^3 for 10 weeks ± poA1 mimetic peptide	Plasma HDL, HDL oxidation index, paraoxonase activity. Plasma, 9-HODE and 12-HETE, SAA and TNF-α. In the aorta, Sudan IV staining for fatty streaks, both in en face and aortic leaflet preparations

7.7 Reference

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CHAPTER 8 NERVOUS SYSTEM EFFECTS

Summary of Causality Determinations for Short- and Long-Term Particulate Matter (PM) Exposure and Nervous System Effects

This chapter characterizes the scientific evidence that supports causality determinations for short- and long-term PM exposure and nervous system effects. The types of studies evaluated within this chapter are consistent with the overall scope of the ISA as detailed in the Preface (see Section P.3.1). In assessing the overall evidence, strengths and limitations of individual studies were evaluated based on scientific considerations detailed in the Appendix. More details on the causal framework used to reach these conclusions are included in the Preamble to the ISA (U.S. EPA, 2015).

Size Fraction	Causality Determination
Short-term Exposure	
$PM_{2.5}$	Suggestive of, but not sufficient to infer
$PM_{10-2.5}$	Inadequate
UFP	Suggestive of, but not sufficient to infer
Long-term Exposure	
$PM_{2.5}$	Likely to be causal
$PM_{10-2.5}$	Suggestive of, but not sufficient to infer
UFP	Likely to be causal

8.1 Short-term $PM_{2.5}$ Exposure and Nervous System Effects

The evidence in the 2009 ISA for PM was characterized as "inadequate" to determine if a causal relationship between short-term $PM_{2.5}$ exposure and nervous system effects exists (U.S. EPA, 2009). A small number of experimental animal studies relevant to the assessment were available for review. Exposure to $PM_{2.5}$ CAPs resulted in pro-inflammatory responses in the brain (Campbell et al., 2005) and modulation of norepinephrine and corticosterone levels, which are indicative of sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) stress axis activation (Sirivelu et al., 2006). Studies found that exposure to $PM_{2.5}$ CAPs could affect the autonomic nervous system (ANS) by activating sensory nerves in the respiratory tract, leading to cardiac oxidative stress and changes in cardiac function (Ghelfi et al., 2008; Rhoden et al., 2005). In addition, multiple studies reported that short-term exposure to $PM_{2.5}$ is associated with changes in heart rate variability (HRV), which reflect an imbalance between the sympathetic and parasympathetic arms of the ANS (Section 6.1.1). Findings from

recent experimental studies are generally consistent with previous studies, adding to the evidence that short-term exposure to $PM_{2.5}$ can lead to brain inflammation and activation of the SNS. The small number of epidemiologic studies published since the 2009 PM ISA do not consistently report positive associations between short-term exposure to $PM_{2.5}$ and hospitalizations for nervous system diseases, depression, or reduced cognitive function.

The discussion of short-term $PM_{2.5}$ exposure and nervous system effects opens with a discussion of biological plausibility (Section 8.1.1) that provides background for the subsequent sections in which groups of related endpoints are presented in the context of relevant disease pathways. These outcome groupings are activation of the SNS and HPA stress Axis (Section 8.1.2), brain inflammation and oxidative stress (Section 8.1.3), and diseases of the nervous system and depression (Section 8.1.4). Evidence pertaining to $PM_{2.5}$ components is summarized in Section 8.1.5. Finally, the collective body of evidence is integrated[71] across and within scientific disciplines, and the rationale for the causality determination is outlined in Section 8.1.6.

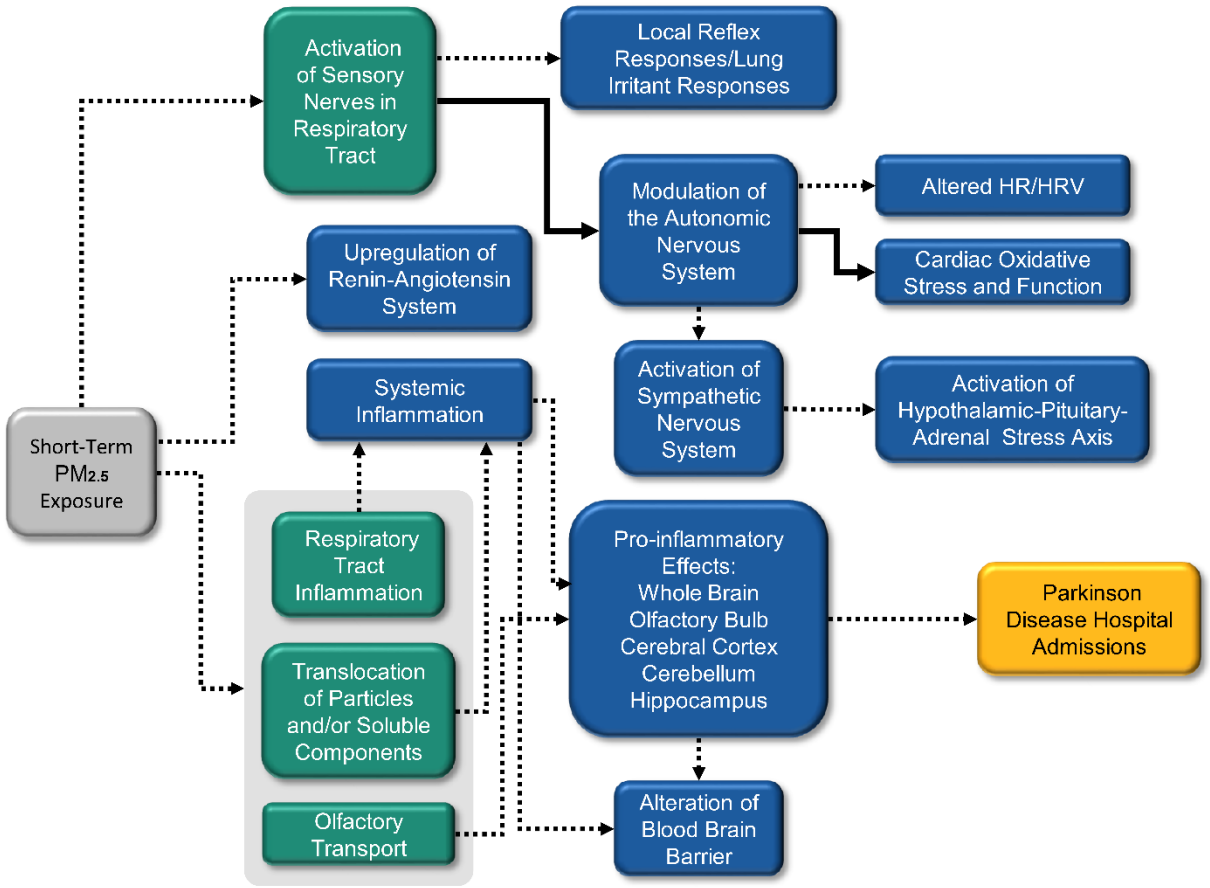
8.1.1 Biological Plausibility

This section describes biological pathways that potentially underlie the development of nervous system effects resulting from short-term exposure to $PM_{2.5}$. Figure 8-1 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" short-term exposure to $PM_{2.5}$ may lead to nervous system effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 8.1.

Once $PM_{2.5}$ deposits in the respiratory tract, it may be retained, cleared, or solubilized (see Chapter 4). $PM_{2.5}$ and its soluble components may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate reactive oxygen species (ROS) and this capacity is termed "oxidative potential". Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see CHAPTER 4). Immune system responses due to the presence of particles in the interstitial space may contribute to health effects. Inflammatory mediators may diffuse from the respiratory tract into the systemic circulation and lead to inflammation in extrapulmonary compartments (Section 6.1.1). Soluble components of $PM_{2.5,}$ and poorly soluble particles

[71] As detailed in the Preface, risk estimates are for a 10 $\mu g/m^3$ increase in 24-hour avg $PM_{2.5}$ concentrations unless otherwise noted.

that are part of the $PM_{2.5}$ fraction and smaller than approximately 200 nm, may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments. A fraction of $PM_{2.5}$ may deposit on the olfactory epithelium. Soluble components of $PM_{2.5,}$ and poorly soluble particles that are part of the $PM_{2.5}$ fraction and smaller than approximately 200 nm, may also be transported via the olfactory nerve to the olfactory bulb of the brain. The extent to which translocation into the systemic circulation or transport to the olfactory bulb occurs is currently uncertain. For further discussion of translocation and olfactory transport, see Chapter 4.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Solid arrows denote direct evidence of the relationship as provided, for example, by an inhibitor of the pathway or a genetic knock-out model used in an experimental study. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 8-1 Potential biological pathways for nervous system effects following short-term $PM_{2.5}$ exposure.

Evidence that short-term exposure to $PM_{2.5}$ may affect the nervous system generally informs two different pathways (Figure 8-1). The first pathway begins with the activation of sensory nerves in the respiratory tract that can trigger local reflex responses and transmit signals to regions of the central nervous system that regulate autonomic outflow. Altered autonomic tone may result in downstream systemic effects. The second pathway begins with pulmonary inflammation and may lead to systemic inflammation and to inflammation in the brain. Inflammation may lead to a worsening of neurodegenerative disease. Evidence for these pathways is described below.

Activation of Sensory Nerves and Modulation of the Autonomic Nervous System (ANS)

With regard to the first pathway, activation of sensory nerves in the respiratory tract leads to modulation of the sympathetic and parasympathetic branches of the ANS. The ANS influences all the internal organs, including the heart. Lung irritant responses, discussed in Chapter 5 (Section 5.1.1, Section 5.1.7, and Section 5.1.8), are local reflex responses triggered by $PM_{2.5}$ exposure-induced activation of sensory nerves. Altered autonomic outflow can manifest as changes in heart rate and heart rate variability, as discussed in Section 6.1.1. Furthermore, an animal toxicological study demonstrated that specific receptors on the sensory nerves, the transient receptor potential (TRP) cation channels, were involved in mediating autonomic responses in the heart (Ghelfi et al., 2008). Treatment with a receptor antagonist blocked cardiac oxidative stress and changes in electrophysiologic parameters resulting from short-term exposure to $PM_{2.5}$. Inhibitors of the parasympathetic nervous system and SNS also blocked cardiac oxidative stress in this model (Rhoden et al., 2005). The solid lines depicted in Figure 8-1, which connect activation of sensory nerves to modulation of the ANS and to cardiac oxidative stress/function, indicate that activation of TRP receptors on sensory nerves in the respiratory tract mediated changes in the heart via the ANS.

The SNS may be especially impacted by $PM_{2.5}$ exposure. Animal toxicological studies demonstrated that short-term $PM_{2.5}$ exposure results in increased norepinephrine in specific hypothalamic regions (Balasubramanian et al., 2013; Sirivelu et al., 2006) and in peripheral tissues (Chiarella et al., 2014). Increases in norepinephrine, both in the brain and peripheral organs, are hallmarks of increased SNS activity. Further, a neuroendocrine response, activation of the HPA stress axis, may be initiated in the hypothalamus via norepinephrine and corticotropin releasing hormone (CRH), resulting in increased levels of circulating glucocorticoids. Sirivelu et al. (2006) and Balasubramanian et al. (2013) found increased CRH levels in the hypothalamus, as well as increased serum glucocorticoids. Thus, short-term exposure to $PM_{2.5}$ may lead to activation of the SNS and to activation of the HPA stress axis.

Furthermore, studies suggest connections between modulation of the ANS resulting from short-term $PM_{2.5}$ exposure and other effects. A study in mice found that exposure to $PM_{2.5}$ increased SNS activity, as indicated by increased norepinephrine levels in the lung and in brown adipose tissue (Chiarella et al., 2014). Inhalation of $PM_{2.5}$ increased BALF cytokine levels, an effect which was enhanced by β2

adrenergic receptor agonists, which mimic the actions of norepinephrine. Using knock-out mice lacking the β2 adrenergic receptor specifically in alveolar macrophage, it was demonstrated that inhalation of $PM_{2.5}$ enhanced cytokine release from alveolar macrophages. This involvement of the SNS in inflammatory responses resulting from $PM_{2.5}$ exposure is depicted by the solid line that connects ANS responses and respiratory tract inflammation in Figure 5-1. This is likely to represent a positive feed-back mechanism by which the ANS may enhance inflammation. Another study found upregulation of the renin-angiotensin (RAS) system in the lung and heart (Aztatzi-Aguilar et al., 2015), as depicted in Figure 5-1. The SNS and RAS are known to interact in a positive feedback fashion (Section 8.2.1), with important ramifications for the cardiovascular system. However, it is not known whether SNS activation or some other mechanism mediated the changes in the RAS observed in the respiratory tract (Aztatzi-Aguilar et al., 2015). Ghelfi et al. (2010) found that short-term exposure to $PM_{2.5}$ increased levels of circulating angiotensin II, which is an important component of the RAS.

Inflammation

With regard to the second pathway, deposition of $PM_{2.5}$ in the respiratory tract may lead to pulmonary inflammation (see Section 5.1.1) and to systemic inflammation (see Section 6.1.1). Brain inflammation may be due to peripheral immune activation (Fonken et al., 2011) or to systemic circulation of $PM_{2.5}$, alone or engulfed by macrophages, that results in particle uptake in the brain (Ljubimova et al., 2013). Inflammation in the brain may alternatively occur following olfactory transport of poorly soluble particles or their soluble components or to a neuroendocrine stress response resulting from activation of the HPA stress axis (Kodavanti, 2016).

Several animal toxicological studies demonstrated pro-inflammatory effects following short-term $PM_{2.5}$ exposure (Campbell et al., 2005), (Bos et al., 2012), (Tyler et al., 2016). Inflammation was observed in the olfactory bulb, cerebral cortex, cerebellum, and hippocampus. Two of these studies demonstrated brain inflammation in the absence of pulmonary or systemic inflammation (Tyler et al., 2016; Bos et al., 2012), pointing to a direct effect of $PM_{2.5}$ on the brain. Evidence for perturbation of the blood brain barrier is provided by a controlled human exposure study (Liu et al., 2017). Circulating inflammatory mediators and soluble components of $PM_{2.5,}$ as well as brain inflammation, may play a role in altering the blood brain barrier. Inflammation may lead to a worsening of neurodegenerative disease and provide support for epidemiologic evidence of hospitalization for Parkinson disease (Zanobetti et al., 2014).

Summary of Biological Plausibility

As described here, there are two proposed pathways by which short-term exposure to $PM_{2.5}$ may lead to nervous system effects. Experimental studies in animals and humans contribute all the evidence of upstream events. The first pathway begins with activation of sensory nerves in the respiratory tract and may potentially lead to modulation of the ANS resulting in increased activity of the SNS and stimulation

of the HPA stress axis. Upregulation of the RAS may also contribute to SNS activation. Thus, the ANS may mediate systemic responses due to exposure to $PM_{2.5}$. The second proposed pathway begins with pulmonary/systemic inflammation or olfactory transport of $PM_{2.5}$ leading to brain inflammation. This pathway provides biological plausibility for epidemiologic results of increased hospital admissions for Parkinson disease. These pathways will be used to inform a causality determination, which is discussed later in the chapter (Section 8.1.6).

8.1.2 Activation of the Sympathetic Nervous System and the Hypothalamic-Pituitary-Adrenal (HPA)Stress Axis

As discussed in the biological plausibility section above, sensory nerves in the respiratory tract can transmit signals to regions of the central nervous system that regulate autonomic outflow. The ANS regulates many different functions in the body (e.g., heart rate). Further, a neuroendocrine response, activation of the HPA stress axis, may be initiated in the hypothalamus via norepinephrine and CRH, resulting in increased levels of circulating glucocorticoids.

8.1.2.1 Controlled Human Exposure Study

A controlled human exposure study examined the effects of a 130 minute exposure to $PM_{2.5}$ CAPs in Toronto on urinary and blood biomarkers associated with neural effects (Liu et al., 2017). No association was observed with SNS or HPA stress axis-related biomarkers (Table 8-1).

Table 8-1 Study-specific details from a controlled human exposure study of short-term $PM_{2.5}$ exposure and activation of the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) stress axis.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Liu et al. (2017) Species: Human Health status: Healthy nonsmokers Sex: 29 females, 26 males Age: 18−60 yr Study design: Single-blind randomized cross-over trial	CAPs from Toronto, ON Particle sizes: 0.15−2.5 µm Control: HEPA filtered ambient air or HEPA-filtered medical air (ultrafine study)	Route: Face mask inhalation Dose/concentration: 238.4 ± 62.0 µg/m^3 Duration of exposure: 130 min Time to analysis: 1 and 21 h	Urinary and blood markers of neural effects

CAPs = concentrated ambient particles, h=hours, HEPA = high efficiency particulate air, yr=years.

8.1.2.2 Animal Toxicological Studies

An animal toxicological study included in the 2009 ISA PM (U.S. EPA, 2009) found that $PM_{2.5}$ CAPs exposure resulted in modulation of norepinephrine in the paraventricular nucleus of the hypothalamus and in the olfactory bulb of nonallergic rats, while rats that were sensitized and challenged with ovalbumin exhibited increases in dopamine in the medial preoptic area (Sirivelu et al., 2006). Increased norepinephrine levels in the hypothalamus indicate activation of the SNS and this study also found an increase in serum corticosterone in non-allergic $PM_{2.5}$ CAPs-exposed rats, suggesting an activation of the HPA stress axis subsequent to changes in these neurotransmitters. Recent studies provide additional support demonstrating an effect of $PM_{2.5}$ on the SNS and HPA stress axis (Table 8-2).

Balasubramanian et al. (2013) found that inhalation of $PM_{2.5}$ CAPs altered levels of neurotransmitters and CRH in specific brain regions of lean and obese rats. Lean Brown Norway rats exposed to $PM_{2.5}$ CAPs in Grand Rapids, MI had increased levels of norepinephrine in the paraventricular nucleus of the hypothalamus 1 day ($p < 0.05$), but not 3 days, after exposure. A similar pattern was observed for 5-hydroxy-indole acetic acid ($p < 0.05$), the main metabolite of serotonin, while dopamine levels were unchanged. An increase in CRH in the median eminence of the hypothalamus was found after 1 day ($p < 0.05$), but not 3 days, of $PM_{2.5}$ CAPs exposure. Corpulent JCR/LA rats exposed for 4 days to CAPs in Detroit, MI had increased norepinephrine and 5-hydroxy-indole acetic acid in the paraventricular nucleus ($p < 0.05$), while the amount of CRH in the median eminence was unchanged. Increased norepinephrine levels in the paraventricular nucleus of the hypothalamus indicate activation of the SNS, while increased CRH levels in the median eminence of the hypothalamus indicate activation of the HPA stress axis. Linkage between the SNS and the HPA stress axis occurs when norepinephrine in the paraventricular nucleus stimulates CRH neurons resulting in the release of CRH from the median eminence. Subsequently, circulating CRH stimulates adrenocorticotropin secretion from the pituitary and adrenocorticotropin acts on the adrenal gland resulting in the secretion of glucocorticoids such as corticosterone. Thus, activation of the SNS may lead to increased glucocorticoid levels. In the current study, an increase in norepinephrine was accompanied by an increase in CRH only in the lean rats exposed for 1 day to $PM_{2.5}$ CAPs.

Findings of Balasubramanian et al. (2013) build on the results of (Sirivelu et al., 2006) that found increases in norepinephrine levels in the paraventricular nucleus of the hypothalamus and in serum corticosterone levels following a 1-day exposure to CAPs. Together, these studies indicate that $PM_{2.5}$ exposure may increase the activity of the SNS and the HPA stress axis via effects on the hypothalamus. In Balasubramanian et al. (2013), increases in neurotransmitter levels were observed in obese animals, but they were not increased in the lean animals, following a multi-day exposure to $PM_{2.5}$. This raises the possibility that an adaptive response dampened the SNS and HPA stress axis in the lean, but not in the obese, animals.

Evidence for SNS activation following short-term exposure to $PM_{2.5}$ is also provided by (Chiarella et al., 2014). In this study, C57BL/6 mice were exposed to $PM_{2.5}$ CAPs in Chicago, IL for

several days. Norepinephrine levels in both lung and brown adipose tissue were increased above controls ($p < 0.05$), indicating activation of the SNS. Norepinephrine was found to enhance the amount of IL−6 in BALF, a pro-inflammatory effect, in the lung (see Section 5.1.7).

Table 8-2 Study-specific details from animal toxicological studies of short-term $PM_{2.5}$ exposure and activation of the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) stress axis.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Balasubramanian et al. (2013) Species: rat Strain: Brown Norway (lean) JCR/LA (corpulent) Sex: male Age/Weight: JCR/LA-4 and 8 mo	CAPs from urban Grand Rapids, MI or urban Detroit, MI Particle Sizes: $PM_{2.5}$ HEPA-filtered clean air	Route: Whole body inhalation Dose/Concentration: 1 day: mean 519 µg/m^3 $PM_{2.5}$ CAPs Grand Rapids 3 day: mean 595 µg/m^3 $PM_{2.5}$ CAPs 4 day: mean 291 µg/m^3 $PM_{2.5}$ CAPs Grand Rapids Duration of exposure: 1, 3, or 4 days Time to analysis: 24 h after the last exposure	Brain tissue—neurotransmitter and corticotrophin releasing hormone levels in the hypothalamus
Chiarella et al. (2014) Species: Mouse Sex: Male Strain: C57BL/6 WT and Adrb2 knockouts Age/Weight: 8−12 week	CAPs from Chicago, IL Particle size: $PM_{2.5}$ Control: filtered ambient air	Route: Whole body inhalation Dose/Concentration: 109.1 ± 6.1 µg/m³ Duration: 8 h/day for 3 days	BALF and lung tissue—IL−6, norepinephrine Brown adipose tissue • norepinephrine Liver tissue • prothrombin and TF mRNA Thrombotic potential

Adrb2 = adrenergic beta 2, BALF = bronchoalveolar lavage fluid, CAPs = concentrated ambient particles, h=hour(s), HEPA=high efficiency particulate air, IL−6 = interleukin−6; TF = tissue factor; WT = wild type.

8.1.3 Brain Inflammation and Oxidative Stress

Chronic brain inflammation is thought to underlie conditions such as neurodegenerative disease. Although repeated exposure may lead to similar downstream health consequences, the effect of acute inflammation is less clear.

8.1.3.1 Controlled Human Exposure Study

A controlled human exposure study examined the effects of a 130 minute exposure to $PM_{2.5}$ CAPs in Toronto, ON on urinary and blood biomarkers associated with neural effects (Liu et al., 2017). An association was observed between exposure to $PM_{2.5}$ CAPs and blood ubiquitin C-terminal hydrolase L1, a biomarker related to blood brain barrier integrity, measured 21 hours post-exposure ($p < 0.1$). Impaired blood brain barrier integrity is associated with brain inflammation (Table 8-3).

Table 8-3 Study-specific details from a controlled human exposure study of short-term $PM_{2.5}$ exposure and brain inflammation and oxidative stress.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Liu et al. (2017) Species: Human Health status: Healthy nonsmokers Sex: 29 females, 26 males Age: 18−60 yr Study design: Single-blind randomized cross-over trial	CAPs from Toronto, ON Particle sizes: 0.15−2.5 µm Control: HEPA filtered ambient air or HEPA-filtered medical air (ultrafine study)	Route: Face mask inhalation Dose/concentration: 238.4 ± 62.0 µg/m^3 Duration of exposure: 130 min Time to analysis: 1 and 21 h	Urinary and blood markers of neural effects

CAPs = concentrated ambient particles, h=hour(s), HEPA = high efficiency particulate absorber, min=minute.

8.1.3.2 Animal Toxicological Studies

An animal toxicological study included in the 2009 PM ISA (U.S. EPA, 2009) provided evidence that short-term exposure to $PM_{2.5}$ can lead to brain inflammation. In this study, Campbell et al. (2005) found that $PM_{2.5}$ CAPs exposure enhanced pro-inflammatory responses including cytokine levels and NFκB activation in the brain of animals that had been sensitized and challenged with ovalbumin. Recent studies of short-term exposure to $PM_{2.5}$ add to the evidence base reporting findings that are consistent with brain inflammation (Table 8-4).

Several recent studies examined the effects of traffic-related $PM_{2.5}$ on gene expression in the brain. In one of these, 2 groups of C57BL/6 mice were placed in a highway tunnel (Antwerp, Belgium) for 5 days in cages with and without a highly efficient particle filter (Bos et al., 2012). Other groups of animals were housed in a building near the tunnel in a cage with a less efficient particle filter and in a cage in the animal facility. Bronchoalveolar lavage was performed and demonstrated the presence of carbon particles in alveolar macrophages only in the animals exposed to unfiltered tunnel air. No evidence

of pulmonary (i.e., bronchoalveolar lavage fluid (BALF) cell counts, histology) or systemic inflammation (i.e., coagulation parameters in blood) was found. Alterations in gene expression were observed in the hippocampus and olfactory bulb of animals exposed to unfiltered tunnel air compared with controls. In the hippocampus, this included upregulation of COX2, NOS2, and NOS3 compared to the group exposed to filtered tunnel air and upregulation of COX2, NOS2, and NFE2L2 compared to the group exposed to the building air ($p < 0.05$). In the olfactory bulb, this included downregulation of IL−2α, COX2, NFE2L2, and BDNF compared to the group exposed to filtered tunnel air and downregulation of IL−2α, COX2, and IL−6 compared to the group exposed to the building air ($p < 0.05$). Some differences in gene expression were noted between responses in the control group exposed to filtered tunnel air and the control group exposed to building air, indicating that upregulation of COX2 in hippocampus and downregulation of IL−6 in olfactory bulb may have been due to confounders such as noise stress.

A second study also found evidence of brain inflammation following short-term exposure to $PM_{2.5}$. Tyler et al. (2016) exposed C67BL/6 and ApoE knockout mice to resuspended diesel exhaust particles (DEP) for 6-hours and found decreased mRNA levels for IL−6 and TGF-β in hippocampus of C67BL/6 mice ($p < 0.05$) and increased mRNA levels for IL−6, TGF-β, and TNFα in hippocampus of ApoE knockout mice ($p < 0.05$). In contrast, no inflammatory effects were seen in BALF (see Section 5.1.7.3). Another study examined changes in global gene expression in the brain, as well as expression of Arc and Rac genes and their protein products, in Fischer 344 rats exposed to CAPs in Riverside, CA for 2 weeks (Ljubimova et al., 2013). Exposure to CAPs did not induce any changes in gene or protein expression.

Table 8-4 Study-specific details from animal toxicological studies of short-term $PM_{2.5}$ exposure and brain inflammation and oxidative stress.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Bos et al. (2012) Species: Mouse Sex: Male Strain: C57BL/6 Age/Weight: 10−12 weeks	Ambient PM– Tunnel in Antwerp, Brussels Particle size: $PM_{2.5}$ Controls: 1) HEPA-filtered tunnel air 2) Ambient air in building near roadside	Route: Whole body inhalation Dose/Concentration: Mean 55.1 µg/m³ $PM_{2.5}$ Duration: 5 days Time to analysis: immediately after exposure	Gene expression of inflammatory-related proteins in hippocampus and olfactory bulb BALF cell counts Blood coagulation parameters Lung histology
Ljubimova et al. (2013) Species: Rat Sex: Male Strain: Fisher 344 Age/Weight: 3−7 weeks	CAPs from Riverside, CA (summer) Particle size: 0.18−2.5 µm Control: Filtered air	Route: Whole body inhalation Dose/Concentration: 149 ± 24 µg/m³ Particle number: 67 ± 6 particles/cm³ 10−3 Duration: 5 h/day, 4 days/week for 0.5 mo	Brain tissue—Immunohistochemistry Gene expression—mRNA
Tyler et al. (2016) Species: Mouse Strain: C67BL/6 and ApoE knockout Age/Weight: 6−8 weeks	DEP, resuspended Particle Size: 1.5−3.0 µm ± 1.3−1.6 µm Control: filtered air	Route: Whole body inhalation Dose/Concentration: 315.3 ± 50.7 µg/m³ Duration: 6 h Time to analysis: overnight	Hippocampal tissue: cytokine mRNA expression

ApoE = apolipoprotein E, CAPs = concentrated ambient particles, DEP = diesel exhaust particle, h=hour(s), HEPA = high efficiency particulate absorber.

8.1.4 Diseases of the Nervous System and Depression

A small number of epidemiologic studies of short-term exposure to $PM_{2.5}$ and nervous system outcomes were conducted since the 2009 PM ISA (U.S. EPA, 2009) was published (Table 8-5). A large U.S. study of Medicare enrollees reported an association with Parkinson Disease [RR: 1.03 (95%CI: 1.01, 1.05)] but not dementia or Alzheimer's disease (Zanobetti et al., 2014). Although only the primary ICD code was used to identify Parkinson disease hospitalizations, the specific reason for the admission is not clear and could reflect a range of complications experienced by Parkinson disease patients. No association of short-term $PM_{2.5}$ exposure with dementia related hospital admissions was reported in a smaller study in Madrid, Spain (quantitative results not presented) (Linares et al., 2017).

Studies of short-term exposure to $PM_{2.5}$ and depression also add to the still limited evidence base. No overall increase in hospital admissions for depressive symptoms was observed in a Canadian study (Szyszkowicz, 2007), although associations were detected in some subgroups (i.e., among females during the cold season [RR: 1.12 (95%CI: 1.03, 1. 21)]). Wang et al. (2014) reported a decrease in depressive

symptoms among older adults enrolled in the Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston (MOBILIZE) study [OR: 0.31 (95%CI: 0.10, 0.94)] in association with $PM_{2.5}$ exposure averaged over 14 days preceding the assessment.

Finally, a study of neuropsychological function in children was conducted at home and at school. In this study, short-term exposure (lagged 0−48 hours), was associated with some of the tests of administered, including those for processing speed (Saenen et al., 2016).

Table 8-5 Epidemiologic studies examining the association between short-term $PM_{2.5}$ exposures and nervous system effects.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†Zanobetti et al. (2014) 121 Communities, U.S. 1999−2010	Medicare >65 yr old	2-day avg for community, 1 or more monitors	NR (community specific only)	HAED visits for Parkinson disease (ICD9: 332), Alzheimer's disease (ICD9: 331.0), Dementia (ICD9: 230)	Correlations (r): NR Copollutant models: NR
†Wang et al. (2014) Boston, MA	MOBILIZE N = 732 Older adults	1 monitor, 14-day avg prior to outcome assessment	Mean (SD) 8.6 (4.9)	CESD-R ≤ 16 (depressive symptoms)	Correlations (r): NR Copollutant models: NR
†Linares et al. (2017) Madrid, Spain 2001−2009	60 plus yr old N = 1,175	24 h avg, lag 0−5, 27 urban monitors	Mean (SD) 17.1 (7.82)	Dementia-related HAED visits (ICD9: 290−294 except 291.0 and 292.0)	Correlations (r): NR Copollutant models: NR
Szyszkowicz (2007) Edmonton Canada 1992−2002	Capital Health System patients for 5 hospitals	24 h avg, lags 0, 1 and 2 days 1 monitor	Mean 8.5 IQR 6.2	HAED Visit Depression (ICD9: 311)	Correlations (r): NR Copollutant models: NR

Table 8-5 (Continued): Epidemiologic studies examining the association between short-term $PM_{2.5}$ exposures and nervous system effects.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†Saenen et al. (2016) Flanders, Belgium	COGNAC Children	Daily avg, spatiotemporal model (satellite, land cover and monitor data), at school and at residential address, lags 0−2 days R2 > 0.80	Residence: Median 16.5 (IQR: 18.9) School: Median 5.14 (IQR: 8.85)	Attention: continuous performance, Stroop Memory: digit span forward, digit span backward Visual processing speed: digit symbol, pattern comparison	Correlations (r): NR Copollutant models: NR

COGNAC = Cognition and Air Pollution in Children study, CESD-R = Center for Epidemiological Studies Depression Scale, HAED = Hospital Admission Emergency Department, ICD9 = International Classification of Disease 9th revision, MOBILIZE = Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston; NR = Not Reported; yr=year

†Studies published since the 2009 PM ISA.

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8.1.5 Components and Sources of $PM_{2.5}$

There are few studies examining components or sources of $PM_{2.5}$ in relation to nervous system effects (Table 8-6). Decreased scores on some of the neurobehavioral tests (e.g., pattern comparison) with increasing 24 hour black carbon (BC) exposure (lagged 0−2 days) were observed in the study by Saenen et al. (2016). Saenen et al. (2016) observed associations with processing speed were observed in association with short-term $PM_{2.5}$ exposure in this study. Wang et al. (2014) did not find evidence indicating that BC exposure is associated with depressive symptoms among older adults in the Boston MOBILIZE study [OR: 1.0 (95%CI: 0.75, 1.33)]. The results of the studies included in this section that pertain to exposure to $PM_{2.5}$ are found in Section 8.1.4.

Table 8-6 Studies of the association between short-term exposure to $PM_{2.5}$ components and nervous system effects.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†Saenen et al. (2016) Flanders, Belgium	COGNAC Children	Daily avg, spatiotemporal model (satellite, land cover and monitor data), at school and at residential address, lags 0−2 days R2 = 0.74	BC Median: 1.54 IQR: 0.20	Attention: continuous performance, Stroop Memory: digit span forward, digit span backward Visual processing speed: digit symbol, pattern comparison	Correlations (r): NR Copollutant models: NR
†Wang et al. (2014) Boston, MA	MOBILIZE N = 732 Older adults	1 monitor, 14-day avg prior to outcome assessment	BC Mean (SD): 0.62 (0.35) SO_4^{2-} Mean (SD): 2.6 (2.1)	CESD-R ≤ 16 (depressive symptoms)	Correlations (r): NR Copollutant models: NR

CESD-R = Center for Epidemiological Studies Depression Scale; COGNAC = Cognition and Air Pollution in Children study; MOBILIZE = Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston; NR = Not Reported

†Studies published since the 2009 PM ISA.

8.1.6 Summary and Causality Determination

The evidence reviewed in the 2009 PM ISA was characterized as "inadequate to infer" a causal relationship between short-term exposure and nervous system effects. Recent studies strengthen the evidence that short-term exposure to $PM_{2.5}$ can affect the nervous system.

Effects on the ANS and downstream consequences on the heart were observed in toxicological studies (Section 8.1.1). In addition, changes in hypothalamic neurotransmitters, including norepinephrine, and CRH were found in a study of mice exposed to $PM_{2.5}$ CAPs (Balasubramanian et al., 2013), and add to evidence described in the 2009 PM ISA of increased norepinephrine in the hypothalamus and olfactory bulb and increased serum corticosterone (Sirivelu et al., 2006). Such evidence that $PM_{2.5}$ exposure leads to changes in norepinephrine indicates that the hypothalamus plays an important role in mediating effects such as activation of the SNS and the HPA stress axis. Preliminary evidence shows a dampening of these responses after repeated exposures in lean, but not obese animals. Findings that short-term exposure to $PM_{2.5}$ results in altered expression of proinflammatory and antioxidant genes in hippocampus and olfactory bulb regions, in the absence of pulmonary or systemic inflammation, point to a direct effect of $PM_{2.5}$ on the brain (Tyler et al., 2016; Bos et al., 2012). They build on evidence, described in the 2009 PM ISA, of increased cytokines and NFκB activation in the cortex following short-term $PM_{2.5}$ CAPs exposure (Campbell et al., 2005). The evidence from epidemiologic studies that focus on specific diseases of the nervous system, however, remains limited. The evidence for the relationship between short-term exposure to $PM_{2.5}$ and effects on the nervous system is summarized in Table 8-7, using the framework for causality determination described in the Preamble to the ISAs (U.S. EPA, 2015). With regard to the epidemiologic studies relating to short-term exposure to $PM_{2.5}$ and diseases of the nervous system or depression, the evidence is limited to a small number of analyses. Positive associations were not observed in studies of hospital admissions for depression, dementia, or Alzheimer's disease. A small increase in hospital admissions for Parkinson disease was reported in a large national study of Medicare recipients indicating that short-term exposure to $PM_{2.5}$ may exacerbate a range of symptoms experienced by Parkinson disease patients (Zanobetti et al., 2014). Finally, a study of school children reported associations with some tests of neuropsychological function. There was no consideration of confounding by copollutant exposures in these epidemiologic studies and studies of components were limited in number.

The strongest evidence to indicate an effect of short-term exposure to $PM_{2.5}$ on the nervous system is provided by experimental animal studies that show effects on the brain. Toxicological studies demonstrate changes in neurotransmitters in the hypothalamus that are linked to SNS and HPA stress axis activation, as well as upregulation of inflammation-related genes, changes in cytokine levels, and NFkB activation that are indicative of brain inflammation. In addition, an association of short-term $PM_{2.5}$ exposure with hospital admissions for PD was observed indicating the potential for exacerbation of the

disease. **Overall, the collective evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term exposure to $PM_{2.5}$ and nervous system effects.**

Table 8-7 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{2.5}$ exposure and nervous system effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Brain Inflammation and Oxidative Stress			
Evidence from toxicological studies at relevant $PM_{2.5}$ concentrations	Activation of NFκB and increased levels of cytokines Altered expression of pro-inflammatory/antioxidant genes in the absence pulmonary or systemic inflammation	Campbell et al. (2005) †Bos et al. (2012) †Tyler et al. (2016)	441.7 μg/m^3 55.1 μg/m^3 315.3 μg/m^3
Activation of the Sympathetic Nervous System and Hypothalamic-Pituitary-Adrenal Stress Axis			
Evidence from toxicological studies at relevant $PM_{2.5}$ concentrations	Increased levels of norepinephrine and CRH in hypothalamus and corticosterone in serum; Increased levels of norepinephrine in BALF and BAT	(Sirivelu et al., 2006) †(Balasubramanian et al., 2013) †Chiarella et al. (2014)	500 μg/m^3 219−595 μg/m^3 109.1 μg/m^3
Evidence from multiple studies report changes in HRV	Evidence across disciplines taken together supports changes in HRV that indicate ANS imbalance	Section 6.1.10	
Biological Plausibility			
Biological plausibility for effects related to the ANS and brain inflammation	Evidence for downstream CV events related to the ANS is stronger than evidence for downstream nervous system events related to inflammation		

Table 8-7 (Continued): Summary of evidence that is suggestive of, but not sufficient to infer a causal relationship between short-term $PM_{2.5}$ exposure and nervous system effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Diseases of the Nervous System and Depression			
Limited evidence of positive associations from epidemiologic studies	No associations with dementia or Alzheimer's disease HAED Association with PD HAED	†Zanobetti et al. (2014) †Linares et al. (2017) †Zanobetti et al. (2014)	NR 17.1
	Inverse or null associations with depressive symptoms or HAED for depression	†Wang et al. (2014) Szyszkowicz (2007)	8.6 8.5
	Associations with some tests of neuropsychological function (e.g., processing speed.	†Saenen et al. (2016)	
Uncertainty regarding confounding by copollutants	No epidemiologic studies reported findings from 2 pollutant models.	Section 8.1.4	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble.

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is characterized.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated (for experimental studies, ≤2 mg/m^3).

†Studies published since the 2009 PM ISA.

8.2 Long-term $PM_{2.5}$ Exposure and Nervous System Effects

The 2009 PM ISA described the limited available studies of the effects of long-term exposures to $PM_{2.5}$ on the nervous system (U.S. EPA, 2009). A study in mongrel dogs from two areas of Mexico with contrasting air pollution levels ($PM_{2.5}$ annual average concentration 21.5 μg/m^3 versus <15 μg/m^3) reported inflammation and stress protein responses in the brain, but had limitations stemming from its ecological design (Calderón-Garcidueñas et al., 2003). Another study found Parkinson disease-like brain histopathology following long-term exposure to $PM_{2.5}$ CAPs in ApoE knockout mice (Veronesi et al., 2005). There were no epidemiologic studies of long-term exposure to $PM_{2.5}$ although an analysis of NHANES III respondents reported an association between annual average PM_{10} concentration and cognitive function, which was approximately null after adjustment for race or ethnicity and SES (Chen and Schwartz, 2009). Recent studies add to the information, specifically strengthening the lines of evidence indicating that long-term exposure to $PM_{2.5}$ can lead to effects on the brain associated with neurodegeneration (i.e., neuroinflammation and reductions in brain volume), as well as cognitive effects in older adults.

The discussion of long-term $PM_{2.5}$ exposure and nervous system effects opens with a discussion of biological plausibility (Section 8.1.1) that provides background for the subsequent sections in which groups of related endpoints are presented in the context of relevant disease pathways. These outcome groupings are activation of the SNS and HPA stress Axis (Section 8.1.2), brain inflammation and oxidative stress (Section 8.1.3), morphologic changes in the brain (Section 8.2.4), cognitive and behavioral effect (Section 8.2.5), neurodegenerative diseases (Section 8.2.6) and neurodevelopmental effects (Section 8.2.7). Evidence pertaining to $PM_{2.5}$ components is summarized in Section 8.2.8. Finally, the collective body of evidence is integrated[72] across and within scientific disciplines, and the rationale for the causality determination is outlined in Section 8.1.6.

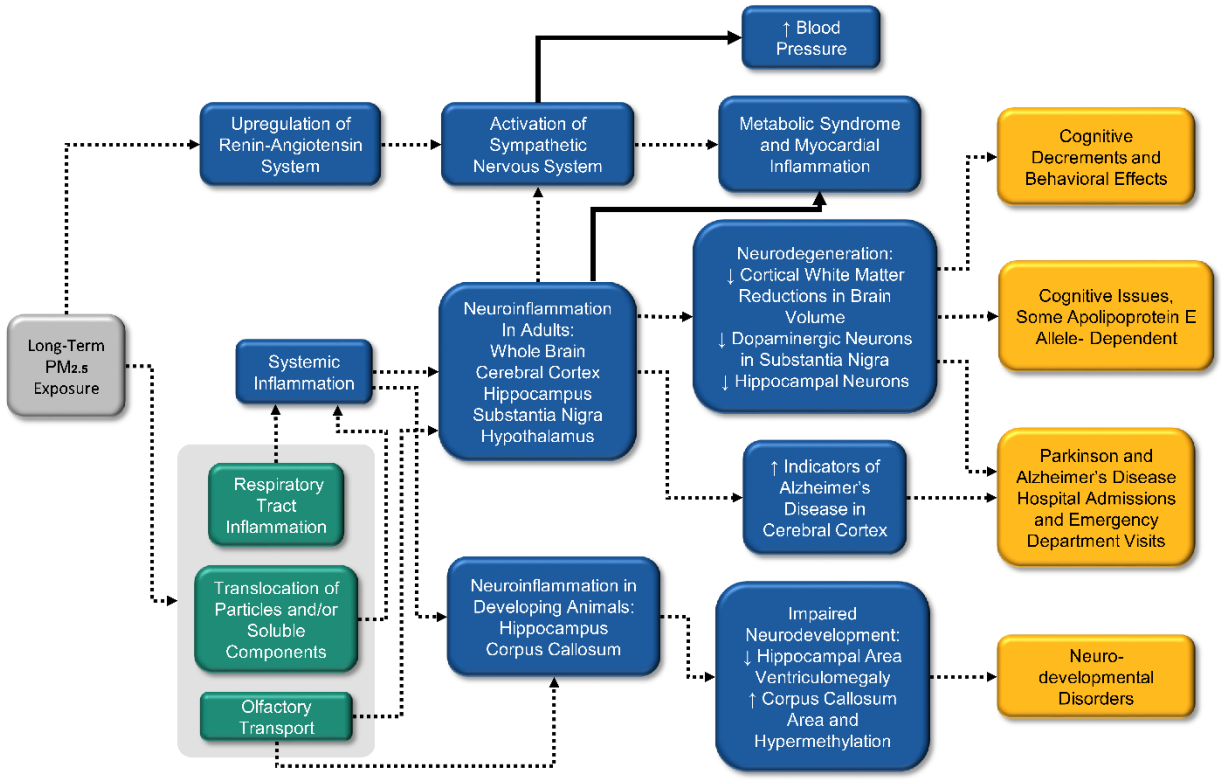
8.2.1 Biological Plausibility

This section describes biological pathways that potentially underlie the development of nervous system effects resulting from long-term exposure to $PM_{2.5}$. Figure 8-2 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" long-term exposure to $PM_{2.5}$ may lead to nervous system effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 8.2.

Once $PM_{2.5}$ deposits in the respiratory tract, it may be retained, cleared, or solubilized (see Chapter 4). $PM_{2.5}$ and its soluble components may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate reactive oxygen species (ROS) and this capacity is termed "oxidative potential". Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see Chapter 4). Immune system responses due to the presence of particles in the interstitial space may contribute to health effects. Inflammatory mediators may diffuse from the respiratory tract into the systemic circulation and lead to inflammation in extrapulmonary compartments (Section 6.2.1). Soluble components of $PM_{2.5,}$ and poorly soluble particles that are part of the $PM_{2.5}$ fraction and smaller than approximately 200 nm, may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments. A fraction of $PM_{2.5}$ may deposit on the olfactory epithelium. Soluble components of $PM_{2.5,}$ and poorly soluble particles that are part of the $PM_{2.5}$ fraction and smaller than approximately 200 nm, may also be transported via the olfactory nerve to the olfactory bulb of the brain. The extent to which translocation

[72] As detailed in the Preface, risk estimates are for a 5 µg/m3 increase in annual PM2.5 concentrations unless otherwise noted.

into the systemic circulation or transport to the olfactory bulb occurs is currently uncertain. For further discussion of translocation and olfactory transport, see Chapter 4.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Solid arrows denote direct evidence of the relationship as provided, for example, by an inhibitor of the pathway or a genetic knock-out model used in an experimental study. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 8-2 Potential biological pathways for nervous system effects following long-term $PM_{2.5}$ exposure.

Evidence that long-term exposure to $PM_{2.5}$ may affect the nervous system generally informs two different pathways (Figure 8-2). The first pathway involves activation of the SNS, possibly by upregulation of the RAS. This pathway may lead to downstream systemic effects. The second pathway begins with pulmonary inflammation, leading to systemic inflammation and resulting in neuroinflammation. Neurodegenerative and neurodevelopmental disorders may be downstream effects of neuroinflammation. Evidence for both pathways is described below.

Upregulation of the Renin-Angiotensin (RAS) and Activation of the Sympathetic Nervous System (SNS)

With regard to the first pathway, activation of the SNS resulting from long-term $PM_{2.5}$ exposure may occur secondarily to RAS upregulation. Unlike the case of short-term exposure to $PM_{2.5}$, there is a lack of evidence that long-term $PM_{2.5}$ exposure results in activation of sensory nerves in the respiratory tract. However, animal toxicological studies support a role for the RAS. Aztatzi-Aguilar et al. (2016); Aztatzi-Aguilar et al. (2015) demonstrated that long-term exposure to $PM_{2.5}$ upregulates components of the RAS in the heart, lung, and kidneys (Section 5.2.8 and Section 6.2.7.2). Interaction between SNS and the RAS has important ramifications for cardiovascular health and disease. Angiotensin II enhances the release of norepinephrine from sympathetic nerve endings via the angiotensin 1 receptor (Brasch et al., 1993). SNS activation, in turn, stimulates secretion of the angiotensin II precursor protein, renin, from the kidney, thus providing positive feedback for the pathway (Gordon et al., 1967). Evidence that increased SNS activity leads to hypertension following long-term $PM_{2.5}$ CAPs exposure was provided by Ying et al. (2014). In this study, acute inhibition of the SNS resulted in decreased blood pressure. The solid line depicted in Figure 8-2 that connects activation of the SNS and increased blood pressure indicates that the SNS mediates the increase blood pressure observed following long-term exposure to $PM_{2.5}$.

Inflammation

With regard to the second pathway, deposition of $PM_{2.5}$ in the respiratory tract may lead to pulmonary inflammation (see Section 5.2.1) and to systemic inflammation (see Section 6.2.1), which in turn may lead to neuroinflammation. This could be due to peripheral immune activation (Fonken et al., 2011) or to systemic circulation of $PM_{2.5}$, alone or engulfed by macrophages, that results in particle uptake in the brain (Ljubimova et al., 2013). Neuroinflammation may alternatively occur following olfactory transport of poorly soluble particles or their soluble components or to a neuroendocrine stress response resulting from activation of the HPA stress axis (Kodavanti, 2016).

Several animal toxicological studies in adult rodents demonstrated neuroinflammation in the cerebral cortex, hippocampus, substantia nigra, and hypothalamus following $PM_{2.5}$ exposure (Tyler et al., 2016; Hogan et al., 2015; Ying et al., 2015; Liu et al., 2014; Ying et al., 2014; Fonken et al., 2011; Veronesi et al., 2005). One study found hippocampal inflammation in the absence of pulmonary inflammation (Tyler et al., 2016). Another found that inflammation in the hypothalamus, but not in the lung, was reversed following cessation of exposure (Ying et al., 2015). Evidence for a link between hypothalamic inflammation and peripheral effects was provided by animal toxicological studies using an inhibitor of inflammation (Zhao et al., 2015; Liu et al., 2014). The solid line depicted in Figure 8-2, which connects neuroinflammation with metabolic syndrome and with myocardial inflammation, indicates that hypothalamic inflammation mediates these peripheral effects following long-term exposure to $PM_{2.5}$. Hypothalamic inflammation may possibly activate the SNS (Ying et al., 2014).

In animal toxicological studies, neuroinflammation and astrocyte activation (an index of injury) were observed in specific brain regions following long-term exposure to $PM_{2.5}$. These responses were accompanied by neurodegeneration in those regions, which included the hippocampus (Hogan et al., 2015; Fonken et al., 2011) and the substantia nigra (Veronesi et al., 2005). Hippocampal changes occurred in conjunction with impaired learning and memory and with behavioral issues. Lesions in the substantia nigra are hallmarks of Parkinson disease. In addition, an animal toxicological study found increased markers of Alzheimer's disease in the cerebral cortex (Bhatt et al., 2015). Epidemiologic studies observed associations between exposure to $PM_{2.5}$ and decreases in cortical white and gray matter and in cerebral brain volume (Casanova et al., 2016; Chen et al., 2015; Wilker et al., 2015). Epidemiologic studies also provide evidence of cognitive impairment and Alzheimer's and Parkinson disease in association with exposure to $PM_{2.5}$ (Section 8.2.6).

Neuroinflammation may potentially lead to neurodevelopmental disorders in developing animals. In an animal toxicological study, prenatal exposure to $PM_{2.5}$ resulted in neuroinflammation in the hippocampus and corpus callosum (Klocke et al., 2017). These changes were sex-specific, occurring only in males. Morphologic changes, which were not sex-specific, were found in these same brain regions and were accompanied by enlarged lateral ventricles (i.e., ventriculomegaly). This study suggests a link between exposure to $PM_{2.5}$ and neurodevelopmental disorders; however, there was no evidence of cognitive or behavioral effects.

Summary of Biological Plausibility

As described here, there are two proposed pathways by which long-term exposure to $PM_{2.5}$ may lead to nervous system effects. The first pathway begins with upregulation of the RAS, which in turn may activate the SNS. Altered autonomic tone may result in a wide range of systemic responses. As proof of this concept, animal toxicological evidence supports a direct link between the SNS and increased blood pressure following long-term $PM_{2.5}$ exposure. The second proposed pathway begins with pulmonary/systemic inflammation or olfactory transport of $PM_{2.5}$ and leads to neuroinflammation. Animal toxicological evidence supports a direct link between neuroinflammation and peripheral effects associated with metabolic syndrome and myocardial inflammation. In addition, neuroinflammation may lead to neurodegeneration and the development of Alzheimer's disease, as well as to impaired learning and memory and to behavioral issues. While experimental studies in animals contribute most of the evidence of upstream events, epidemiologic studies report associations between long-term exposure to $PM_{2.5}$ and reduced brain volume and cognitive impairment in adults. Neuroinflammation and neurodegeneration provide biological plausibility for epidemiologic results of increased hospital admissions or emergency department visits for Alzheimer's and Parkinson disease. In developing animals, neuroinflammation may potentially lead to neurodevelopmental disorders. These pathways will be used to inform a causality determination, which is discussed later in the chapter (Section 8.2.9).

8.2.2 Activation of the Sympathetic Nervous System and the Hypothalamic-Pituitary-Adrenal (HPA)Stress Axis

Activation of the SNS by long-term $PM_{2.5}$ exposure was investigated in animal toxicological studies (Table 8-8). Ying et al. (2014) evaluated the contribution of SNS to sustained increases in blood pressure, which have previously been observed in animals chronically exposed to $PM_{2.5}$. While studies have identified several mechanisms underlying this response, sympathetic activation had not been tested. C57BL/6J mice were exposed for 6 months to $PM_{2.5}$ CAPs in Columbus, OH. Exposure to $PM_{2.5}$ CAPs increased mean arterial blood pressure ($p < 0.05$), but did not affect heart rate or locomotor activity. Exposure to $PM_{2.5}$ CAPs also resulted in vascular dysfunction, which was measured ex vivo in terms of contractile response to phenylephrine and relaxation response to acetylcholine in mesenteric arteries (a type of resistance vessel) ($p < 0.05$). Two measures of sympathetic tone, low-frequency blood pressure variability and urinary norepinephrine excretion, were also increased in $PM_{2.5}$ CAPs-exposed mice ($p < 0.05$). Pharmacologic agents were used to test the role of the ANS in mediating responses to CAPs. Propranolol decreased heart rate in $PM_{2.5}$ CAPs exposed mice ($p < 0.05$), but not in controls. However, propranolol did not alter blood pressure in either group. Atropine had no effect on heart rate or blood pressure in either group. Acute inhibition of the central SNS with guanfacine resulted in a large decrease in blood pressure in both controls and $PM_{2.5}$ CAPs-exposed mice. This decrease was greater in $PM_{2.5}$ CAPs-exposed mice than in controls ($p < 0.05$). $PM_{2.5}$ CAPs exposure also increased the hypertensive response to air-jet stress ($p < 0.05$). Since sympathetic tone is modulated by hypothalamic inflammation in response to several pathophysiological signals, markers of hypothalamic inflammation were examined in $PM_{2.5}$ CAPs-exposed animals. Results, described in Section 8.2.3, provide evidence that $PM_{2.5}$ CAPs exposure mediates hypothalamic inflammation that may be linked to activation of the SNS and to an increase in sympathetic tone. Results of this study also indicate that increased sympathetic tone contributes to hypertension in response to $PM_{2.5}$ CAPs exposure.

Fonken et al. (2011) examined stress-related responses in C57BL/6J mice exposed for 10 months to $PM_{2.5}$ CAPs in Columbus, OH. No differences were found in serum corticosterone concentrations between control and $PM_{2.5}$-exposed mice, despite evidence of inflammation and morphological changes in the brain as described in Section 8.2.3 and Section 8.2.4.

In addition, the RAS may contribute to SNS activity. Long-term exposure to $PM_{2.5}$ CAPs resulted in upregulation of components of the RAS such as angiotensin I receptor and angiotensin converting enzyme in the heart, lung, and kidneys (Aztatzi-Aguilar et al., 2016; Aztatzi-Aguilar et al., 2015) (see Section 5.2.8, Section 6.2.7.2). Activity of the angiotensin converting enzyme results in angiotensin II formation from angiotensin I. Angiotensin II enhances the release of norepinephrine from sympathetic nerve endings via the angiotensin 1 receptor (Brasch et al., 1993). Sympathetic nerve activation, in turn, stimulates secretion of the angiotensin II precursor protein, renin, from the kidney, thus providing positive feedback for the pathway (Gordon et al., 1967).

Table 8-8 Study-specific details from animal toxicological studies of long-term exposure and activation of the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) stress axis.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Fonken et al. (2011) Species: mouse Strain: C57BL/6J Sex: male Age/Weight: 4 weeks	CAPs from Columbus, OH Particle sizes: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 94.4 µg/m^3 Duration: 6 h/day, 5 days/week for 10 mo Time to analysis: Behavioral testing occurred after approximately 9 mo Exposures were suspended for 3 weeks then resumed for 1 mo prior to tissue collection	Serum corticosterone
Ying et al. (2014) Species: mouse Strain: C57BL/6J Sex: male Age/Weight: 8 weeks	CAPs from Columbus, OH Particle sizes: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 107 µg/m^3 Duration: 6 h/day, 5 days/week for 6 mo	Sympathetic tone • urinary norepinephrine levels • low frequency variation of blood pressure Blood pressure Vascular dysfunction Heart rate Locomotion

CAPs = concentrated ambient particles; HEPA = high efficiency particulate absorber.

8.2.3 Brain Inflammation and Oxidative Stress

Recent experimental animal studies showing that long-term exposure to $PM_{2.5}$ CAPs can result in brain inflammation (Table 8-9) and oxidative stress add to the sparse evidence presented in the 2009 PM ISA. Several studies demonstrated that $PM_{2.5}$ CAPs exposure induced neuroinflammation and astrocyte activation in specific brain regions, as described below. Findings from these studies as they relate to neurodegeneration (Section 8.2.6), cognitive impairment, and behavioral effects (Section 8.2.5) are discussed in more detail in sections that follow.

Hippocampal inflammation was examined in several recent studies. Fonken et al. (2011) investigated the effects of a 10-month exposure to $PM_{2.5}$ CAPs from Columbus, OH on neuroinflammation and oxidative stress in the hippocampus of C57BL/6 mice. $PM_{2.5}$ CAPs exposure increased gene expression of proinflammatory cytokines TNFα and IL−1β ($p < 0.05$), but not of IL−6 and HMGB1. Upregulation of HO−1, a marker of oxidative stress ($p < 0.05$), was also seen, while the

microglial marker MAC1 was unchanged. Another study by the same group of investigators evaluated neuroinflammation in the hippocampus of $PM_{2.5}$ CAPs-exposed C3H/HeNHsd mice (Hogan et al., 2015). This mouse model is a nocturnal species with intact melatonin production. CAPs exposures for 4 weeks in Columbus, OH during a 14:10 light/dark cycle resulted in upregulation of IL−6 ($p < 0.05$), but not TNF or IL−1β. Tyler et al. (2016) exposed C67BL/6 and ApoE knockout mice to resuspended DEP for 30 days. In the hippocampus, there were increases in levels of mRNA for TGF-β in C67BL/6 mice ($p < 0.05$), but no changes in cytokine gene expression in ApoE knockout mice ($p < 0.05$). No inflammatory effects were seen in BALF although particle uptake into bronchial macrophages was increased in ApoE knockout, but not in C57BL/6 mice (see Section 5.2.9).

Ying et al. (2014) found evidence of hypothalamic inflammation in C57BL/6J mice exposed for 6 months to $PM_{2.5}$ CAPs from Columbus, OH. Increased hypothalamic gene expression of E-selectin, TNFα and ICAM−1 ($p < 0.05$) were observed. In addition, phosphorylation of IKK was increased in the arcuate nucleus but not in the paraventricular nucleus of the hypothalamus, while the number of c-fos positive cells was increased in both ($p < 0.05$). These results indicate activation of the NFκB pathway and upregulation of pro-inflammatory genes as a result of exposure to $PM_{2.5}$ CAPs. Hypothalamic inflammation was also demonstrated in Liu et al. (2014), in a genetically susceptible model of Type II diabetes, the KKay mouse, following exposure to $PM_{2.5}$ CAPs from Columbus, OH for 5−8 weeks. Increased gene expression of IL−6, TNFα, and IKKβ was observed ($p < 0.05$). In addition, the amount of oxidized phospholipid Ox-PAPC, which can activate TLR pathways, was increased in brain tissue. TLR pathways are involved in activation of the innate immune system. Subsequently, mice were treated with an inhibitor of IKKβ, which blocks NFκB activation, by inter-cerebroventricular infusion during a 4-week exposure to $PM_{2.5}$ CAPs. Central IKKβ inhibition dampened the effects of CAPs exposure on hypothalamic inflammation, including IL−6 and IKKβ gene expression and activation of microglia and astrocytes, as indicated by IBA−1 and GFAP immunostaining, respectively ($p < 0.05$). Exposure to $PM_{2.5}$ CAPs enhanced hyperglycemia, insulin resistance, and peripheral inflammation (see Section 7.2.3.2) that was dampened by IKKβ inhibition. Liu et al. (2014) provides evidence that the central nervous system, possibly via hypothalamic inflammation, contributes to the diabetic phenotype in CAPs-exposed susceptible mice. Treatment with this same inhibitor of IKKβ by intra-cerebroventricular infusion blocked myocardial inflammation in a separate study of long-term $PM_{2.5}$ CAPs exposure in KKay mice (Zhao et al., 2015). Evidence of hypothalamic inflammation was also found in spontaneously hypertensive (SH) rats exposed to CAPs from Columbus, OH for 15 weeks (Ying et al., 2015). Expression of TNFα mRNA in the hypothalamus was increased ($p < 0.05$) and returned to baseline 5 weeks following the end of exposure.

Bhatt et al. (2015) investigated the effects of $PM_{2.5}$ CAPs exposure on brain inflammation and markers of Alzheimer's disease in C57BL/6 mice. Exposure to $PM_{2.5}$ CAPs from Columbus, OH for 9 months, but not 3 months, resulted in increases in several indices of inflammation and early Alzheimer's disease-related pathology in the temporal cortex. This included a subset of cytokines, COX−1 and COX−2, PSD−95, and amyloidβ 1−40 ($p < 0.05$). A decrease in amyloid precursor protein

(APP) levels was observed, along with an increase in the beta-site APP cleaving enzyme (BACE) ($p < 0.05$). No changes in tau, synaptophysin, markers of oxidative stress, DNA methylation or activation of astrocytes (GFAP), glia (1BA−1), or endothelial cells (VCAM−1) were found.

However, changes in gene expression were not found in every study involving $PM_{2.5}$ CAPs. Ljubimova et al. (2013) examined changes in global gene expression in the brain, as well as expression of Arc and Rac genes and their protein products, in Fischer 344 rats exposed to $PM_{2.5}$ CAPs in Riverside, CA for 10 months. Exposure did not induce changes in gene or protein expression in this study.

In summary, inflammation was observed in the hippocampus, hypothalamus, and temporal cortex of several different mice strains exposed for 1−10 months to $PM_{2.5}$ CAPs. Hippocampal inflammation, in the absence of pulmonary inflammation, was also found in mice exposed to traffic-related $PM_{2.5}$. In a mouse model of diabetes, $PM_{2.5}$ CAPs-exposure induced hypothalamic inflammation that was linked to a worsening of the diabetic phenotype and to myocardial inflammation. Hypothalamic inflammation was found to be reversible with cessation of exposure in SH rats. In the temporal cortex, brain inflammation was observed in conjunction with markers of Alzheimer's disease following $PM_{2.5}$ CAPs exposure. Oxidative stress was also seen in the hippocampus and hypothalamus.

Table 8-9 Study-specific details from animal toxicological studies of long-term exposure to $PM_{2.5}$ and brain inflammation and oxidative stress.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Bhatt et al. (2015) Species: mouse Sex: male Strain: C57BL/6 Age/Weight: 8 weeks	CAPs from Columbus, OH Particle size: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 65.7 ± 354.2 µg/m^3 Duration: 6 h/day, 5 days/week for 3 or 9 mo	Immunoassays of temporal cortex • cytokines • COX−1, COX−2 • Markers of oxidative stress 3NT, HNE-adducts • Markers of astrocyte (GFAP), glial (IBA−1) or vascular (VCAM−1) activation • Markers of Alzheimer's disease: Aβ, tau, APP and cleaving enzyme BACE • Postsynaptic marker PSD−95 • DNA methylation

Table 8-9 (Continued): Study-specific details from animal toxicological studies of long-term exposure to $PM_{2.5}$ and brain inflammation and oxidative stress.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Fonken et al. (2011) Species: mouse Strain: C57BL/6J Sex: male Age/Weight: 4 weeks	CAPs from Columbus, OH Particle sizes: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 94.4 µg/m^3 Duration: 6 h/day, 5 days/week for 10 mo Time to analysis: Exposures were suspended for 3 weeks then resumed for 1 mo prior to tissue collection	Brain tissue—hippocampus • morphology • gene expression
Hogan et al. (2015) Species: mouse Strain: C3H/HeNHsd Sex: male Age/Weight: 8 weeks	CAPs from Columbus, OH Particle Sizes: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 94.4 µg/m^3 Duration: 6 h/day, 5 days/week for 4 weeks Time to Analysis: Exposures were suspended for 3 weeks then resumed for 1 mo prior to tissue collection	Brain tissue—hippocampus • morphology • gene expression
Liu et al. (2014) Species: mouse Strain: KKay Sex: Age/Weight: 5−7 weeks	CAPs from Columbus, OH Particle sizes: $PM_{2.5}$ Control: filtered air	Route: Whole body inhalation Dose/Concentration: 107 µg/m^3 Duration: 6 h/day, 5 days/week for 4, 5 or 8 weeks	Hypothalamic tissue: Gene expression and immunostaining—inflammatory markers in hypothalamus Brain tissue: LC/MS— Oxidized phospholipids Glucose homeostasis Insulin sensitivity Oxygen consumption Heat production Blood and peripheral tissues: Markers of inflammation
Ljubimova et al. (2013) Species: Rat Sex: Male Strain: Fisher 344 Age/Weight: 3−7 weeks	CAPs from Riverside, CA (summer) Particle size: 0.18−2.5 µm Control: Filtered air	Route: Whole body inhalation Dose/Concentration: 149 ± 24 µg/m^3 67 ± 6 particles/cm^3 10−3 Duration: 5 h/day, 4 days/week for 1, 3, and 10 mo	Brain tissue—Immunohistochemistry Gene expression—mRNA

Table 8-9 (Continued): Study-specific details from animal toxicological studies of long-term exposure to $PM_{2.5}$ and brain inflammation and oxidative stress.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Tyler et al. (2016) Species: Mouse Strain: C57BL/6 and ApoE knockout Age/Weight: 6−8 weeks	DEP, resuspended Particle size: 1.5−3.0 μM ± 1.3−1.6 μM Control: filtered air	Route: Whole body inhalation Dose/Concentration: 315.3 ± 50.7 μg/m^3 Duration: 6 h/d for 30 days	Hippocampus tissue: Cytokine gene expression
Ying et al. (2014) Species: mouse Strain: C57BL/6J Sex: male Age/Weight: 8 weeks	CAPs from Columbus, OH Particle sizes: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 107 μg/m^3 Duration: 6 h/day, 5 days/week for 6 mo	Brain tissue: Gene expression—inflammatory markers in hypothalamus
Ying et al. (2015) Species: Rat Strain: SHR Sex: Male Age/Weight: 5 weeks	CAPs from Columbus, OH Particle sizes: $PM_{2.5}$ Control: filtered air	Route: Whole body inhalation Dose/Concentration: 128.3 ± 60.4 μg/m^3 Duration: 6 h/day, 5 days/week for 15 weeks Time to analysis: immediately or 5 weeks later	Gene expression—inflammatory markers In hypothalamic, lung, heart tissue

3−NT = 3−nitrotyrosine; Aβ = amyloid beta; ApoE = apolipoprotein E; APP = amyloid precursor protein; BACE = beta-secretase 1; CAPs = concentrated ambient particles; COX = cyclooxygenase; GFAP = glial fibrillary acidic protein; HEPA = high efficiency particulate absorber; HNE = hydroxynonenol; IBA−1 = ionized calcium binding adaptor molecule; LC/MS = liquid chromatography/mass spectrometry, PSD = postsynaptic density protein; VCAM = vascular cell adhesion molecule.

8.2.4 Morphologic Changes in the Brain

There were no epidemiologic studies relating long-term exposure to $PM_{2.5}$ to changes in brain morphology evaluated in the 2009 PM ISA. However, an animal toxicological study found Parkinson disease-like brain histopathology following long-term exposure to $PM_{2.5}$ CAPs in ApoE knockout mice (Veronesi et al., 2005). Dopaminergic neurons were decreased in substantia nigra, which is part of the midbrain, and GFAP immunoreactivity, an indicator of astrocyte activation, was increased in the nucleus compacta, which is part of the substantia nigra.

Recent analyses from two established cohorts (Casanova et al., 2016; Chen et al., 2015; Wilker et al., 2015), using magnetic resonance imaging (MRI) to identify attributes or changes in brain structure that may stem from neurodegenerative processes or cerebrovascular dysfunction, report $PM_{2.5}$ associated reductions in brain volume (Table 8-10). Morphologic changes in the brain were also demonstrated in experimental animal studies (Table 8-11). These changes were accompanied by inflammation (Section 8.2.3).

Epidemiologic Studies

The effect of long-term exposure to $PM_{2.5}$ on brain morphology, using MRI scans, was studied in older women (age 65−80) who were free of dementia at baseline when they were enrolled in the Women's Health Initiative Memory Study (WHIMS) (Chen et al., 2015). Information on a wide array of covariates including individual characteristics such as hormone replacement therapy, BMI, lifestyle, depression, cardiovascular risk factors and SES was collected for WHIMS. A pattern of lower white matter (WM) volume of the frontal, parietal and temporal areas of the brain in fully adjusted models with increasing cumulative $PM_{2.5}$ exposures was observed [−8.30 cm^3 (95% CI: −4.70, −11.89) decrease in total WM]. Details on the quantitative relationship between $PM_{2.5}$ and gray matter (GM) were not reported because they did not reach statistical significance. This research was extended through the analyses conducted by Casanova et al. (2016) using finely grained voxel-wise methods, which are better able to detect patterns that extend across multiple brain regions. Increased 3-year average $PM_{2.5}$ concentrations was associated with smaller subcortical WM and smaller cortical GM volumes in the multi-variable models used in this study. The exposure metrics (3 year average and cumulative average) used in WHIMS analysis were highly correlated ($r = 0.93$).

In a cross-sectional analysis of the Framingham Heart Offspring Study, Wilker et al. (2015) examined the association of long-term $PM_{2.5}$ exposure with total cerebral brain volume, hippocampal volume, WM hyperintensity volume, and preclinical brain infarcts among older men and women (≥60 years old) who were free of dementia and stroke. Wilker et al. (2015) reported that total cerebral brain volume was smaller with increasing $PM_{2.5}$ exposure after adjustment for covariates [−0.80 cm^3 (95% CI: −0.13, −1.48) total cerebral brain volume]. After further adjustment for risk factors for cardiovascular disease, this association persisted but lost precision. An increased risk of covert brain infarcts was also observed [OR: 2.58 (95%CI: 1.27, 5.24)].

Table 8-10 Epidemiologic studies examining the association between long-term $PM_{2.5}$ exposures and brain morphology using magnetic resonance imaging (MRI).

Study Location/Years	Study Population	Exposure Assessment	Concentration $\mu g/m^3$	Outcome	Copollutant Examination
†(Chen et al., 2015) 2 RCTs, U.S. $PM_{2.5}$: 1999−2006 Outcome: 2005−2006	WHIMS n = 1,403	Cumulative avg for geocoded residential history, BME-based spatiotemporal model, C-V R2 = 0.9	Median: 12.24 IQR: 10.67−14.16	GM, WM volumes	Correlations (r): NR Copollutant models: NR
†(Casanova et al., 2016) $PM_{2.5}$: 1999−2010 Outcome: 1996/98−2005−2006	WHIMS N = 1,365	3-yr avg at residence, BME spatio-temporal model to estimate C-V R2 = 0.74	NR	GM, WM, hippocampal volumes	Correlations (r): NR Copollutant models: NR
†(Wilker et al., 2015) Cross-sectional $PM_{2.5}$: 2000 Outcome: 1998−2001	Framingham Offspring Study N = 943	Satellite derived AOD with LUR, see (Kloog et al., 2012)	Median = 11.1 IQR = 1.7	Hippocampal volume, WM hyper-intensity volume Total cerebral brain volume	Correlations (r): NR Copollutant models: NR

BME = Bayesian Maximum Entropy; C-V = cross validation; GM = grey matter; LUR = land use regression; MRI = Magnetic Resonance Imaging; NR = Not Reported; RCT = Randomized Clinical Trial; WHIMS = Women's Health Initiative Memory Study; WM = white matter; y=year(s).

†Studies published since the 2009 PM ISA.

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Animal Toxicological Studies

Fonken et al. (2011) investigated morphologic changes in the hippocampus of C57BL/6 mice exposed for 10 months to $PM_{2.5}$ CAPs from Columbus, OH. $PM_{2.5}$ CAPs exposure resulted in structural changes in the hippocampus. Apical spine density in the CA1 region of the hippocampus was decreased ($p < 0.05$). Basilar spine density in the CA1 region and spine density in the CA3 and dentate gyrus (DG) regions were unchanged. Apical dendritic length and cell complexity were also decreased by $PM_{2.5}$ CAPs exposure ($p < 0.05$), although cell body area was unchanged. Another study by the same group of investigators found altered brain morphology in C3H/HeNHsd mice exposed for 4 weeks to $PM_{2.5}$ CAPs during a 14:10 light/dark cycle (Hogan et al., 2015). This mouse model is a nocturnal species with intact melatonin production. $PM_{2.5}$ CAPs exposures resulted in decreased apical and basilar spine densities, apical dendritic length, and cell body area in the CA1 region of the hippocampus ($p < 0.05$).

Table 8-11 Study-specific details from animal toxicological studies of long-term $PM_{2.5}$ exposure and morphologic effects.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Fonken et al. (2011) Species: mouse Strain: C57BL/6J Sex: male Age/Weight: 4 weeks	CAPs from Columbus, OH Particle sizes: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 94.4 µg/m^3 Duration: 6 h/day, 5 days/week for 10 mo Time to analysis: Exposures were suspended for 3 weeks then resumed for 1 mo prior to tissue collection	Brain tissue—hippocampus • morphology
Hogan et al. (2015) Species: mouse Strain: C3H/HeNHsd Sex: male Age/Weight: 8 weeks	CAPs from Columbus, OH Particle sizes: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 94.4 µg/m^3 Duration: 6 h/day, 5 days/week for 4 weeks Time to analysis: Exposures were suspended for 3 weeks then resumed for 1 mo prior to tissue collection	Brain tissue—hippocampus • morphology

CAPs = concentrated ambient particles; HEPA = high efficiency particulate absorber; mo=month(s).

8.2.5 Cognitive and Behavioral Effects

8.2.5.1 Animal Toxicological Studies

Fonken et al. (2011) investigated affective and cognitive processes in C57BL/6 mice exposed for 10 months to $PM_{2.5}$ CAPs in Columbus, OH (Table 8-12). Behavioral testing showed that $PM_{2.5}$ CAPs exposure had a number of effects – impaired spatial learning and spatial memory, as measured in the Barnes maze ($p < 0.05$); increased behavioral despair and a more rapid onset of behavioral despair as measured in the Porsolt forced swim test ($p < 0.05$); and increased anxiety-like behavior in one of two tasks (time spent in the center of an open field, $p < 0.05$). Neuroinflammation and morphologic changes, described in Section 8-26 and Section 8-30, may be related to changes in cognition and affective processes. Another study by the same group of investigators examined affective and cognitive processes in C3H/HeNHsd mice exposed for 4 weeks to $PM_{2.5}$ CAPs during a 14:10 light/dark cycle (Hogan et al., 2015). This mouse model is a nocturnal species with intact melatonin production. Behavioral testing demonstrated an effect of CAPs exposure on locomotion and anxiety-like responses (time spent in the center of an open field, $p < 0.05$), but no effects on depressive responses.

Table 8-12 Study-specific details from animal toxicological studies of long-term $PM_{2.5}$ exposure and cognitive and behavioral effects.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Fonken et al. (2011) Species: mouse Strain: C57BL/6J Sex: male Age/Weight: 4 weeks	CAPs from Columbus, OH Particle Sizes: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 94.4 µg/m^3 Duration: 6 h/day, 5 days/week for 10 mo Time to analysis: Behavioral testing occurred after approximately 9 mo. Exposures were suspended for 3 weeks then resumed for 1 mo prior to tissue collection	Behavioral testing Physical measurements Locomotor behavior and anxiety-like responses Cognitive processes—learning and memory

Table 8-12 (Continued): Study-specific details from animal toxicological studies of long-term $PM_{2.5}$ exposure and cognitive and behavioral effects.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Hogan et al. (2015) Species: mouse Strain: C3H/HeNHsd Sex: male Age/Weight: 8 weeks	CAPs from Columbus, OH Particle Sizes: $PM_{2.5}$ Control: HEPA-filtered ambient air	Route: Whole body inhalation Dose/Concentration: 94.4 µg/m^3 Duration: 6 h/day, 5 days/week for 4 weeks Time to analysis: Behavioral testing occurred after approximately 9 mo. Exposures were suspended for 3 weeks then resumed for 1 mo prior to tissue collection	Behavioral testing • locomotor behavior • anxiety-like responses • depressive-like responses

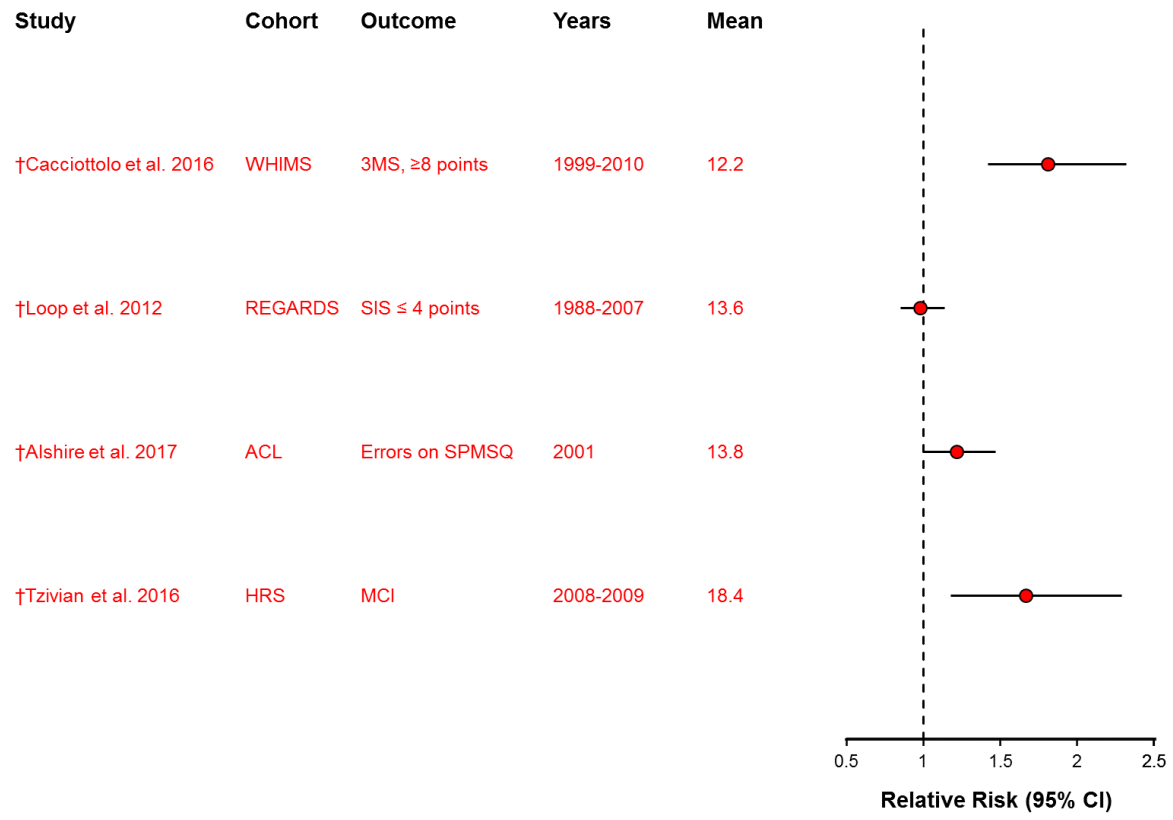
CAPs = concentrated ambient particulates; HEPA = high efficiency particulate absorber.

8.2.5.2 Epidemiologic Studies

Although there were no studies of long-term exposure to $PM_{2.5}$ evaluated in the 2009 PM ISA (U.S. EPA, 2009), Chen and Schwartz (2009) reported a cross-sectional association of annual average exposure to PM_{10} with cognitive function using data from NHANES III. Multiple additional studies reporting associations with dichotomous measures of cognitive function or effects on continuous measures of global or domain specific subtests of cognitive function add to the evidence in the current review. Overall, these studies were heterogeneous in their methods and design, and their findings were not entirely consistent. Several high-quality studies reported associations with long-term exposure to $PM_{2.5}$, however.

Studies that modeled cognitive decline as a dichotomous outcome are presented in Figure 8-3. Cacciottolo et al. (2017) examined the effect of long-term $PM_{2.5}$ exposure on accelerated global cognitive decline among WHIMS participants using a cutpoint of ≥8 points on the Modified Mini-Mental State (3MS). The authors report an increased risk of accelerated global cognitive decline in adjusted models [HR: 1.81 (95%CI: 1.42, 2.32) comparing 3-year moving average concentration >12 to ≤12 µg/m^3] in the women, with a larger HR among carriers of the APOE allele Ɛ4/4. Cacciottolo et al. (2017) considered potential confounders including age, geographic region, education income, employment, lifestyle factors, and clinical characteristics (i.e., hormone treatment, depression, BMI, hypercholesterolemia, hypertension, diabetes, history of CVD) in their analysis. In a study of the effect of $PM_{2.5}$ on pre-clinical cognitive impairment, Loop et al. (2013) analyzed data from a large U.S. cohort designed to study stroke (REGARDS). Authors conducted a cross-sectional analysis of incident cognitive impairment using logistic regression and adjusting for length of follow-up. $PM_{2.5}$ exposure was not associated with

cognitive impairment, defined as a score of ≤4 on a telephone administered Six-Item Screener (SIS), after full adjustment for potential confounders including demographic factors and incident stroke. Ailshire et al. (2017) analyzed U.S. national scale data from the Americans Changing Lives (ACL) survey reporting and increased error rate on the Short Portable Mental Status Questionnaire (SPMSQ) in association with $PM_{2.5}$ exposure that was worse in areas of high neighborhood stress. Tzivian et al. (2016) reported a positive association between long-term $PM_{2.5}$ exposure and prevalence of mild cognitive impairment (MCI) in the HRS study [OR: 1.67 (95%CI: 1.18, 2.29)] that remained after adjustment for noise. MCI was defined to identify cases with subjective cognitive complaints and objective impairment that did not reach the criteria for dementia.



Circles represent beta coefficients; horizontal lines represent 95% confidence intervals. Red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Concentrations are in μg/m^3. Results are standardized to a 5 μg/m^3 increase in $PM_{2.5}$ concentrations. Corresponding quantitative results are reported in Supplemental Table S8-1 (U.S. EPA, 2018).

3MS = Modified Mini-Mental State; ACL = Americans Changing Lives; HRS = Health and Retirement Survey; REGARDS = Reasons for Geographic and Racial Differences in Stroke; SIS = Six-Item Screener; SPMSQ = Short Portable Mental Status Questionnaire; WHIMS = Women's Health Initiative Memory Study.

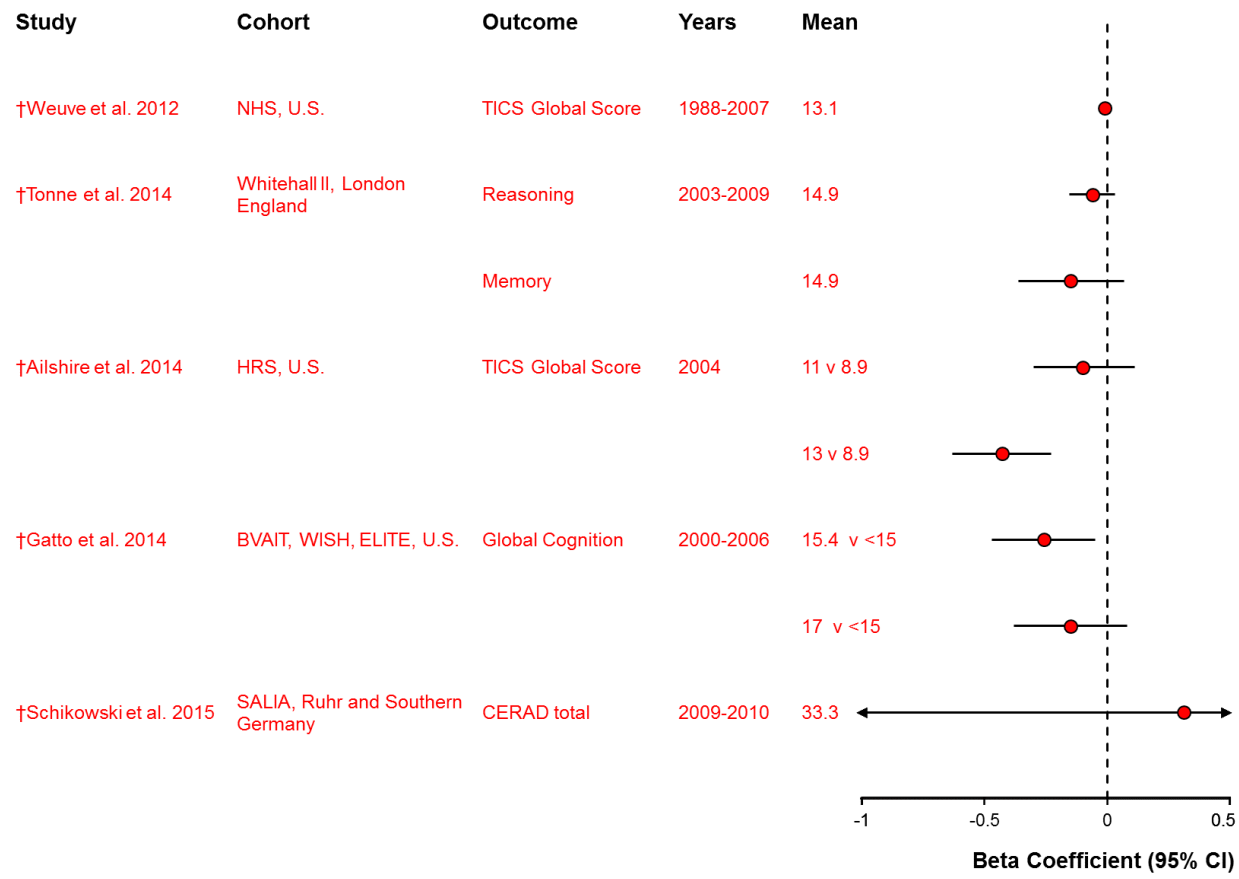
†Studies published since the 2009 PM ISA.

Figure 8-3 Associations between long-term exposure to $PM_{2.5}$ and cognitive effects. Associations are presented per 5 μg/m^3 increase in pollutant concentration (unless otherwise noted).

Small changes on cognitive test scores were observed in some but not all studies that evaluated these changes using continuous variables (Table 8-13, Figure 8-4). Weuve et al. (2012) measured the change in cognitive function of women enrolled in the Nurses' Health Study (NHS) with no history of stroke, using the validated Telephone Interview for Cognitive Status (TICS) instrument. Investigators used month-long average $PM_{2.5}$ concentrations to compute metrics indicating $PM_{2.5}$ exposures for several highly correlated time periods prior to the cognitive function assessment. Results for the longest duration

multi-year exposure metric are included in Figure 8-4. $PM_{2.5}$ was associated with a small decrease in global cognitive test score during the 2-year period between successive outcome measurements ($\beta = -0.01$ (95%CI: −0.02, 0.00) that is approximately equivalent to a decrease expected with 1 year of aging. This association persisted after adjustment for potential confounders including SES and cardiovascular conditions (i.e., high blood pressure, CHD, CHF, coronary artery bypass graft, TIA, and carotid endarterectomy). Tonne et al. (2014) used a set of tests designed to measure reasoning, memory, semantic fluency, and phonemic fluency to examine the association with long-term exposure to $PM_{2.5}$. Only associations with 5-year average concentrations are presented in Figure 8-4 because results were generally similar across exposure metrics. Authors reported 5-year declines on several cognitive tests [e.g., Reasoning: −0.06 (95% CI: −0.15, 0.03) and Memory: −0.15 (95% CI: −0.36, 0.07)].

Several cross-sectional analyses were also conducted. Ailshire and Crimmins (2014) used the TICS instrument to assess the cross-sectional association of annual average $PM_{2.5}$ concentration with cognitive effects reporting associations comparing the upper and third quartiles of exposure to the reference category (8.9 μg/m^3). The component of the TICS score reflecting episodic memory, rather than mental status, appeared to drive the observed association. In a cross-sectional analysis of several clinical trial participants enrolled through the University of Southern California, Gatto et al. (2014) found small decreases in global cognition, as well as decreases in several domain-specific tests that comprised a global cognition score. In the SALIA cohort, Schikowski et al. (2015) examined the association of $PM_{2.5}$ exposure with several domain-specific tests of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery, which includes the Mini Mental State Examination (MMSE). Although no association of $PM_{2.5}$ with global cognition was observed, associations with a figure copying subtest measuring constructional praxis was reported (ten subtests were administered).



Note: Ailshire and Crimmins (2014) and Gatto et al. (2014) specify exposure categories and compare the categories to a reference group (8.9 μg/m$_3$). Circles represent beta coefficients; horizontal lines represent 95% confidence intervals. Red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Concentrations are in μg/m^3. Results are standardized to a 5 μg/m^3 increase in $PM_{2.5}$ concentrations. Corresponding quantitative results are reported in Supplemental Table S8-2 (U.S. EPA, 2018).

BVAIT = B-Vitamin Atherosclerosis Intervention Trial, ELITE = Early versus Late Intervention Trial with Estradiol, CERAD = Consortium to Establish a Registry for Alzheimer's Disease, HRS = Health and Retirement Study, NHS=Nurses' Health Study, SALIA = Study of the Influence of Air Pollution on Lung Function, TICS = Telephone Interview for Cognitive Status, Whitehall II=Study of British Civil Servants, v = versus; WISH = Women's Isoflavone Soy Health.

†Studies published since the 2009 PM ISA.

Figure 8-4 Associations between long-term exposure to $PM_{2.5}$ and cognitive effects. Associations are presented per 5 μg/m^3 increase in pollutant concentration (unless otherwise noted).

Table 8-13 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and cognitive function.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†Cacciottolo et al. (2017) Prospective cohort $PM_{2.5}$: 1999−2010 Outcome: 1995/99−2010	WHIMS n = 3,467 women (65−79 yr) w/specific APOE alleles	3-yr moving avg for geocoded residential history, BME-based spatiotemporal model, C-V R2 = 0.7	Median: 12.24 IQR: 10.67−14.16	Accelerated cognitive decline (≥8 point loss on 3MS) and dementia (determined by central adjudication) Interaction with APOE alleles	Correlations (r): NR Copollutant models: NR
†Loop et al. (2013) 48 contiguous US states Prospective cohort $PM_{2.5}$: 2003−2009 Outcome: 2003/07−2009	REGARDS (mean age 64 yr) N = 20,150	1 yr avg (prior to baseline), AOD plus monitors, 10 × 10 km grid, see (Al-Hamdan et al., 2014)	Median: 13.6 IQR: 12.2−14.8	SIS score ≤4	Correlations (r): NR Copollutant models: NR
†Tzivian et al. (2016) German Ruhr area Cross-sectional $PM_{2.5}$: 2008−2009 Outcome: 2006/2008	HNR study N = 4,086 50−80 yr	Annual avg at residential address, LUR, R2 comparing modelled and measured $PM_{2.5}$ = 0.88	Mean: 18.39 (SD: 1.05) IQR: 1.4	MCI (Petersen/International Working group on MCI criteria) (Petersen, 2004)	Correlations (r): NR Copollutant models: NR
†Weuve et al. (2012) 11 US states Longitudinal Cohort $PM_{2.5}$: 1988−2007	NHS Women ≥70 yr N = 19,409	1 mo, 1 yr, 2 yr, 5 yr avg prior to baseline assessment. Pre- and post−1999	5 yr Avg: 8.5	TICS Global score	$PM_{10-2.5}$ R = 0.1−0.22 depending on metric (*r* across averaging times of each size fraction 0.97−0.98)
†Tonne et al. (2014) greater London Longitudinal Cohort $PM_{2.5}$ 2003−2009 Outcome: 2007/2009	Whitehall II (mean 66 yr) N = 2,867	Annual avg, 1 yr lag 4, 3 yr avg, 5 yr avg, dispersion model, *r* = 0.74 (2008, 15 monitors)	5 yr Avg: 14.9 IQR: 0.25	Cognitive test performance 5 yr decline	$PM_{2.5}$ exhaust

Table 8-13 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and cognitive function.

Study Location/Years	Study Population	Exposure Assessment	Concentration $\mu g/m^3$	Outcome	Copollutant Examination
†Ailshire and Crimmins (2014) Cross-sectional US National Survey 2004	HRS N = 13,996 ≥50 yr	Annual avg (2004), within 60 km census tract centroid for residence	Median: 12.2 IQR: 3.9	Episodic memory and mental status TICs	Correlations (r): NR Copollutant models: NR
†Ailshire et al. (2017) U.S. National Survey $PM_{2.5}$ = 2001 Outcome: 2001/2002	ACL N = 79 ≥55 yr	Annual avg, within 60 km of census tract centroid	Mean (SD) 13.78 (3.13)	Rate of incorrect response on SPMSQ	Correlations (r): NR Copollutant models: NR
†Gatto et al. (2014) Los Angeles Cross-sectional 2000−2006	BVAIT, WISH, ELITE (mean age 60.5 yr) N = 1,496	1 yr avg for year of randomization at residence, IDW interpolation of monitor concentration (within 5 km or avg of 3 monitors within 100 km) See (Peters et al., 2004)	NR	14 cognitive tests and global score	Copollutant correlations (r): Ozone (r = 0.62), NO_2 (r = 0.8)
†Schikowski et al. (2015) Ruhr and Southern Muensterland, Germany Cross-sectional Outcome 2007−2009 $PM_{2.5}$: 2009−10 Back-extrapolation: 1985/1995 (baseline exam)	SALIA Women (mean 73.4 yr) N = 789	Multi-yr avg, LUR with back extrapolation, see (Eeftens et al., 2012a) Mean model explained variance R2 = 0.71 (range: 0.32−0.81) C-R R2 8−11% lower	Median 33.3 and IQR 4.7 at baseline (1995) Median 17.4 and IQR 1.8 at follow-up (2007)	Global Cognition (MMSE and CERAD) Fig-C Modification by APOE allele	Correlations (r): NR Copollutant models: NR

ACL = Americans' Changing Lives; BVAIT = B-Vitamin Atherosclerosis Intervention Trial; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; ELITE = Early versus Late Intervention Trial with Estradiol; BMI = Body Mass Index; HRS = Health and Retirement Study; MCI = Mild Cognitive Impairment; NHS = Nurses Health Study; RCT = Randomized Controlled Trial; REGARDS = Reasons for Geographic and Racial Differences in Stroke; SALIA = Study of the Influence of Air Pollution on Lung Function, Inflammation, and Aging; SIS = Six-Item Screener (cognitive function); SPMSQ = Short Portable Mental Status Questionnaire; TICS = Telephone interview for Cognitive Status; WISH = Women's Isoflavone Soy Health.

†Studies published since the 2009 PM ISA.

Anxiety and Depression

There were no analyses of the association of long-term exposure to $PM_{2.5}$ with anxiety or depression evaluated in the 2009 PM ISA. Several studies are currently available that examine associations with depressive, anxiety, or use of psychiatric medication (Figure 8-5, Table 8-14). Overall, these studies do not report consistently positive associations and the magnitude of the association varies substantially by study. Within the European ESCAPE project, statistical evidence of heterogeneity across cohorts was observed, precluding meta-analysis of cohort-specific results.

Power et al. (2015) analyzed data from the NHS to determine the association between several exposure metrics averaged from 1 month to multiple years (1988−2004) and anxiety among older women. Authors observed positive associations between prevalent anxiety and multi-year average concentration [OR: 1.04 (95% CI: 1.00, 1.09)]. The associations with shorter averaging times were also present [e.g., 1.06 (95% CI: 1.03, 1.09) per 5 μg/m^3 increase in 1-mo avg concentration], and models that adjusted for averaging time indicated the strongest associations were with shorter averaging times. In a cross-sectional analysis of ESCAPE, Zijlema et al. (2015) observed heterogenous results across cohorts with a large imprecise positive association among FINRISK participants [OR: 1.39 (95% CI: 0.64, 3.05)] and associations that were close to the null in other cohorts. In a longitudinal analysis of use of psychiatric medication reported in the national registry of Sweden, (Oudin et al., 2016) reported a small positive association between use of psychiatric medication and PM_{10} [1.02 (95% CI: 1.00, 1.04)], noting that the association was similar to the association with $PM_{2.5}$. A relatively large association with major depressive disorder was reported by Kim et al. (2016) in an analysis of the National Health Insurance Database (NHID) of Korea [HR: 1.21 (95% CI: 1.07, 1.38)], where the annual average $PM_{2.5}$ concentration was 26.7 μg/m^3.

Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Mean concentrations in $\mu g/m^3$. Hazard Ratios are standardized to a 5 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations. Corresponding quantitative results are reported in Supplemental Table S8-3 (U.S. EPA, 2018).

ESCAPE = European Study of Cohorts for Air Pollution Effects; FINRISK = Finland Risk; KORA = Kooperative Gesundheitsforschung in der Region Augsburg; NHS = Nurses' Health Study; NR = Not Reported.

†Studies published since the 2009 PM ISA.

Figure 8-5 Associations between long-term exposure to $PM_{2.5}$ and indicators of depression or anxiety. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration.

Table 8-14 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and indicators of depression or anxiety.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†Power et al. (2015) $PM_{2.5}$: 1988−2004 Outcome: 2004	NHS N = 71,271 Mean age 70 yr	Multi-year, annual avg, 1 mo, 3 mo and 6 mo prior to outcome, spatio-temporal, at residence (pre-1999 $PM_{2.5}$ estimated from PM_{10} ratio)	Mean (SD): 1 mo = 12.74 (4.18); 3 mo = 12.13 (3.4), 6 mo = 11.59 (2.60); 12 mo = 11.38 (2.60); 1988−2003 = 13.75 (2.82)	Crown-Crisp phobic anxiety scale score ≥6 (prevalent)	$PM_{10-2.5}$ Correlations (r); 0.24 Copollutant model: NR
†Zijlema et al. (2015) Cross-sectional $PM_{2.5}$ ESCAPE: 2008−2011 $PM_{2.5}$ EU-wide protocols: 2005−2007	ESCAPE plus LifeLines N = 70,928	LUR, at residence using ESCAPE and EU-wide protocols incorporating satellite derived AOD. (Vienneau et al., 2013; Eeftens et al., 2012b)	Lifelines (highest): Median 15.4 IQR 0.16	Depressed mood, questionnaire or interview	ESCAPE correlations (r): 0.44−0.53 NO_2 EU-wide correlations (r): 0.33−0.53
†(Oudin et al., 2016) Longitudinal 4 counties, Sweden $PM_{2.5}$: 2005−2010 Outcome: 2005−2010	Swedish National Register N = 552,221	Annual avg for year of inclusion, LUR (estimated from ratio with PM_{10}), resolution of 1 km; C-V R2 PM_{10} = 0.85−0.95	NR	Medication for psychiatric disorders	Correlations (r): NR Copollutant models: NR Note: PM_{10} results presented because they were similar to $PM_{2.5}$ results
†Kim et al. (2016) Seoul, South Korea Longitudinal $PM_{2.5}$: 2007−2010 Outcome: 2008−2010	NHID N = 27,270	1 yr moving avg, 27 monitors	26.7 Range across districts 2007: 19.8−27.4	Major depressive disorder (ICD10 F32.x, F33.x, F34.1, F41.2)	Correlations (r): NR Copollutant models: NR

AOD = Aerosol Optical Depth; CESD-R = Center for Epidemiologic Studies Depression Scale-Revised; ESCAPE = European Study of Cohorts for Air Pollution Effects; IQR = Inter-quartile Range; LUR = land use regression; MOBILIZE = Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston; NHID = National Health Insurance Database; N, n = number of subjects; NR = Not Reported; SD = Standard Deviation; yr = year(s).

†Studies published since the 2009 PM ISA.

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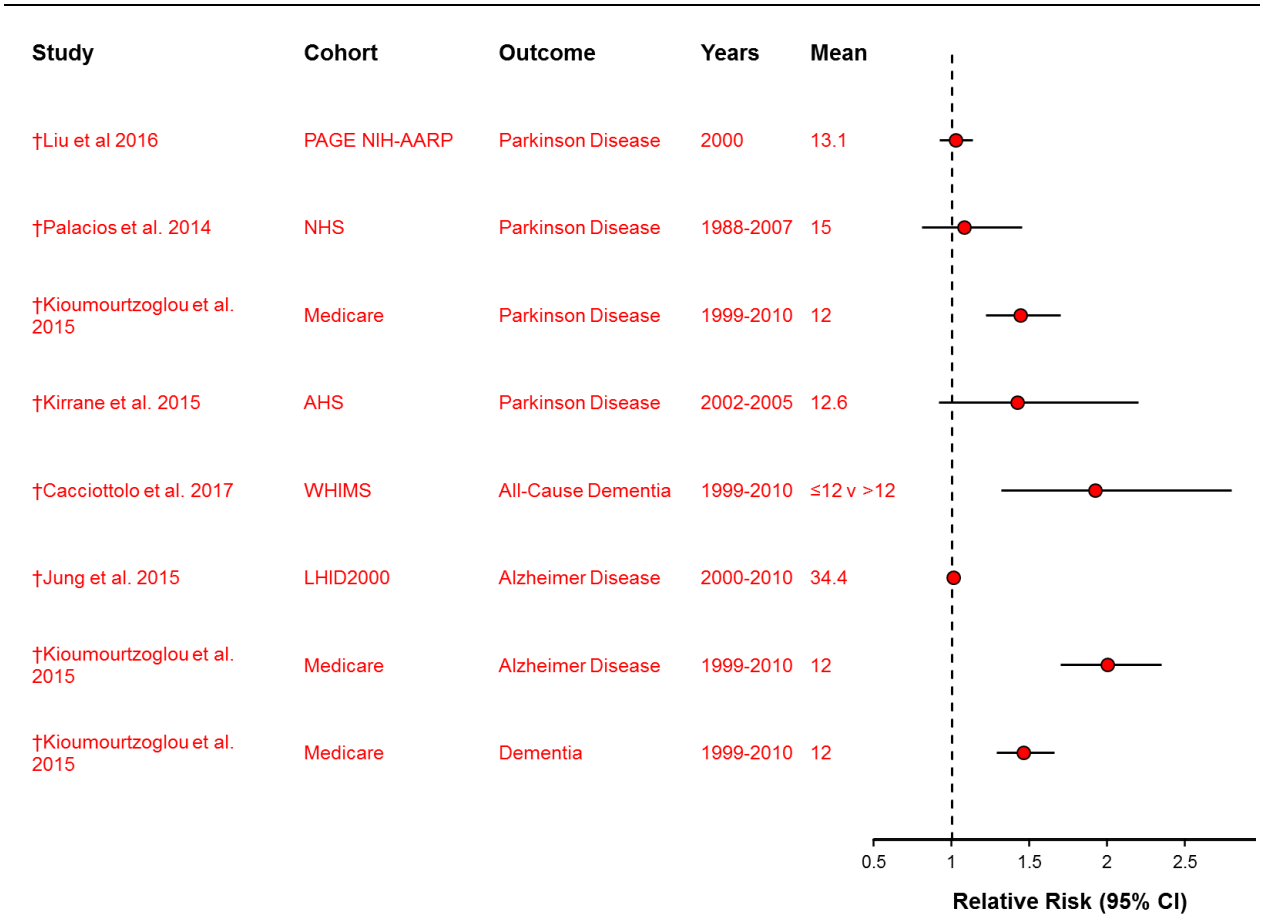
8.2.6 Neurodegenerative Diseases

There were no epidemiologic studies of the effect of long-term exposure to $PM_{2.5}$ and neurodegenerative disease evaluated in the previous ISA (U.S. EPA, 2009). A limited number of studies of Parkinson disease, Alzheimer's disease, and dementia are currently available for review (Figure 8-6, Table 8-15). Animal toxicological evidence of neurodegenerative diseases following long-term $PM_{2.5}$ exposure includes the demonstration of Parkinson disease-like brain histopathology (Veronesi et al., 2005), which is discussed in the 2009 PM ISA and in Section 8.2.4, and the demonstration of early markers of Alzheimer's disease (Bhatt et al., 2015), which is discussed in Section 8.2.3.

The set of studies of Parkinson disease includes a case control analysis from the Parkinson Genes and Environment study, National Institutes of Health, American Association of Retired People (PAGE NIH-AARP) study (Liu et al., 2016) and a prospective analysis from the NHS (Palacios et al., 2014). These studies are well-conducted in that self-reported outcomes were validated and individual-level data on an array of covariates including sex, smoking, and caffeine use was considered in the analyses. Although slightly increased, the relative risks reported in both studies were small relative to their wide confidence intervals, providing little evidence of an association [HR: 1.03 (95% CI 0.92, 1.13) in the PAGE NIH-AARP study and HR: 1.08 (95% CI: 0.81, 1.45) in the NHS study]. Kioumourtzoglou et al. (2015) reported large positive associations between long-term exposure to $PM_{2.5}$ and first hospital admission for Parkinson disease (ascertained using primary or secondary diagnosis code) indicating higher risk of Parkinson-related complications that require hospitalization among older adults receiving Medicare benefits in 50 Northeastern U.S. cities [HR: 1.44 (95% CI 1.22, 1.70)]. Although age and sex were controlled in the analysis, individual level data on smoking or dietary covariates was not available, nor was the outcome validated in this study. The other study of $PM_{2.5}$ exposure and Parkinson disease analyzed data from rural populations in North Carolina and Iowa reporting an imprecise, positive association between 4-year average $PM_{2.5}$ concentration and Parkinson disease (OR 1.34 95% CI: 0.93, 1.93) among farmers in North Carolina while no association was observed in among farmers in Iowa where exposures were much lower [OR: 0.91 (95% CI: 0.75, 1.11) per IQR (0.7 $\mu g/m^3$) increase] (Kirrane et al., 2015). Self-reported doctor-diagnosed Parkinson disease was validated for a subset of participants in this study.

Studies of Alzheimer's disease and dementia are also plotted on Figure 8-6. Some studies report positive associations with long-term $PM_{2.5}$ exposure, but findings are not consistent overall. In the analysis of the WHIMS cohort described previously, Cacciottolo et al. (2017) found an increased risk of all-cause dementia comparing 3-year moving average exposure to $PM_{2.5}$ of <12 $\mu g/m^3$ to ≥ 12 $\mu g/m^3$ [HR: 1.92 (95%CI: 1.32, 2.8)]. In a study in China where concentrations are relatively high, Jung et al. (2014) found little evidence of an association between annual average $PM_{2.5}$ exposure at baseline and Alzheimer's disease, although an increase in $PM_{2.5}$ during follow-up was associated with the disease. Similar to their

results for Parkinson disease Kioumourtzoglou et al. (2015) reported large associations of hospital admissions for Alzheimer's disease and dementia with $PM_{2.5}$ among Medicare recipients [HR: 2.0 (95%CI: 1.7, 2.35) and HR: 1.46 (95%CI: 1.29, 1.66), respectively].



Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Mean concentrations in $\mu g/m^3$. Hazard Ratios are standardized to a 5 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations. Corresponding quantitative results are reported in Supplemental Table S8-4 (U.S. EPA, 2018).

AHS = Agricultural Health Study; LHID2000 = Longitudinal Health Insurance Database for 2000; NHS = Nurses Health Study, PAGE NIH-AARP = Parkinson's Genes and Environment study, National Institutes of Health-American Association of Retired People, WHIMS = Women's Health Initiative Memory Study.

†Studies published since the 2009 PM ISA.

Figure 8-6 Associations between long-term exposure to $PM_{2.5}$ and neurodegenerative diseases. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration unless otherwise noted.

Table 8-15 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and neurodegenerative diseases.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
†Liu et al. (2016) 6 States, U.S. Case-control $PM_{2.5}$: 2000 Outcome: 1995−2006	PAGE NIH-AARP N = 1,556 cases N = 3,313 controls	Annual avg 1990 and 2000, kriging interpolation at residence, C-V R2 = 0.88	Range: 4.4−26.9 IQR 3.8	Neurologist confirmed PD in validation study (88% of cases)	Correlations (r): NO_2 r = 0.62 Copollutant model: NR
†Palacios et al. (2014) Longitudinal cohort $PM_{2.5}$: 1988−2007 (estimated from PM_{10} ratio prior to 1999) Outcome: 1990−2008	NHS N = 115,767 N = 508 PD cases	Cumulative avg up to 2 yr prior to PD onset, estimated spatiotemporal model at residential address [see (Puett et al., 2008)]	NR	Neurologist confirmed or medical record review PD	Correlations (r): PM_{10} r = 0.73; $PM_{10-2.5}$ r = 0.26 Copollutant model: NR
†Kioumourtzoglou et al. (2015) 50 cities, Northeastern US Longitudinal cohort $PM_{2.5}$: 1999−2010 Outcome: 1999−2010	Medicare 65+ yr N = 119,425 PD admissions N = 266,735 AD admissions N = 203,463 dementia admissions	City-specific avg assigned for each year of follow-up (1999−2010), adjusted for calendar year	12 (SD 1.6) IQR: 3.8	PD: ICD9 332 AD: ICD9 331 Dementia: ICD9 290	Correlations (r): NR Copollutant models: NR
†Kirrane et al. (2015) Case-control $PM_{2.5}$: 2002−2005 Outcome: 1993−2010	AHS farmers and spouses N = 301 cases N = 83,042 controls	4 yr avg, monitor plus CMAQ, 12 × 12 grid at residential address	NC: 12.6 IQR: 4.2 Iowa: 8.9 IQR 0.5	Self-reported doctor diagnosed Parkinson disease	Correlations (r): NR Copollutant models: NR
†Cacciottolo et al. (2017) Prospective cohort $PM_{2.5}$: 1999−2010 Outcome: 1995/99−2010	WHIMS n = 3,467 women (65−79 yr) w/specific APOE alleles	3 yr moving avg for geocoded residential history, BME-based spatiotemporal model, C-V R2 = 0.7	Median: 12.24 IQR: 10.67−14.16	Dementia (determined by central adjudication)	Correlations (r): NR Copollutant models: NR

Table 8-15 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and neurodegenerative diseases.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
†Jung et al. (2014) Taiwan Longitudinal Cohort $PM_{2.5}$: 2000−2010 Outcome: 2001−2010	LHID2000 N = 95,960	Annual avg at baseline, IDW of 3 monitors within 25 km of postal code centroid for residence (also computed change in $PM_{2.5}$ from follow-up)	Mean (IQR) 34.4 (13)	ICD9 331 (consensus diagnosis in administrative database)	Correlations (r): Ozone r = 0.4, SO_2 r = 0.51 Copollutant model: NR

AD = Alzheimer's disease; AHS = Agricultural Health Study; BMI = Body Mass Index; BVAIT = B-Vitamin Atherosclerosis, Intervention Trial; CMAQ = Community Multiscale Air Quality; ELITE = Early versus Late Intervention Trial with Estradiol; LHID2000 = Longitudinal Health Insurance Database for 2000, NHS = Nurses' Health Study; PAGE NIH-AARP = Parkinson's Genes and Environment study, National Institutes of Health, American Association of Retired People; PD = Parkinson Disease; RCT = Randomized Clinical Trial; REGARDS = Reasons for Geographic and Racial Differences in Stroke; SALIA = Study of the Influence of Air Pollution on Lung Function, Inflammation, and Aging; WISH = Women's Isoflavone Soy Health.

†Studies published since the 2009 PM ISA.

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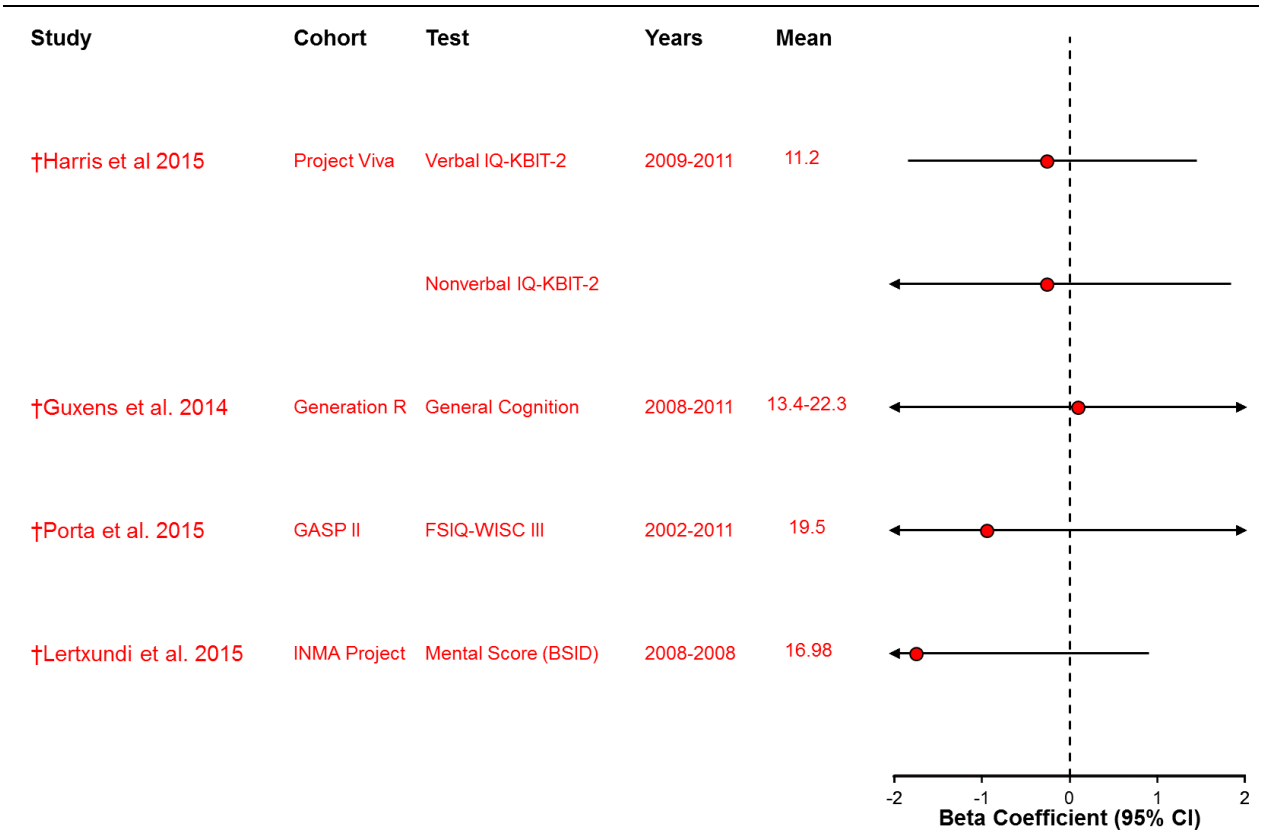
8.2.7 Neurodevelopmental Effects

There were no epidemiologic studies of neurodevelopmental effects in children available for review in the 2009 PM ISA. Currently there is a small body of literature examining the association of exposure to $PM_{2.5}$ during perinatal and childhood lifestages with cognitive and behavioral effects that do not provide consistent evidence of an association (Figure 8-7, Table 8-16). In addition, there is a limited number of studies examining the association of $PM_{2.5}$ during these lifestages with autism spectrum disorder (ASD). This set of studies report positive associations that are coherent with findings from an experimental animal study of $PM_{2.5}$ CAPs exposure demonstrating neuroinflammation and morphologic change that is associated with various human neuropathologies, including ASD.

8.2.7.1 Cognitive and Behavioral Effects

Harris et al. (2015) examined the effect of long-term $PM_{2.5}$ exposure during pregnancy and from birth through 6 years of age on cognition in children enrolled in Project Viva, which follows mother-infant pairs (N = 1,109) from birth through various lifestages during childhood. The weakly positive and negative associations with cognitive assessment scores that were reported did not provide evidence for an effect of $PM_{2.5}$ on cognition in these children. Porta et al. (2015) followed a cohort of infants born (n = 719) in Rome between 2003 to 2004 and administered the Wechsler Intelligence Scale for Children (WISC) III at age seven (n = 474). Authors reported associations with Full Scale [−0.95 (95% CI: −3.95, 2.05)], Verbal [0.22 (95% CI: −2.75, 3.20)] and Performance IQ [−2.05 (95% CI: −1.70, 0.60)], as well as results for several WISC subscales that provided little support for an association between pregnancy or childhood $PM_{2.5}$ exposures and cognitive effects. Guxens et al. (2014) reported no decrease in general cognition score in association with $PM_{2.5}$ exposure [β = 0.09 (95% CI: −2.95, 3.12)], although a decrease in psychomotor development was observed [β = −1.64 (95% CI: −3.47, 0.18)]. Lertxundi et al. (2015) reported decrements in motor scale score with increasing $PM_{2.5}$ concentrations but little evidence of an association with mental score on the Bayle Scale of Infant Development (BSID). Results persisted after adjustment for NO_2, and associations were relatively large closer to roads and pollution producing facilities. $PM_{2.5}$ exposures was associated with decreases on tests of attention (continuous performance and stroop) but not with other neurobehavioral tests in the COGNAC study (Saenen et al., 2016).



Circles represent beta coefficients; horizontal lines represent 95% confidence intervals. Red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Concentrations are in μg/m^3. Results are standardized to a 5 μg/m^3 increase in $PM_{2.5}$ concentrations. Corresponding quantitative results are reported in Supplemental Table S8-5 (U.S. EPA, 2018).

BSID = Bayley Scale of Infant Development, FSIQ = Full Scale Intelligence Quotient, GASP = Gene and Environment Prospective Study on Infancy, INMA = Childhood and the Environment Cohort, KBIT−2 = Kaufman Brief Intelligence Test Second Edition, WISC = Wechsler Intelligence Scale for Children.

†Studies published since the 2009 PM ISA.

Figure 8-7 Associations between long-term exposure to $PM_{2.5}$ and cognitive effects. Associations are presented per 5 μg/m^3 increase in pollutant concentration (unless otherwise noted).

Table 8-16 Studies of the association between short-term $PM_{2.5}$ exposure and cognitive effects in children.

Study Location/Years	Study Population	Exposure Assessment	Concentration $\mu g/m^3$	Outcome	Copollutant Examination
†Harris et al. (2015) Eastern Massachusetts $PM_{2.5}$: 2009−2011 Outcome: 1999/02−2011	Project Viva Children (mean = 8 yr) N = 1,109	6 yr avg, LUR with satellite derived AOD	Mean: 11.3 (SD: 1.7)	Verbal IQ Non-verbal IQ Visual motor Design memory Picture memory	Correlations (r): NR Copollutant models: NR
†Guxens et al. (2014) 6 European Cohorts $PM_{2.5}$: 2008−2011 Outcome: 1997−2008	Generation R N = 9,482 Children 1−6 yr	LUR to estimate concentration at residence of birth, back extrapolated through pregnancy	Mean Range: 13.4−22.3	General cognition, language development, global psychomotor development at 1−6 yr of age (test depended on cohort):	Correlations (r): NR Copollutant models: NR
†Porta et al. (2015) Rome, Italy Prospective Cohort $PM_{2.5}$: 2010−2011 Outcome: 2002−2011	GASPII Children 7 yr N = 474	Pregnancy avg and avg from birth to age 7, LUR fit using 40 monitors, assigned at residence, C-V R2 = 0.79	Mean 19.5 (SD: 2.2) IQR 2	WISC III (13 subtests)	Correlations (r): NR Copollutant models: NR
†Lertxundi et al. (2015) Guipuzcoa valleys, Spain 2006−2008	INMA N = 438	Trimester avg of nearest monitor (van Buuren, 2007)	16.98 (SD: 6.57)	BSID at 13−18 mo	Correlations (r): r = 0.045 NO_2 Copollutant correlations: NR

Table 8-16 (Continued): Studies of the association between short-term $PM_{2.5}$ exposure and cognitive effects in children.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†Saenen et al. (2016) Flanders, Belgium $PM_{2.5}$: 2011−2013	COGNAC Children	Daily avg, spatiotemporal model (satellite, land cover and monitor data), at school and at residential address, lags 0−2 days R2 = 0.8	Median 15.7 IQR 1.16 at home	Attention: continuous performance, Stroop Memory: digit span forward, digit span backward Visual processing speed: digit symbol, pattern comparison	Correlations (r): NR Copollutant models: NR

BC = Black Carbon; BSID = Bayley Scale of Infant Development; COGNAC = Cognition and Air Pollution in Children study; GASP = Gene and Environment Prospective Study on Infancy; INMA = Childhood and the Environment Cohort; NR = Not Reported; WISC = Wechsler Intelligence Scale for Children.

†Studies published since the 2009 PM ISA.

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8.2.7.2 Autism

Autism is a condition that includes a spectrum of impairments affecting social interaction, language development, and communication skills that often involves rigid and repetitive behaviors.

Epidemiologic Studies

At present, there is a European pooled cohort study that examined autistic traits and multiple U.S.-based case-control studies that examine ASD in association with $PM_{2.5}$ exposure during pregnancy. Guxens et al. (2015) observed no associations between $PM_{2.5}$ during pregnancy and either borderline clinical or clinical autistic traits using information from cohort studies across four European countries. Of the case-control studies examining ASD, two used monitors to assign $PM_{2.5}$ exposures (Becerra et al., 2013; Volk et al., 2013), while the others used LUR methods to assign exposure (Raz et al., 2015; Talbott et al., 2015). Positive associations were observed between $PM_{2.5}$ exposures and ASD in studies that used both monitors and LUR models to assign exposure and for various exposure periods used in different studies. Volk et al. (2013), Talbott et al. (2015), and Raz et al. (2015) observed positive associations similar in magnitude for both entire pregnancy exposure and first year of life exposure. Specifically, Volk et al. (2013) observed positive associations for both entire pregnancy exposure (OR range: 1.52, 95% CI: 1.46, 1.59) and first year of life exposure (OR: 1.54, 95% CI: 1.24, 1.92) in a California population. In a six-county region of southwestern Pennsylvania, Talbott et al. (2015) observed positive associations with $PM_{2.5}$ exposure during pregnancy (OR: 1.38, 95% CI: 0.80, 2.36]) and first year of life (OR: 1.74, 95% CI: 0.91, 3.30), as well as cumulative exposures from three months pre-conception through first year of life (OR: 1.97, 95% CI: 0.97, 4.04). Raz et al. (2015) reported a positive OR for ASD with entire pregnancy exposure, after adjusting for exposures nine months before and after pregnancy (OR: 1.74, 95% CI: 1.08, 2.47). In Los Angeles, Becerra et al. (2013) reported a positive OR for ASD with entire pregnancy exposure (OR: 1.07, 95% CI: 1.00, 1.16), though the magnitude was lower than that observed in the other studies. Building on the positive associations observed by Volk et al. (2013), follow-up studies provide some initial evidence for gene-environment interactions with $PM_{2.5}$ concentrations and MET receptor variants (Volk et al., 2014) but not for copy number variation (Kim et al., 2017). Interpretation of these results is limited by the lack of control for potential confounding by copollutants, the small number of studies, and uncertainty regarding critical exposure windows (Table 8-17).

Table 8-17 Studies of the association of long-term exposure to $PM_{2.5}$ and Autism Spectrum Disorders.

Study Location/Years	Study Population	Exposure Assessment	Concentration $\mu g/m^3$	Outcome	Copollutant Examination
†Guxens et al. (2015) Cross-sectional $PM_{2.5}$: 2008−2011 with back extrapolation	ESCAPE Mother child pairs, n = 8,079	LUR to estimate $PM_{2.5}$ at birth residence (pregnancy period)	NR	Autistic traits using A-TAC	Correlations (r): NR Copollutant models: NR
†Volk et al. (2013) Population based case-control California (state-wide) 1997-2008	CHARGE n = 279 cases, n = 245 controls 24−60 mo old	IDW of 4 closest monitors within 50 km	NR	Evaluation in person using ADOS and parent administered ADI-R	Correlations (r): PM_{10} r = 0.84, Ozone r = 0.26, NO_2 = 0.64 Copollutant models: NR
†Becerra et al. (2013) Case control Los Angeles, CA Births: 1995-2006 AD diagnosis: 1998-2009	N = 7,603 cases (10 controls per case) 3−5 yr	Nearest ambient monitor and LUR, concentration during pregnancy linked to residence at birth	Mean: 19.6	Primary diagnosis of AD (DSM IV-R)	Correlations (r): CO r = 0.6, NO r = 0.58, Ozone r = −0.47, PM_{10} r = 0.58 Copollutant models: NR
†Raz et al. (2015) Nested case control 50 states, US	NHS n = 245 cases, n = 1,522 controls	Spatiotemporal model (Yanosky et al., 2009) to estimate exposure at residence before, during and after pregnancy.	NR	Self-report on telephone interview to ascertain autistic disorder using parent administered ADI-R; SRS for 90% of eligible cases	Correlations (r): NR Copollutant models: NR

Table 8-17 (Continued): Studies of the association of long-term exposure to $PM_{2.5}$ and Autism Spectrum Disorders.

Study Location/Years	Study Population	Exposure Assessment	Concentration $\mu g/m^3$	Outcome	Copollutant Examination
†Talbott et al. (2015) Case-control S.W. Pennsylvania 2005−2009	Mother, infant pairs, n = 217 cases and 226 controls	LUR to estimate exposure at residence 3 mo prior and 2 yr after birth	14.1 (pre-pregnancy through age 2)	Score ≥15 on SCQ, documentation including ADOS or diagnosis from psychologist	Correlations (r): NR Copollutant models: NR

AD = Autism Disorder, ADI-R = Autism Diagnostic Interview-Revised, A-TAC = Autism—Tics, Attention Deficit and Hyperactivity Disorders, and Other Comorbidities, ADOS = Autism Diagnostic Observation Schedule, CHARGE=Childhood autism risks from Genetics and the Environment Study, DSM IV-R, Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision, ESCAPE = European Study of Cohorts for Air Pollution Effects, IDW = inverse distance weighting, LUR = land use regression, N, n = number of subjects, NHS II = Nurses' Health Study II, NR = not reported, SCQ = Social Communication Questionnaire, SRS = Social Responsiveness Scale.

†Studies published since the 2009 PM ISA.

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Animal Toxicological Studies

Klocke et al. (2017) examined the effects of prenatal exposure (GD0.5 to GD16.5) to $PM_{2.5}$ CAPs in Sterling Forest, NY using B6C3F1 mice (Table 8-18). At postnatal day (PND) 11−15, both male and female offspring had increased microglial activation, an indicator of inflammation, in the corpus callosum ($p < 0.05$). Males had decreased total number of microglia ($p < 0.05$) and females trended in this direction (not significant) but had increased iron deposition in the corpus callosum ($p < 0.05$). In the hippocampus, female offspring had increases in activated microglia ($p < 0.01$) with no change in number of microglia; the male hippocampal microglia were not affected. In addition, both male and female offspring had ventriculomegaly, increased corpus callosum area and hypermyelination, and reduced hippocampal area ($p < 0.05$). Frontal cortex thickness was not affected by CAPs exposure. Various human neuropathologies are associated with ventriculomegaly including schizophrenia, ASD, and ADHD.

Table 8-18 Study-specific details from an animal toxicological study of long-term exposure and neurodevelopmental effects.

Study	Study Population	Exposure Details	Endpoints Examined
Klocke et al. (2017)	Male and female B6C3F1 mice (8−10 weeks old) were mated and then dams were exposed to Sterling Forest, NY CAPs.	Prenatal exposure to filtered air or Sterling Forest $PM_{2.5}$ CAPs for 6h/day during gestation (GD0.5 to GD 16.5). Mean CAPs concentration over the exposure period averaged 92.7 ± 19.2 (mean ± SD) μg/m^3 compared to 3.5 ± 0.9 μg/m^3 for FA controls. CAPs exposure levels ranged from 32.95 to 184.43 μg/m^3 over the duration of the exposure period. PM was a mixture of $PM_{2.5}$ and UFP	Offspring neuropathological outcomes including brain structure and size (ventriculomegaly), microglial activation (inflammation), myelination, corpus callosum iron content in association with myelination.

CAPs = concentrated ambient particles; FA = filtered air; GD = gestational day.

8.2.8 Components and Sources of $PM_{2.5}$

No studies relevant to our understanding of the effect of long-term exposure to components or sources of $PM_{2.5}$ were evaluated in the 2009 PM ISA (U.S. EPA, 2009). Currently, there are several studies of traffic exposures among children as well as a study of adults available for consideration (Table 8-18). These studies examine cognitive effects in the populations studied. Overall, the evidence

base remains limited and the few available studies do not provide evidence to support an independent effect of sources or components of $PM_{2.5}$ that is distinct from the effect long-term exposure to $PM_{2.5}$ mass.

Basagaña et al. (2016) conducted an analysis of the data previously examined by Sunyer et al. (2015) and described in Section 8.6.6. In this longitudinal repeated measures study, the authors report lower growth in memory and attentiveness in association with metrics for traffic-related $PM_{2.5}$ derived using constrained positive matrix factorization (PMF) based on 33 chemical species. Chen et al. (2016) conducted a repeated measures analysis of the association of long-term $PM_{2.5}$ and BC exposure with measures of attention, memory and processing in children. Long-term exposure to $PM_{2.5}$ was associated with decreased performance on measure of attention, while little evidence of associations with BC was provided by the study. Finally, the cross-sectional analysis of Project Viva participants reported by Harris et al. (2015) did not show an association between BC and cognitive effects. Among adults, Tonne et al. (2014) used a set of tests designed to measure reasoning, memory, semantic fluency, and phonemic fluency to examine the association with long-term exposure to $PM_{2.5}$ from traffic, estimated using a dispersion model. $PM_{2.5}$ from traffic was exhibited a similar pattern of association with cognition as with $PM_{2.5}$ mass.

Table 8-19 Characteristics of the studies examining the association between long-term exposure to $PM_{2.5}$ sources and components and cognitive function.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†Harris et al. (2015) Eastern Massachusetts BC: 2009−2011 Outcome: 1999/02−2011	Project Viva Children (mean = 8 yr) N = 1,109	6 yr avg, LUR with satellite derived AOD	Mean: 0.56 (SD: 0.16)	Verbal IQ Non-verbal IQ Visual motor Design memory Picture memory	Correlations (r): NR Copollutant models: NR
†Basagaña et al. (2016) Barcelona, Spain Jan 2012-Mar 2013	N = 2,618 School Children, Barcelona	Source specific $PM_{2.5}$ using source apportionment assigned to the school: mineral, traffic, organic/textile/chalk, secondary sulfate and organics, secondary nitrate, road dust, metallurgy, sea spray, heavy oil combustion	Median $PM_{2.5}$ outdoors 28 Median $PM_{2.5}$ indoors 36	Working memory Superior working memory Inattentiveness	Correlations (r): NR Copollutant models: NR
†Saenen et al. (2016) Flanders, Belgium 2011-2013	COGNAC Children	Annual avg BC prior to testing, spatiotemporal model (satellite, land cover and monitor data) C-V R2 = 0.8	Median 1.54 IQR 0.20	Stroop (selective attention), Continuous performance (sustained attention), Digit Span Forward and Backward (short-term memory), Digit Symbol and Pattern Comparison (visual processing)	Correlations (r): NR Copollutant models: NR

Table 8-19 (Continued): Characteristics of the studies examining the association between long-term exposure to $PM_{2.5}$ sources and components and cognitive function.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†Tonne et al. (2014) Greater London Longitudinal Cohort $PM_{2.5}$ (exhaust) 2003−2009 Outcome: 2007/2009	Whitehall II (mean 66 yr) N = 2,867	1 yr avg, 1 yr lag 4, 3 yr avg, 5 yr avg, dispersion model, *r* = 0.74 (2008, 15 monitors)	5 yr avg 0.64 IQR: 1.1	Cognitive test performance 5 yr decline	Correlations (r): NR Copollutant models: NR

AOD = Aerosol Optical Depth, BC = Black Carbon; COGNAC = Cognition and Air Pollution in Children study; C-V = Cross-Validation; IQR = Inter-quartile Range; LUR = Land Use Regression; NR = Not Reported; TRAP = Traffic Related Air Pollution.

†Studies published since the 2009 PM ISA.

8.2.9 Summary and Causality Determination

The evidence that long-term exposure to $PM_{2.5}$ can affect the nervous system has grown substantially since the 2009 PM ISA (U.S. EPA, 2009). There is evidence from animal toxicological studies demonstrating a link between long-term $PM_{2.5}$ exposure-mediated activation of the SNS and downstream cardiovascular effects. In addition, evidence for neuroinflammation and downstream consequences is well substantiated and coherent across experimental animal and epidemiologic studies. Specifically, toxicological studies in adult animals demonstrate neuroinflammation, neurodegeneration, indicators of Alzheimer's disease, impaired learning and memory, and altered behavior. High quality epidemiologic studies provide support, reporting changes in brain morphology (i.e., neurodegeneration), cognitive decrements and dementia in adult populations. The evidence characterizing the relationship between long-term exposure to $PM_{2.5}$ and effects on the nervous system is detailed below (Table 8-20), using the framework for causality determination described in the Preamble to the ISAs (U.S. EPA, 2015).

Animal toxicological studies of long-term $PM_{2.5}$ exposure provide evidence that the central nervous system mediates responses outside of the brain, i.e., peripheral responses. One study linked hypertension to an increase in sympathetic tone (Ying et al., 2014). Another study in a mouse model of diabetes linked exaggeration of the diabetic phenotype to hypothalamic inflammation (Liu et al., 2014). A relationship between hypothalamic inflammation and sympathetic tone was proposed (Ying et al., 2014).

Long-term exposure of adult animals resulted in inflammation and neurodegeneration in specific regions of the brain including the hippocampus (Fonken et al., 2011). Changes in the hippocampus were accompanied by impaired learning and memory and by altered behavior (Fonken et al., 2011). Long-term exposure to $PM_{2.5}$ was associated with accelerated global cognitive decline in longitudinal analysis of women enrolled in WHIMS (Cacciottolo et al., 2017). This decline was larger among those with APOE alleles thought to confer an increased risk of Alzheimer's disease. Further, morphologic changes (i.e., reduction in total WM, subcortical WM and cortical GM) compatible with these observations of cognitive decline were also observed in this cohort (Casanova et al., 2016; Chen et al., 2015). In a cross-sectional analysis of the Framingham Heart Offspring study Wilker et al. (2015) reported that total cerebral brain volume was smaller with increasing $PM_{2.5}$. Decrements on cognitive tests were observed in longitudinal analyses of the NHS and in the British Whitehall II cohort (Tonne et al., 2014; Weuve et al., 2012). Wilker et al. (2015) and Weuve et al. (2012) are notable in that they controlled for a wide range of covariates including SES and vascular factors. None of these studies considered copollutant confounding, however. Cross-sectional analyses were less consistent in their observation of associations between long-term $PM_{2.5}$ exposure and cognitive function. Specifically, cognitive impairment was not associated with long-term $PM_{2.5}$ exposure in the REGARDS (Loop et al., 2013) or SALIA cohorts (Schikowski et al., 2015) while positive associations were reported in U.S. surveys (Tzivian et al., 2016; Ailshire and

Crimmins, 2014) and in an analysis of clinical trial participants from southern California (Gatto et al., 2014).

Evidence for a relationship between long-term $PM_{2.5}$ exposure and Alzheimer's disease and dementia is provided by both animal toxicological and epidemiologic studies. Early markers of Alzheimer's disease pathology were increased in the temporal cortex of mice exposed to $PM_{2.5}$ CAPs for 9 months, but not 3 months (Bhatt et al., 2015). An association between long-term $PM_{2.5}$ exposure and all-cause dementia was observed among WHIMS participants (Cacciottolo et al., 2017) and with hospitalizations among Medicare recipients for Alzheimer's disease and dementia, which may be related to complications from the disease (Kioumourtzoglou et al., 2015). However, a large registry-based study conducted in China, where exposure levels are high relative to the U.S., reported no evidence of an association with Alzheimer's disease (Jung et al., 2014).

Although an experimental animal study demonstrating loss of dopaminergic neurons in the substantia nigra (Veronesi et al., 2005) provides biological plausibility for an association of long-term $PM_{2.5}$ exposure with Parkinson disease, associations were not consistently observed in epidemiologic studies. Incident case control or longitudinal analyses relying on neurologist confirmed Parkinson disease, provided no evidence of an association with $PM_{2.5}$ (Liu et al., 2016; Palacios et al., 2014). There was some evidence that long-term exposure to $PM_{2.5}$ was associated with hospital admission for Parkinson disease in the aforementioned study of Medicare recipients indicating the potential for long-term exposure to $PM_{2.5}$ to increase the risk of complications that require hospitalization in neurodegenerative disease patients (Kioumourtzoglou et al., 2015).

Several studies of the association of $PM_{2.5}$ exposure during pregnancy or other childhood lifestage with cognitive or motor development in children were conducted. Studies have generally found little evidence of association with cognitive development for entire pregnancy, third trimester or childhood exposures (Harris et al., 2015; Lertxundi et al., 2015; Porta et al., 2015; Guxens et al., 2014). Where decrements on tests of cognition were observed, confidence intervals were wide. Associations with ASD were observed in several epidemiologic studies but the interpretation of these findings was limited by the lack of control for potential confounding by copollutants, the small number of studies, and uncertainty regarding critical exposure windows. Biological plausibility for associations observed of $PM_{2.5}$ with ASD is provided by an animal toxicological study. Klocke et al. (2017) reported inflammatory and morphologic changes in corpus callosum and hippocampus, as well as ventriculomegaly in young animals exposed prenatally to $PM_{2.5}$ CAPs.

The strongest evidence of an effect of long-term exposure to $PM_{2.5}$ on the nervous system is provided by animal toxicological studies that show inflammation, oxidative stress, morphologic changes, and neurodegeneration in multiple brain regions following long-term exposure to $PM_{2.5}$ CAPs. These findings are coherent with a number of epidemiologic studies report consistent associations with cognitive decrements and with all cause dementia. **Overall, the collective evidence is sufficient to conclude that a causal relationship is likely to exist between long-term $PM_{2.5}$ exposure and nervous system effects.**

Table 8-20 Summary of evidence for a likely to be causal relationship between long-term $PM_{2.5}$ exposure and nervous system effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Brain Inflammation and Oxidative Stress			
Consistent evidence from multiple toxicological studies at relevant $PM_{2.5}$ concentrations	Multiple toxicological studies in adult animals demonstrate changes in the hippocampus	†Fonken et al. (2011) †Hogan et al. (2015) †Tyler et al. (2016)	94.4 µg/m^3 94.4 µg/m^3 315.3 µg/m^3
	cerebral cortex	Campbell et al. (2005) †Bhatt et al. (2015)	441.7 µg/m^3 65.7 µg/m^3
	hypothalamus	†Ying et al. (2014) †Ying et al. (2015) †Liu et al. (2014) †Tyler et al. (2016)	107 µg/m^3 128.3 µg/m^3 107 µg/m^3 315.3 µg/m^3
	Inhibition of hypothalamic inflammation blocked metabolic effects.	†Liu et al. (2014)	107 µg/m^3
Activation of the Sympathetic Nervous System			
Limited toxicological evidence at relevant $PM_{2.5}$ concentrations	Inhibition of SNS resulted in decreased blood pressure	†(Ying et al., 2014)	107 µg/m^3
Reduced Cognitive Function and Neurodegeneration Adults			
High quality epidemiologic studies of established cohorts report reductions in brain volume	Evidence from WHIMS and Framingham Offspring report associations with reduced WM volume	†(Chen et al., 2015) †(Casanova et al., 2016) †(Wilker et al., 2015)	12.24 µg/m^3 NR 11.1 µg/m^3
Uncertainty regarding the independent effect of the PM2.5 association	Copollutant model results lacking		
Coherence provided by evidence from toxicological studies at relevant $PM_{2.5}$ concentrations	Toxicological studies demonstrate neurodegenerative changes in substantia nigra or hippocampus	†Veronesi et al. (2005) †Fonken et al. (2011) †(Hogan et al., 2015, pp. author-year)	110 µg/m^3 94.4 µg/m^3 94.4 µg/m^3

Table 8-20 (Continued): Summary of evidence for a likely to be causal relationship between long-term $PM_{2.5}$ exposure and nervous system effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
High quality epidemiologic studies of established cohorts report consistent associations with reduced cognitive function.	Longitudinal analyses of WHIMS, NHS and Whitehall II report associations with cognitive decline.	†Cacciottolo et al. (2017) †Weuve et al. (2012) †Tonne et al. (2014)	12.2 µg/m^3 8.5 µg/m^3 (5 yr avg) 14.9 µg/m^3
Coherence provided by toxicological studies of cognitive effects	Impaired learning and memory demonstrated in mice	†Fonken et al. (2011) †Hogan et al. (2015)	94.4 µg/m^3 94.4 µg/m^3
Inconsistent evidence from studies of neurodegenerative diseases	High quality studies relying on neurologist confirmed PD provided no evidence of an association. Association with all-cause dementia determined by physician adjudication observed in WHIMS but not in registry based follow-up study of Alzheimer's disease in China.	†Liu et al. (2016) †Palacios et al. (2014) †Cacciottolo et al. (2017) †Jung et al. (2014)	4.4−26.9 µg/m^3 NR 12.2 µg/m^3 34.4 µg/m^3
Neurodevelopmental Effects in Children			
Evidence from limited number epidemiologic studies of autism generally positive, but with substantial uncertainties remaining	U.S. case-control studies observe positive associations with $PM_{2.5}$ exposures and ASD. European pooled cohort study observed no associations with clinical autistic traits.	Section 8.2.7.2	14.0−19.6 µg/m^3
Uncertainty regarding the independent effect of PM2.5 and the critical window of exposure	Copollutant model results are lacking and the critical expsoure window is not known		
Limited and inconsistent epidemiologic evidence for other neurodevelopmental outcomes	Generally null or inconsistent associations between $PM_{2.5}$ exposures and cognitive assessment scores	Section 8.2.7.1	

Table 8-20 (Continued): Summary of evidence for a likely to be causal relationship between long-term $PM_{2.5}$ exposure and nervous system effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Limited toxicological evidence providing coherence	Neuroinflammation and morphologic changes including ventriculomegaly were demonstrated following prenatal exposure	†Klocke et al. (2017)	92.7 μg/m^3
Biological Plausibility			
Biological plausibility provided by animal toxicological and epidemiologic studies	Pathways involving (1) SNS activation and (2) inflammation leading to morphologic changes in the brain, neurodegeneration and neurodevelopmental effects are demonstrated	Section 8.2.1	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble.

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is characterized.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated (for experimental studies, ≤2 mg/m^3).

†Studies published since the 2009 PM ISA.

8.3 Short-term $PM_{10-2.5}$ Exposure and Nervous System Effects

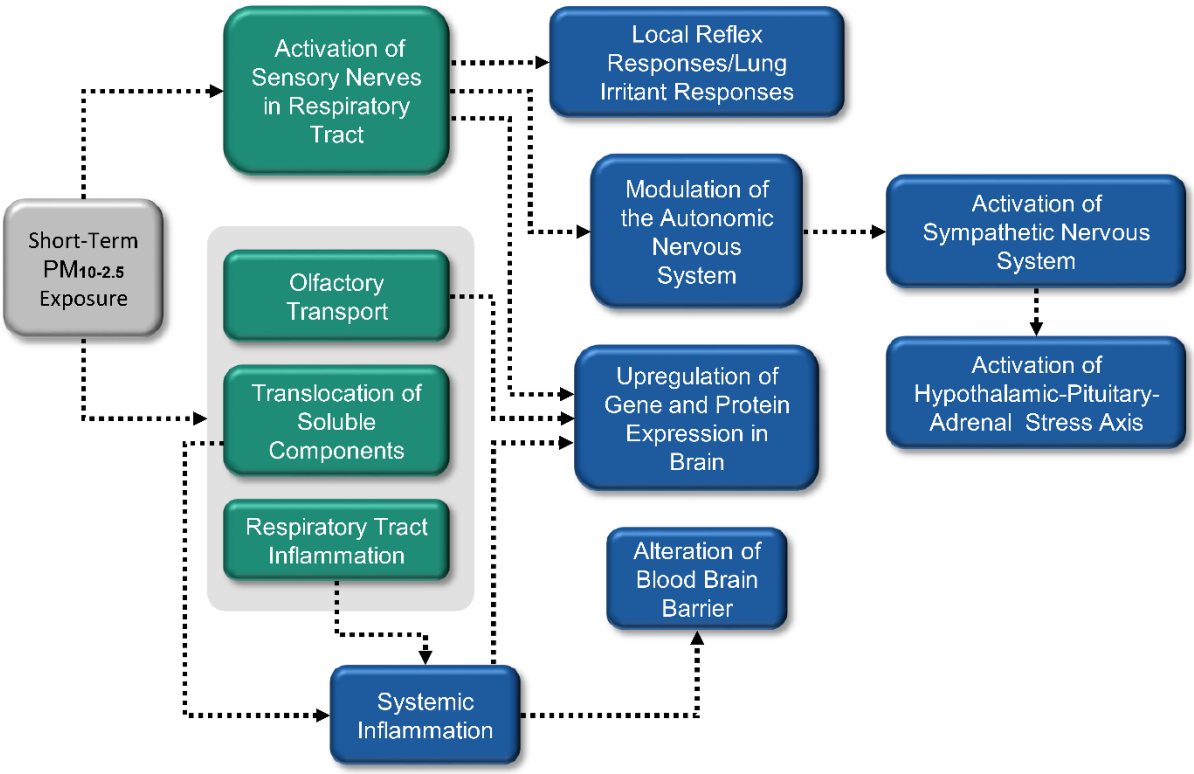
The previous ISA did not report any studies of nervous system effects as a result of short-term exposure to $PM_{10-2.5}$. Although the evidence continues to be limited, there are some recent studies available for review. The discussion opens with a discussion of biological plausibility (Section 8.1.1) that provides background for the subsequent sections in which groups of related endpoints are presented in the context of relevant disease pathways. These outcome groupings are activation of the SNS and HPA stress Axis (Section 8.1.2) and brain inflammation and oxidative stress (Section 8.1.3). The collective body of evidence is integrated[73] across and within scientific disciplines, and the rationale for the causality determination is outlined in Section 8.3.4.

[73] As detailed in the Preface, risk estimates are for a 10 μg/m3 increase in 24-hour avg PM10−2.5 concentrations unless otherwise noted.

8.3.1 Biological Plausibility

This section describes biological pathways that potentially underlie nervous system effects resulting from short-term exposure to $PM_{10-2.5}$. Figure 8-8 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" short-term exposure to $PM_{10-2.5}$ may lead to nervous system effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 8.3.

Once $PM_{10-2.5}$ deposits in the respiratory tract, it may be retained, cleared, or solubilized (see Chapter 4). $PM_{10-2.5}$ and its soluble components may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate ROS and this capacity is termed "oxidative potential". Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see CHAPTER 4). Immune system responses due to the presence of particles in the interstitial space may contribute to health effects. Inflammatory mediators may diffuse from the respiratory tract into the systemic circulation and lead to inflammation in extrapulmonary compartments (Section 6.3.1). Although $PM_{10-2.5}$ is mostly insoluble, it may contain some soluble components such as endotoxin and metals. Soluble components of $PM_{10-2.5}$ may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments. A fraction of $PM_{10-2.5}$ may deposit on the olfactory epithelium. Soluble components of $PM_{10-2.5}$ may be transported via the olfactory nerve to the olfactory bulb of the brain. The extent to which translocation into the systemic circulation or transport to the olfactory bulb occurs is currently uncertain. For further discussion of translocation and olfactory transport, see CHAPTER 4.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 8-8 Potential biological pathways for nervous system effects following short-term $PM_{10-2.5}$ exposure.

Evidence that short-term exposure to $PM_{10-2.5}$ may affect the nervous system generally informs one pathway that begins with activation of sensory nerves in the respiratory tract. This can trigger local reflex responses and transmit signals to regions of the central nervous system that regulate autonomic outflow. Altered autonomic tone may result in effects in other organs (Figure 8-8). Decrements in lung function seen immediately after a 4-hour exposure to $PM_{10-2.5}$ in an animal toxicological study by Amatullah et al. (2012) indicates that activation of sensory nerves in the respiratory tract may have triggered a reflex response in the lung or that modulation of the ANS may have contributed to the observed effects (Section 5.3.6.3). In addition, evidence from a controlled human exposure study supports a link between short-term $PM_{10-2.5}$ exposure and activation of the HPA stress axis (Liu et al., 2017). In this way, the ANS may mediate systemic responses due to exposure to $PM_{10-2.5}$. Currently there are no epidemiologic studies evaluating the relationship between short-term exposure to $PM_{10-2.5}$ and nervous system effects.

An animal toxicological study found upregulation of gene and protein expression in the brain following short-term exposure to $PM_{10–2.5}$ (Ljubimova et al., 2013). Whether this response was due to altered autonomic tone or to systemic inflammation or olfactory transport is uncertain. This study was conducted in rodents, which are obligatory nasal breathers (as opposed to humans who are oro-nasal breathers). Deposition of $PM_{10–2.5}$ in the tracheobronchial or pulmonary regions of the lung of rodents is expected to be minimal. An effect seen in the brain of rodents indicates that $PM_{10–2.5}$, which deposited in the nose, may have activated sensory nerves in the nose. It is also possible that soluble components may have translocated into the systemic circulation or have been transported from the olfactory epithelium in the nose to the olfactory bulb in the brain via the axons of olfactory sensory neurons. Responses seen in the controlled human exposure study by Liu et al. (2017), which also found evidence linking exposure to $PM_{10–2.5}$ to altered blood brain barrier function, may reflect different patterns of deposition in oro-nasal breathers.

Summary of Biological Plausibility

As described here, there is one proposed pathway by which short-term exposure to $PM_{10–2.5}$ may lead to nervous system effects. Stimulation of receptors on sensory nerves, possibly in the nose, may trigger local reflex responses or transmit signals to the regions of the central nervous system that regulate autonomic outflow, resulting in activation of the SNS and the HPA stress axis. Experimental studies in animals and humans contribute all the evidence of upstream and downstream events. This proposed pathway will be used to inform a causality determination, which is discussed later in the chapter (Section 8.3.4).

8.3.2 Activation of the Sympathetic Nervous System and the Hypothalamic-Pituitary-Adrenal (HPA)Stress Axis

A controlled human exposure study examined the effects of a 130 minute exposure to $PM_{10–2.5}$ CAPs on urinary and blood biomarkers associated with neural effects (Liu et al., 2017). Associations between exposure to $PM_{10–2.5}$ CAPs and decreases in biomarkers related to blood brain barrier integrity, including blood S100 calcium-binding protein B and neuron-specific enolase, were observed at 21 hours post-exposure ($p < 0.1$). In addition, exposure to $PM_{10–2.5}$ CAPs was associated with increases in stress-related markers such as urinary vanillylmandelic acid and cortisol at 21 hours post-exposure ($p < 0.05$) and decreases in blood cortisol at 1 and 21 hours post-exposure ($p < 0.05$). Since vanillylmandelic acid is the primary metabolite resulting from breakdown of the stress-related hormones epinephrine and norepinephrine, its presence in urine indicates that exposure to $PM_{10–2.5}$ CAPs led to secretion of epinephrine and/or norepinephrine into the blood by the adrenal medulla subsequent to activation of the HPA stress axis. Increased levels of urinary cortisol, which is secreted into the blood by the adrenal cortex, also indicates that exposure to $PM_{10–2.5}$ CAPs led to activation of the HPA stress axis (Table 8-21).

Table 8-21 Study-specific details from a controlled human exposure study of short-term exposure to $PM_{10-2.5}$ and activation of the sympathetic nervous system (SNS)/hypothalamic-pituitary-adrenal (HPA) stress axis.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Liu et al. (2017) Species: Human Health status: Healthy nonsmokers Sex: 29 females, 26 males Age: 18−60 yr Study design: Single-blind randomized cross-over trial Single-blind randomized cross-over trial	CAPs from Toronto, ON Particle sizes: 2.5−10 μm Control: HEPA filtered ambient air or HEPA-filtered medical air (ultrafine study)	Route: Face mask inhalation Dose/concentration: 212.9 ± 52.0 μg/m^3 Duration of exposure: 130 min Time to analysis: 1 and 21 h	Urinary and blood markers of neural effects

CAPs = concentrated ambient particles; HEPA = high efficiency particulate absorber.

8.3.3 Brain Inflammation and Oxidative Stress

An animal toxicological study examined changes in global gene expression in the brain, as well as expression of Arc and Rac genes and their protein products, in Fischer 344 rats exposed to $PM_{10-2.5}$ CAPs in Riverside, CA for 2 weeks (Ljubimova et al., 2013). No changes in global gene expression were found. However, increased Arc gene expression ($p < 0.05$) and increased Arc immunostaining were observed. In contrast, exposure to $PM_{2.5}$ CAPs and UFP CAPs had no effects on these genes or their protein products (Table 8-22).

Table 8-22 Study-specific details from an animal toxicological study of short-term exposure to $PM_{10-2.5}$ and brain inflammation and oxidative stress.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Ljubimova et al. (2013) Species: Rat Sex: Male Strain: Fisher 344 Age/Weight: 3−7 weeks	CAPs from Riverside, CA (summer) Particle size 3,000 nm Control: Filtered air	Route: Whole body inhalation Dose/Concentration: 58 ± 7 μg/m³ Duration: 5 h/day, 4 days duration: 5 h/day, 4 days/week for 0.5 mo	Brain tissue—Immunohistochemistry Gene expression—mRNA

CAPs = concentrated ambient particles.

8.3.4 Summary and Causality Determination

There were no studies of the effect of $PM_{10-2.5}$ on the nervous system effects in adults or children reviewed in the 2009 PM ISA. The evidence characterizing the relationship between short-term exposure to $PM_{10-2.5}$ and effects on the nervous system is detailed below (Table 8-23), using the framework for causality determination described in the Preamble to the ISAs (U.S. EPA, 2015). The evidence base consists of a limited number of experimental studies without supporting epidemiologic studies. The toxicological study examined the potential for inhalation of $PM_{10-2.5}$ to affect the nervous system and found altered gene expression in the brain (Ljubimova et al., 2013). The controlled human exposure study indicated activation of the HPA stress axis in relation to short-term exposure to $PM_{10-2.5}$(Liu et al., 2017). **Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between short-term $PM_{10-2.5}$ exposure and nervous system effects.**

Table 8-23 Summary of evidence that is inadequate to infer the presence or absence of a causal relationship between short-term $PM_{10-2.5}$ exposure and nervous system effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Limited controlled human exposure study evidence	Changes in levels of metabolite of epinephrine/epinephrine and cortisol in urine indicate HPA stress axis activation	Liu et al. (2017)	212.9 µg/m^3
Lack of epidemiologic evidence	No studies of the association between short-term exposure to PM10-2.5 and nervous system effects reviewed		
Limited biological plausibility	Limited toxicological evidence of altered gene expression in brain	Ljubimova et al. (2013)	58 µg/m^3

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble.

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is characterized.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated (for experimental studies, ≤2 mg/m^3).

HPA = hypothalamic-pituitary-adrenal; SNS = sympathetic nervous system.

8.4 Long-term $PM_{10-2.5}$ Exposure and Nervous System Effects

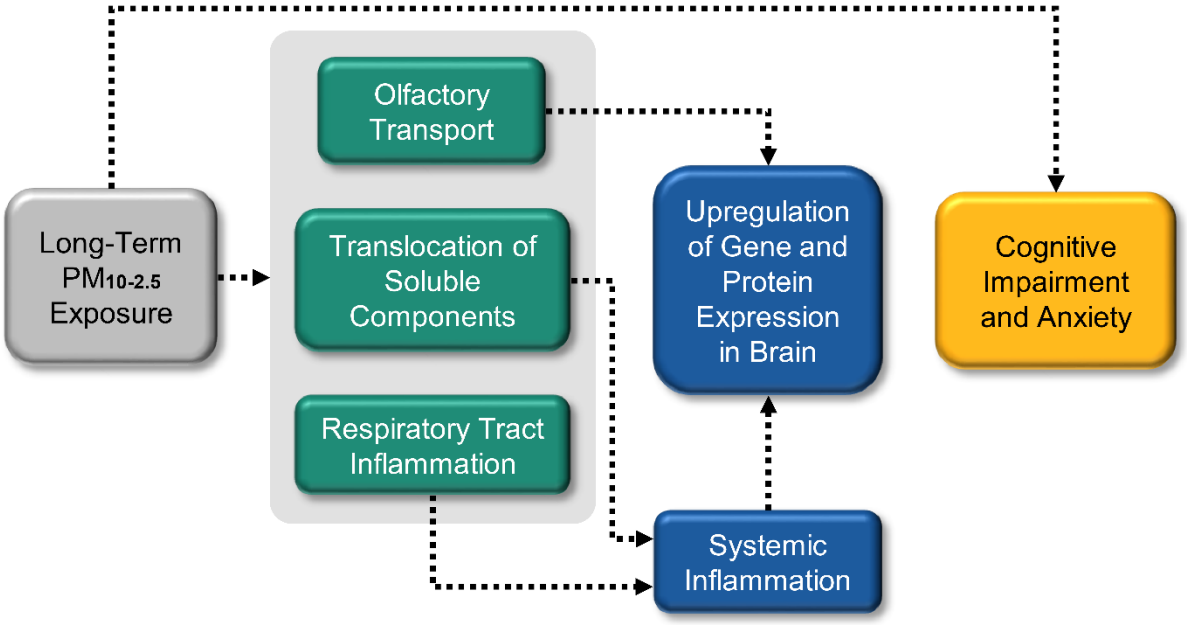
The previous ISA did not report any studies of nervous system effects as a result of long-term exposure to $PM_{10-2.5}$. There are some recent studies available for review. The discussion opens with a discussion of biological plausibility (Section 8.1.1) that provides background for the subsequent sections in which groups of related endpoints are presented in the context of relevant disease pathways. These outcome groupings are brain inflammation and oxidative stress (Section 8.4.2), cognitive and behavioral effects in adults (Section 8.4.3), and neurodevelopmental effects (Section 8.4.4). Finally, the collective body of evidence is integrated[74] across and within scientific disciplines, and the rationale for the causality determination is outlined in Section 8.1.6.

[74] As detailed in the Preface, risk estimates are for a 5 µg/m3 increase in annual PM10−2.5 concentrations unless otherwise noted.

8.4.1 Biological Plausibility

This section describes biological events that potentially underlie nervous system effects resulting from long-term exposure to $PM_{10-2.5}$. Figure 8-9 graphically depicts the continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" long-term exposure to $PM_{10-2.5}$ may lead to nervous system effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 8.4.

Once $PM_{10-2.5}$ deposits in the respiratory tract, it may be retained, cleared, or solubilized (see Chapter 4). $PM_{10-2.5}$ and its soluble components may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate ROS and this capacity is termed "oxidative potential". Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see Chapter 4). Immune system responses due to the presence of particles in the interstitial space may contribute to health effects. Inflammatory mediators may diffuse from the respiratory tract into the systemic circulation and lead to inflammation in extrapulmonary compartments (Section 6.4.1). Although $PM_{10-2.5}$ is mostly insoluble, it may contain some soluble components such as endotoxin and metals. Soluble components of $PM_{10-2.5}$ may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments. A fraction of $PM_{10-2.5}$ may deposit on the olfactory epithelium. Soluble components of $PM_{10-2.5}$ may be transported via the olfactory nerve to the olfactory bulb of the brain. The extent to which translocation into the systemic circulation or transport to the olfactory bulb occurs is currently uncertain. For further discussion of translocation and olfactory transport, see Chapter 4.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 8-9 Potential biological pathways for nervous system effects following long-term $PM_{10-2.5}$ exposure.

Evidence that long-term exposure to $PM_{10-2.5}$ may affect the nervous system is very sparse (Figure 8-9). Unlike the case for short-term exposure to $PM_{10-2.5}$, there is a lack of evidence that long-term $PM_{10-2.5}$ exposure results in activation of sensory nerves in the respiratory tract. An animal toxicological study found upregulation of gene and protein expression in the brain following long-term exposure to $PM_{10-2.5}$ (Ljubimova et al., 2013). Whether this response occurred secondarily to systemic inflammation or olfactory transport is uncertain. This study was conducted in rodents, which are obligatory nasal breathers. Deposition of $PM_{10-2.5}$ in the tracheobronchial or pulmonary regions of the lung of rodents is expected to be minimal. An effect seen in the brain of rodents indicates that soluble components of $PM_{10-2.5}$ that was deposited in the nose, may have translocated into the systemic circulation or have been transported from the olfactory epithelium in the nose to the olfactory bulb in the brain via the axons of olfactory sensory neurons. Currently, epidemiologic evidence is limited to studies linking long-term $PM_{10-2.5}$ exposure to impaired cognition and to anxiety. The evidence of upstream events is insufficient to support a pathway that could be used to inform a causality determination, which is discussed later in the chapter (Section 8.4.5).

8.4.2 Brain Inflammation and Oxidative Stress

The previous ISA did not report any studies of nervous system effects as a result of long-term exposure to $PM_{10–2.5}$. The body of evidence continues to be limited (Table 8-24) and consists of an animal toxicological study that examined changes in global gene expression in the brain, as well as expression of Arc and Rac genes and their protein products in Fischer 344 rats exposed to $PM_{10–2.5}$ CAPs from Riverside, CA for 10 months (Ljubimova et al., 2013). No changes in global gene expression were found. However, exposure to $PM_{10–2.5}$ CAPs upregulated Arc at 1 and 3 months and downregulated Arc at 10 months ($p < 0.05$). Expression of Rac1 was increased following 10 months of exposure to $PM_{10–2.5}$ CAPs ($p < 0.01$). Immunostaining for Arc and Rac1 protein following 10-month exposure to $PM_{10–2.5}$ CAPs demonstrated no increases. In contrast, exposure to $PM_{2.5}$ CAPs and UFP CAPs had no effects on these genes or their protein products.

Table 8-24 Study-specific details from an animal toxicological study of long-term exposure to $PM_{10–2.5}$ and brain inflammation and oxidative stress.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Ljubimova et al. (2013) Species: Rat Sex: Male Strain: Fisher 344 Age/Weight: 3−7 weeks	CAPs from Riverside, CA (summer) Particle size: 3,000 nm Control: Filtered air	Route: Whole body inhalation Dose/Concentration: 58 ± 7 μg/m^3 Duration: 5 h/day, 4 days/week for 1, 3, and 10 mo	Brain tissue—Immunohistochemistry Gene expression—mRNA

CAPs = concentrated ambient particles.

8.4.3 Cognitive and Behavioral Effects in Adults

There were no studies examining the association of $PM_{10–2.5}$ with nervous system effects in adults reviewed in the 2009 PM ISA. Although the evidence remains limited, a small number of studies indicate the potential for long-term exposure to $PM_{10–2.5}$ to affect the nervous system of adults (Table 8-24).

The evidence relevant to the effect of long term exposure to $PM_{10–2.5}$ is limited to a small number of epidemiologic studies. Among women enrolled in the NHS, Weuve et al. (2012) reported faster cognitive decline in association with increased $PM_{10–2.5}$ exposure. The magnitude of the change between successive 2−year outcome measurement [−0.018 (95% CI: −0.035, −0.002)] persisted after adjustment for potential confounders (i.e., age, education, physical activity, alcohol consumption.). The correlation between long-term $PM_{2.5}$ and $PM_{10–2.5}$ concentrations was low (spearman correlation 0.20). Notably, the

association with cognitive decline remained after additional adjustment for cardiovascular risk factors and SES. In another analysis of the NHS cohort, Power et al. (2015) observed a small positive association between high anxiety and the annual average concentration of $PM_{10–2.5}$ [OR: 1.03 (95% CI: 0.99, 1.06)]. Associations generally weakened with shorter averaging times in this study. A large imprecise association between long-term exposure to $PM_{10–2.5}$ and mild cognitive impairment (MCI) was observed in a cross-sectional analysis of the HNR study [OR: 1.69 (95% CI: 0.90, 3.18)] (Tzivian et al., 2016). The association was stronger when MCI was defined to identify cases of amnestic MCI (i.e., objective impairment in at least one memory domain).

8.4.4 Neurodevelopmental Effects

There were no studies examining the association of $PM_{10–2.5}$ with neurodevelopmental effects reviewed in the 2009 PM ISA. The limited number of recently available studies do not provide strong evidence of an association (Table 8-25).

In a prospective study of children born in Rome and followed through age 7 when the WISC-III was administered to measure cognitive function, Porta et al. (2015) reported small (relative to the size of the confidence interval), imprecise associations between $PM_{10–2.5}$ and decrement on FSIQ in fully adjusted models [−1.10 (95% CI: −2.80, 0.50)]. A slightly larger decrease was observed on the Performance IQ subtest. Raz et al. (2015) reported little evidence association between PM10-2.5 and ASD in a case control study nested within the NHS cohort [e.g. OR: 1.07 (95%CI: 0.92, 1.24) third trimester exposure, which was the strongest association]. Findings from the Guxens et al. (2014) analysis of six European cohorts did not support a strong association with reduced general cognition or global psychomotor development [Coefficient: 0.59 (95%CI: −0.99, 2.17) and Coefficient: 0.42 (95% CI: −1.28, 0.45), respectively].

Table 8-25 Characteristics of the studies examining the association of long-term $PM_{10-2.5}$ exposures with cognitive function, behavioral and neurodevelopmental effects.

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†(Weuve et al., 2012) 11 US states Longitudinal Cohort $PM_{10-2.5}$: 1988−2007	NHS Women ≥70 yr N = 19,409	1 mo, 1 yr, 2 yr, 5 yr avg prior to baseline assessment. spatio-temporal, at residence (pre−1999 $PM_{2.5}$ estimated from PM_{10} ratio) Yanosky et al. (2008)	5 yr avg: 8.5	TICS Global score	Correlations (r): $PM_{2.5}$ r = 0.1−0.22 depending on metric Copollutant model: NR
†Power et al. (2015) Longitudinal cohort $PM_{10-2.5}$: 1988−2004 Outcome: 2004	NHS N = 7,1271 Mean age 70 yr	Multi-yr, annual avg, 1 mo, 3 mo and 6 mo prior to outcome, spatio-temporal, at residence (pre−1999 $PM_{2.5}$ estimated from PM_{10} ratio) Yanosky et al. (2008)	Mean (SD): 1 mo 7.27 (4.84); 3 mo 7.58 (4.72); 6 mo 6.99 (4.39); 12 mo 7.08 (4.25); 1988−2003 = 9.0 (4.1)	Crown-Crisp phobic anxiety scale score ≥6 (prevalent)	Correlations (r); $PM_{2.5}$ r=0.24 multi-yr avg Copollutant model: NR
†Tzivian et al. (2016) German Ruhr area Cross-sectional $PM_{10-2.5}$: 2008−2009 Outcome: 2006/2008	HNR study N = 4,086 50−80 yr	Annual avg at residential address, LUR, R2 for modelled and measured $PM_{10-2.5}$ = 0.66	Mean 18.39 (SD: 1.05) IQR: 1.4	MCI (Petersen/International Working group on MCI criteria) (Petersen, 2004)	Correlations (r): NR Copollutant models: NR
†(Porta et al., 2015) Rome, Italy Prospective Cohort $PM_{10-2.5}$: 2010−2011 Outcome: 2010−2011	GASPII Children 7 yr N = 474	Avg during pregnancy and from birth through age 7 at residence, LUR, C-V R2 = 0.57	Mean 19.5	WISC III	Correlations (r): NR Copollutant models: NR

Study Location/Years	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutant Examination
†Raz et al. (2015) 14 States, U.S. Nested case-control Births: 1990-2002	NHS n = 245 cases, n = 1522 noncases 1-3 yr	Spatiotemporal model to estimate concentration before, during, after pregnancy, at residence, difference method for $PM_{10-2.5}$ Yanosky et al. (2008)	Mean 9.9	ASD	Correlations (r): NR Copollutant models: NR
†Guxens et al. (2014) Six European cohorts 1997-2008 $PM_{10-2.5}$: 2008-2011 (back extrapolated)	ESCAPE N = 9482, 1-6 yr	LUR to estimated exposure during pregnancy at residence at time of birth,	NR	Cognitive and psychomotor development (BSID, DDST, MCDI, MIDI, MSCA)	Correlations (r): dependent on the cohort Copollutant models: NR

ASD=autism spectrum disorder; BSID=Bayley Scales of Infant Development; DDST=Denver Developmental Screening Test II; GASPII = Italian Cohort of the Environmental Health Risk in European Birth Cohorts; HNRS = Heinz Nixdorf Recall Study; LUR = Land Use Regression; MCDI=McArthur Communicative Development Inventory; MIDI = Minnesota Infant Development Inventory; MSCA= McCarthy Scales of Children's Abilities; MCI = Mild Cognitive Impairment; NHS = Nurses' Health Study; TICS = Telephone interview for Cognitive Status; WISC = Wechsler Intelligence Scale for Children.

†Studies published since the 2009 PM ISA.

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8.4.5 Summary and Causality Determination

There were no studies of the effect of $PM_{10-2.5}$ on the nervous system effects included in the 2009 PM ISA. Several recent epidemiologic studies that report the association of long-term exposure to $PM_{10-2.5}$ with cognitive and behavioral effects in adults but not with neurodevelopmental effects in children, are available for review. The evidence characterizing the relationship between long-term exposure to $PM_{2.5}$ and effects on the nervous system is detailed below (Table 8-25), using the framework for causality determination described in the Preamble to the ISAs (U.S. EPA, 2015).

Although there is a limited number of studies overall, the evidence base includes well-conducted epidemiologic studies reporting associations with impaired cognition and anxiety in longitudinal analyses of women enrolled in the NHS (Power et al., 2015; Weuve et al., 2012). Studies of long-term exposure during pregnancy or childhood were not consistently associated with neurodevelopmental effects. There is uncertainty stemming from exposure assessment methods relying on the difference method to estimate $PM_{10-2.5}$ concentration (Sections 2.4.2) and related uncertainties due to the potentially uncharacterized spatial variation in $PM_{10-2.5}$ (Section 2.5 and Section 3.3.1.1). None of the available studies adjusted for copollutant exposures. An experimental animal study examined the potential for inhalation of $PM_{10-2.5}$ CAPs to affect the nervous system and found altered gene expression in the brain (Ljubimova et al., 2013). **Overall, the evidence is suggestive of, but not sufficient to infer, a causal relationship between long-term $PM_{10-2.5}$ exposure and nervous system effects.**

Table 8-26 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between long-term $PM_{10-2.5}$ exposure and nervous system effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Cognitive and Behavioral Effects			
High quality epidemiologic study shows an association	Accelerated 2-yr decline in cognitive score (TICs) in longitudinal analysis women of NHS Associations with anxiety in NHS and MCI in the HNR study	Weuve et al. (2012) Power et al. (2015) Tzivian et al. (2016)	8.5 µg/m^3 7.08 µg/m^3 18.39 µg/m^3
Uncertainty related to exposure measurement error	Epidemiologic studies use difference method to estimate exposure to $PM_{10-2.5}$	Section 2.4.2 Section 2.5 Section 3.3.1.1	

Table 8-26 (Continued): Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between long-term exposure to $PM_{10-2.5}$ and nervous system effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
	Potentially uncharacterized spatial variation adds additional uncertainty		
Uncertainty related to the independent effect of PM10-2.5	No studies reported copollutant model results.		
Biological Plausibility	Limited toxicological evidence of altered gene expression in brain	Ljubimova et al. (2013)	58 μg/m^3

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble.

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is characterized.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated (for experimental studies, ≤2 mg/m^3).

†Studies published since the 2009 PM ISA.

8.5 Short-term UFP Exposure and Nervous System Effects

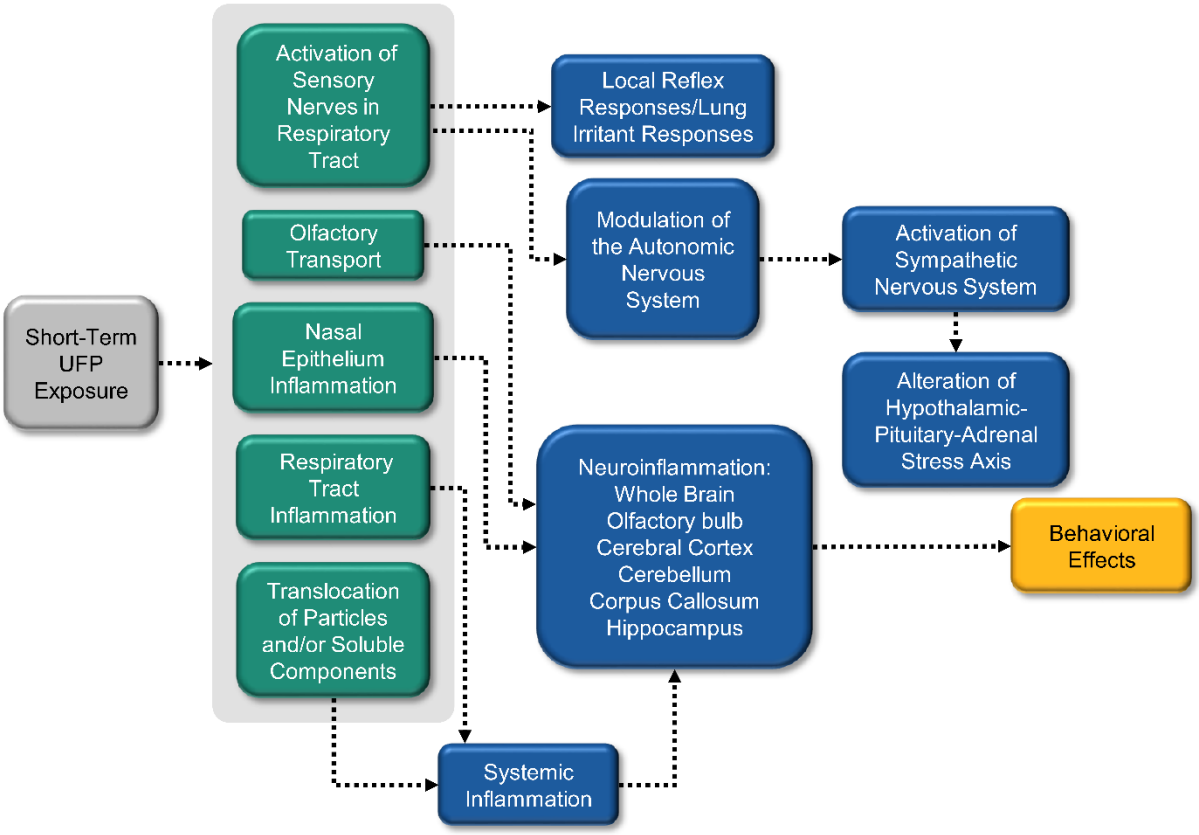
The previous ISA reported limited evidence of a relationship between exposure to ultrafine PM (UFP) and nervous system effects. An experimental study demonstrated that inhalation of UFP CAPs enhanced pro-inflammatory responses in the brains of mice that had been sensitized and challenged with ovalbumin (Campbell et al., 2005). Non-allergic mice were not tested. In addition, experimental studies in rodents previously found that inhaled laboratory-generated UFP can translocate from the olfactory epithelium to the olfactory bulb via the axons of olfactory sensory neurons (Elder et al., 2006; Oberdörster et al., 2004). Furthermore, magnetite UFP (10−150 nm), likely derived from combustion sources, have recently been found in frontal tissue from brains of humans (Maher et al., 2016). These findings suggest that ambient UFP may reach the brain via olfactory transport; however, other routes of translocation have not been ruled out (see Chapter 4).

The discussion of short-term UFP exposure and nervous system effects opens with a discussion of biological plausibility (Section 8.1.1) that provides background for the subsequent sections in which groups of related endpoints are presented in the context of relevant disease pathways. These outcome groupings are activation of the SNS and HPA stress axis (Section 8.5.2), brain inflammation and oxidative stress (Section 8.5.3), cognitive and behavioral effects in adults (Section 8.5.4). Finally, the collective body of evidence is integrated across and within scientific disciplines, and the rationale for the causality determination is outlined in Section 8.1.6.

8.5.1 Biological Plausibility

This section describes biological pathways that potentially underlie nervous system effects resulting from short-term exposure to UFP. Figure 8-10 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" short-term exposure to UFP may lead to nervous system effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 8.5.

Once UFP deposits in the respiratory tract, it may be retained, cleared, or solubilized (see Chapter 4). UFP and its soluble components may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate ROS and this capacity is termed "oxidative potential". Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see Chapter 4). Immune system responses due to the presence of particles in the interstitial space may contribute to health effects. Inflammatory mediators may diffuse from the respiratory tract into the systemic circulation and lead to inflammation in extrapulmonary compartments (Section 6.5.1). UFP and its soluble components may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments. A fraction of UFP may deposit on the olfactory epithelium. UFP and its soluble components may be transported via the olfactory nerve to the olfactory bulb of the brain. The extent to which translocation into the systemic circulation or transport to the olfactory bulb occurs is currently uncertain. For further discussion of translocation and olfactory transport, see Chapter 4.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 8-10 Potential biological pathways for nervous system effects following short-term UFP exposure.

Evidence that short-term exposure to UFP may affect the nervous system generally informs two different pathways (Figure 8-10). The first pathway begins with the activation of sensory nerves in the respiratory tract that can trigger local reflex responses and transmit signals to regions of the central nervous system that regulate autonomic outflow. The second pathway begins with pulmonary inflammation, leading to systemic inflammation and resulting in inflammation in the brain. Inflammation may lead to a worsening of neurodegenerative disease. Evidence for these pathways is described below.

Activation of Sensory Nerves and Modulation of the Autonomic Nervous System (ANS)

With regard to the first pathway, activation of sensory nerves in the respiratory tract may trigger local reflex responses in the lungs or modulate the ANS. Changes in lung function observed in controlled human exposure (Jr et al., 2008) and epidemiologic (McCreanor et al., 2007) (Mirabelli et al., 2015) studies potentially link short-term UFP exposure to the triggering of local reflex responses. However, inflammation (see below) may also play a role in lung function changes observed following short-term UFP exposure.

Evidence for changes in the HPA stress axis is provided by a controlled human exposure study that demonstrated an increase in a marker of the HPA stress axis in association with UFP exposure (Liu et al., 2017). Decreased levels of norepinephrine in the hypothalamus and decreased levels of serum glucocorticoids were observed in an animal toxicological study (Allen et al., 2014b) and indicate that UFP exposure may lead to other perturbations of the SNS and HPA stress axis.

Inflammation

With regard to the second pathway, deposition of UFP in the respiratory tract may lead to pulmonary inflammation (see Section 5.5.1) and to systemic inflammation (see Section 6.5.1), which in turn may lead to inflammation in the brain. Brain inflammation may be due to peripheral immune activation (Fonken et al., 2011) or to systemic circulation of UFP that results in particle uptake in the brain (Ljubimova et al., 2013). Inflammation in the brain may alternatively occur following olfactory transport of poorly soluble particles or their soluble components or to a neuroendocrine stress response resulting from activation of the HPA stress axis (Kodavanti, 2016).

Animal toxicological studies demonstrated neuroinflammation in several brain regions, including olfactory bulb, cerebral cortex, cerebellum, corpus callosum, and hippocampus following short-term UFP exposure (Cheng et al., 2016), (Allen et al., 2014b), (Tyler et al., 2016), (Campbell et al., 2005). Some responses were sex-specific (Allen et al., 2014b). Inflammation, oxidative stress, and apoptotic responses were also observed in nasal epithelium (Cheng et al., 2016). These changes preceded changes measured in olfactory bulb, cerebral cortex, and cerebellum in the same study. Evidence of these time-dependent and region-specific responses indicates that both olfactory transport and systemic inflammation may have played a role in responses to UFP exposure. In addition, paracrine signaling of inflammatory mediators between the nasal epithelium and proximal regions of the brain may have contributed to inflammation. In Tyler et al. (2016), inflammation in the brain occurred in the absence of pulmonary or systemic inflammation, pointing to a direct effect of UFP on the brain. Behavioral effects were found in conjunction with neuroinflammation in one study (Allen et al., 2013).

Summary of Biological Plausibility

As described here, there are two proposed pathways by which short-term exposure to UFP may lead to nervous system effects. The first pathway begins with activation of sensory nerves in the respiratory tract and may lead to triggering of lung reflex responses and modulation of the ANS resulting in increased activity of the SNS and stimulation of the HPA stress axis. In this way, the ANS may mediate systemic responses resulting from UFP exposure. The second proposed pathway begins with pulmonary/systemic inflammation or olfactory transport of UFP and may lead to pro-inflammatory effects in the brain and subsequently to behavioral effects. Animal toxicological and controlled human exposure studies provide the evidence for upstream and downstream events. There are no epidemiologic studies that evaluated the relationship between short-term exposure to UFP and nervous system effects. The proposed pathways will be used to inform a causality determination, which is discussed later in the chapter (Section 8.5.5).

8.5.2 Activation of the Sympathetic Nervous System and the Hypothalamic-Pituitary-Adrenal (HPA) Stress Axis

8.5.2.1 Controlled Human Exposure Study

A controlled human exposure study (Table 8-27) examined the effects of a 130 minute exposure to UFP CAPs on urinary and blood biomarkers associated with neural effects (Liu et al., 2017). An association between exposure to UFP CAPs and an increase in urinary vanillylmandelic acid, a stress-related biomarker, was observed at 1-hour post-exposure ($p < 0.1$). Vanillylmandelic acid is the primary metabolite resulting from the breakdown of the stress hormones epinephrine and norepinephrine. Its presence in urine indicates that exposure to UFP CAPs led to secretion of epinephrine and/or norepinephrine into the blood by the adrenal medulla subsequent to activation of the HPA stress axis.

Table 8-27 Study-specific details from a controlled human exposure study of short-term exposure to UFP and activation of the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) stress axis.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Liu et al. (2017) Species: Human Health status: Healthy nonsmokers Sex: 29 females, 26 male Age: 18−60 yr	CAPs from Toronto, ON Particle sizes: <0.3 μm	Route: Face mask inhalation Dose/concentration: 135.8 ± 67.2 μg/m^3 Particle number count 227,767 ± 63,902	Urinary and blood markers of neural effects

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Study design: Single-blind randomized cross-over trial	Control: HEPA filtered ambient air or HEPA-filtered medical air (ultrafine study)	Duration of exposure: 130 min Time to analysis: 1 and 21 h	

CAPs = concentrated ambient particles; HEPA = high efficiency particulate absorber.

8.5.2.2 Animal Toxicological Study

Allen et al. (2014b) reported changes in neurotransmitters in adult mice exposed for 4 days to UFP CAPs beginning at PND 56 (Table 8-28). Brain tissue was analyzed at 9 months. Neurotransmitters were altered by exposure to CAPs in a sex- and brain region-specific manner. Most notably, exposure resulted in decreased norepinephrine in the hypothalamus of male mice and increased norepinephrine in the midbrain of female mice ($p < 0.05$). Allen et al. (2014b) also examined serum corticosterone levels in male and female mice exposed to UFP CAPS. Blood samples were collected at PND 60 and at about 6 months of age. At both time points, exposure decreased serum corticosterone levels in males ($p < 0.05$), but had no effect in females.

Table 8-28 Study-specific details from an animal toxicological study of short-term exposure to UFP and activation of the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) stress axis.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Allen et al. (2014b) Species: Mouse Sex: male and female Strain: C57BL/6J Age/Weight: Adult exposure at PND 56-60	CAPs collected in Rochester, NY from a "nearby highly trafficked roadway" using the Harvard University Concentrated Ambient Particle System Particle size: ≤100 nm Control: HEPA-filtered room air	Route: Whole body inhalation Dose/Concentration: 67.9 µg/m^3 Particle number: 180,000−200,000 particles/cm^3 Duration: 4 h/day, 4 days Time to analysis: 9 mo of age for brain tissue analysis PND 60 and 6 mo of age for blood collection	Brain tissue—Region specific levels of monoamines, amino acids Blood—corticosterone

CAPs = concentrated ambient particle; HEPA = high efficiency particulate absorber; PND = postnatal day.

8.5.3 Brain Inflammation and Oxidative Stress

Several animal toxicological studies provide evidence for brain inflammation and oxidative stress following short-term exposure to UFP (Table 8-29). Cheng et al. (2016) examined the effects of exposure to UFP on inflammatory and oxidative stress responses in olfactory epithelium, olfactory bulb, cerebral cortex, and cerebellum. Ambient UFP was collected near a freeway in Los Angeles, CA and re-aerosolized in order to expose C57BL/6J mice for 5, 20, and 45 hours over 3 weeks. Increases in oxidative stress markers, 4-hydroxy-2-nonenal and 3-nitrotyrosine, were seen after 5 hours of exposure in olfactory epithelium ($p < 0.05$), but not in the other regions. The number of IBA−1 positive-macrophages, an indicator of injury or inflammation, increased in olfactory epithelial turbinates and in the olfactory bulb after 5 hours of exposure ($p < 0.05$). Exposure for 45 hours resulted in increased oxidative stress markers, decreased levels of olfactory marker protein (expressed by mature olfactory sensory nerves), and increased levels of cleaved caspase and a related protein, PARP1, in nasal epithelium ($p < 0.05$). Caspase and PARP1 are markers of apoptosis. In olfactory bulb, oxidative stress markers were increased after 45 hours of exposure to UFP ($p < 0.05$). TNFα mRNA was increased after 20 hours and protein levels were increased after 45 hours in the nasal epithelium and olfactory bulb ($p < 0.05$). Exposure for 45 hours resulted in increased TNFα mRNA and protein in cerebral cortex and cerebellum ($p < 0.05$). CD88 mRNA was increased in olfactory bulb, as well as in cerebral cortex and cerebellum, after 20 and 45 hours of exposure ($p < 0.05$). This study demonstrated rapid responses to inhaled UFP in olfactory epithelium, and to a lesser extent, in olfactory bulb. Responses to UFP inhalation in cerebral cortex and cerebellum required longer exposures. This delay suggests a role for systemic inflammation, rather than particle translocation, in mediating the effects of UFP in these brain regions. Decreased olfactory marker protein and increased markers of apoptosis suggest an impact of UFP exposure on olfactory sensory neurons.

In addition, Allen et al. (2014b) reported changes in GFAP and IBA−1 in adult mice exposed for 4 days to UFP CAPs beginning on PND 56. Brain tissue was analyzed at 9 months. Exposure to CAPs resulted in microglial activation, measured as IBA−1 immunoreactivity, in the corpus callosum of the male mice ($p < 0.05$). A trend was observed in astrocyte activation, measured as GFAP immunoreactivity, in the cortex of the male mice. Microglial activation is an indicator of inflammation and astrocyte activation is an indicator of injury. No CAPs-related changes in either GFAP or IBA−1 were observed in the corpus callosum or cortex brain regions of female mice. Furthermore, Tyler et al. (2016) also reported changes in inflammatory markers in C67BL/6 and ApoE knockout mice exposed for 6 hours to UFP that were generated from motor vehicle exhaust. Increased mRNA levels for CCL5, CXCL1, TGF-β, and TNF-α in hippocampus of C67BL/6 mice ($p < 0.05$) and increased mRNA levels for IL−1β, IL−6, TGF-β, and TNF-α in hippocampus of ApoE knockout mice ($p < 0.05$) were observed. Minimal inflammatory effects were seen in BALF in either mouse strain although increased uptake of UFP was seen in bronchial macrophages in ApoE knockout mice (see Section 5.6.3). In contrast, exposure to UFP CAPs from Riverside, CA for 2 weeks did not induce any changes in global gene expression in the brain, or expression of Arc and Rac genes and their protein products, in Fischer 344 rats (Ljubimova et al., 2013).

Table 8-29 Study-specific details from animal toxicological studies of short-term exposure to UFP and brain inflammation and oxidative stress.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Allen et al. (2014b) Species: Mouse Sex: male and female Strain: C57BL/6J Age/Weight: Adult exposure at PND 56−60	CAPs collected in Rochester, NY from a "nearby highly trafficked roadway" using the Harvard University Concentrated Ambient Particle System Particle size: ≤100 nm Control: HEPA-filtered room air	Route: Whole body inhalation Dose/Concentration: 67.9 µg/m^3 Particle number: 180,000−200,000 particles/cm^3 Duration: 4 h/day, 4 days Time to analysis: 9 mo of age for brain tissue analysis	Brain tissue—Region specific levels of GFAP, IBA−1
Cheng et al. (2016) Species: Mouse Strain: C57BL/6J Sex: Male Age: 3 mo	Re-aerosolized collected ambient PM near a Los Angeles freeway Particle sizes: Ultrafine PM <180 nm Control: Re-aerosolized extracts of sham filters	Route: whole body inhalation Dose/concentration: 343 µg/m^3 Duration of exposure: 5 h/day, 3 d/week for 5, 20 and 45 h over 3 weeks	Immunohistochemistry of nasal epithelium and brain tissue • Oxidative stress markers • macrophage activation marker Protein expression in brain tissue • Cytokines • Oxidative stress markers
Ljubimova et al. (2013) Species: Rat Sex: Male Strain: Fisher 344 Age/Weight: 3−7 weeks	CAPs from Riverside, CA (summer) Particle size: <150 nm Control: Filtered air	Route: Whole body inhalation Dose/Concentration: 63 ± 8 µg/m^3 Particle number: 65,000 particles/cm^3 Duration: 5 h/day, 4 days/week for 0.5 mo	Brain tissue—Immunohistochemistry Gene expression—mRNA
Tyler et al. (2016) Species: Mouse Strain: C57BL/6 and ApoE knockout Age/Weight: 6−8 weeks	Motor vehicle exhaust (DEE and GEE) passed through a denuder to generate UFP Particle size: 147.1 nm ± 1.3 nm Control: filtered air	Route: Whole body inhalation Dose/Concentration: 371.3 ± 15.6 µg/m^3 Duration: 6 h	Hippocampal tissue: Cytokine gene expression

ApoE = apolipoprotein E; CAPs = concentrated ambient particles; DEE = diesel engine exhaust; GEE = gasoline engine exhaust; GFAP = glial fibrillary acidic protein; PND = postnatal day; IBA−1 = ionized calcium binding adaptor molecule.

8.5.4 Cognitive and Behavioral Effects

8.5.4.1 Epidemiologic Studies

Wang et al. (2014) examined the association of UFP (2-week average concentration) with depressive symptoms among older adults in the MOBILIZE study and reported findings that did support an effect of UFP on increased CESD-R score ≥ [OR=1.04 (95%CI: 0.68,1.57). Uncharacterized temporal and spatial variation in UPF concentration was an uncertainty in this study because PN concentration was measured using one monitor up to 20 km from the participant's residence.

8.5.4.2 Animal Toxicological Studies

In an animal toxicological study, Allen et al. (2013) investigated behavioral effects of short-term exposure to UFP CAPs (Table 8-30). Adult C57BL/6J mice were exposed for 4 days to UFP CAPs beginning at PND 56. Behavioral testing to evaluate responding for delayed reward was carried out. Exposure to UFP CAPs resulted in changes in mean wait time/fixed ratio completion time ($p < 0.05$), one of the behaviors related to delay of reward. Locomotor activity was evaluated and was not altered by exposure to UFP CAPs. Thus, hyperactivity was unlikely to explain the enhanced bias towards immediate rewards. When mice were exposed both postnatally (Section 8.6.5) and as adults, interactions were found for fixed ratio overall rate, fixed ratio completion time, and fixed ratio resets ($p < 0.05$).

Table 8-30 Study-specific details from animal toxicological studies of short-term UFP exposure and cognitive and behavioral effects.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Allen et al. (2013) Species: Mouse Sex: male and female Strain: C57BL/6J Age/Weight: Adult exposure at PND 56−60	CAPs collected in Rochester, NY from a "nearby highly trafficked roadway" using the Harvard University Concentrated Ambient Particle System Particle size: ≤100 nm Control: HEPA-filtered room air	Route: Whole body inhalation Dose/Concentration: Adult exposure mean 67.9 μg/m^3 Particle number: Mean 180,000−200,000 particles/cm^3 Duration: 4 h/day, 4 days Time to analysis: PND 71	Behavioral tests: • Preference for immediate reward • Learning/memory—novel object recognition • Locomotion

CAPs = concentrated ambient particles; HEPA = high efficiency particulate absorber; PND = postnatal day.

8.5.5 Summary and Causality Determination

The 2009 PM ISA reported limited animal toxicological evidence of a relationship between short-term exposure to UFP and nervous system effects, without supporting epidemiologic studies. Several recent experimental studies add to this evidence base. The evidence for the relationship between short-term exposure to UFP and effects on the nervous system is summarized in Table 8-31, using the framework for causality determination described in the Preamble to the ISAs (U.S. EPA, 2015).

Multi-day exposures of adult mice to UFP resulted in oxidative stress, astrocyte and microglial activation, increased cytokine levels, increased markers of apoptosis, and altered neurotransmitter levels in brain-region specific patterns (Cheng et al., 2016), (Allen et al., 2014b), (Tyler et al., 2016), (Campbell et al., 2005). Cheng et al. (2016) demonstrated the time-dependence of oxidative stress and inflammatory responses, with early changes occurring in nasal epithelium and olfactory bulb and later changes occurring in cerebellum and cerebral cortex. This finding suggests that early effects may be due to UFP translocation from nasal olfactory epithelium to olfactory bulb via olfactory sensory nerves, while later effects in more distal regions of the brain may be due to systemic inflammation. Possibly, the close proximity of the nose to the brain may enhance the ability of inflammatory mediators released by nasal epithelium to reach the brain. In addition, a controlled human exposure study links HPA stress axis activation to short-term exposure to UFP (Liu et al., 2017). Animal toxicological studies found decreases in hypothalamic norepinephrine and serum cortisol in males, but not in females, and effects on behavior related to mediating delay of reward (Allen et al., 2014b).

The strongest evidence for a relationship between short-term UFP exposure and nervous system effects is provided by animal toxicological studies that show inflammation and oxidative stress in multiple brain regions following exposure to UFP. There is a lack of evidence from epidemiologic studies because UFP is not typically measured. In addition, a study in humans found evidence for activation of the HPA stress axis in association with UFP exposure. **Overall, the collective evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term UFP exposure and nervous system effects.**

Table 8-31 Summary of evidence for a suggestive of, but not sufficient to infer, a causal relationship between short-term UFP exposure and nervous system effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Brain Inflammation and Oxidative Stress			
Evidence from multiple animal toxicological studies	Inflammation observed in several brain regions. Time-dependent changes in inflammatory and oxidative stress markers in one study	Cheng et al. (2016) Allen et al. (2014b) Tyler et al. (2016)	343 µg/m^3 67.9 µg/m^3 371.3 µg/m^3
Activation of the Hypothalamic-Pituitary-Adrenal Stress Axis			
Limited evidence from a controlled human exposure study Inconsistent evidence from an animal toxicological study	Change in level of metabolite of epinephrine/epinephrine in urine indicates HPA stress axis activation Brain region- and sex-dependent changes in norepinephrine; decreases in serum cortisol in males	Liu et al. (2017) Allen et al. (2014b)	135.8 µg/m^3 67.9 µg/m^3
Cognitive and Behavioral Effects			
Limited evidence from an animal toxicological study	Altered behavior related to mediating delay of reward which is not due to hyperactivity	Allen et al. (2013)	67.9 µg/m^3
Overall			
Lack of evidence from epidemiologic studies	Concentration data are not frequently available	Section 3.5	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble.

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is characterized.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated (for experimental studies, ≤2 mg/m^3).

†Studies published since the 2009 PM ISA.

8.6 Long-term UFP Exposure and Nervous System Effects

The previous ISA reported one study involving long-term exposure to UFP. Subchronic exposure of Apo E knockout mice to UFP CAPs resulted in pro-inflammatory changes in the cortical region of the brain, including activation of cell signaling pathways and upregulation of cytokine genes (Kleinman et al.,

2008). Furthermore, magnetite UFP (10−150 nm), likely derived from combustion sources, have recently been found in frontal tissue from brains of humans (Maher et al., 2016). These findings suggest that ambient UFP may reach the brain via olfactory transport; however other routes of translocation have not been ruled out (see Chapter 4).

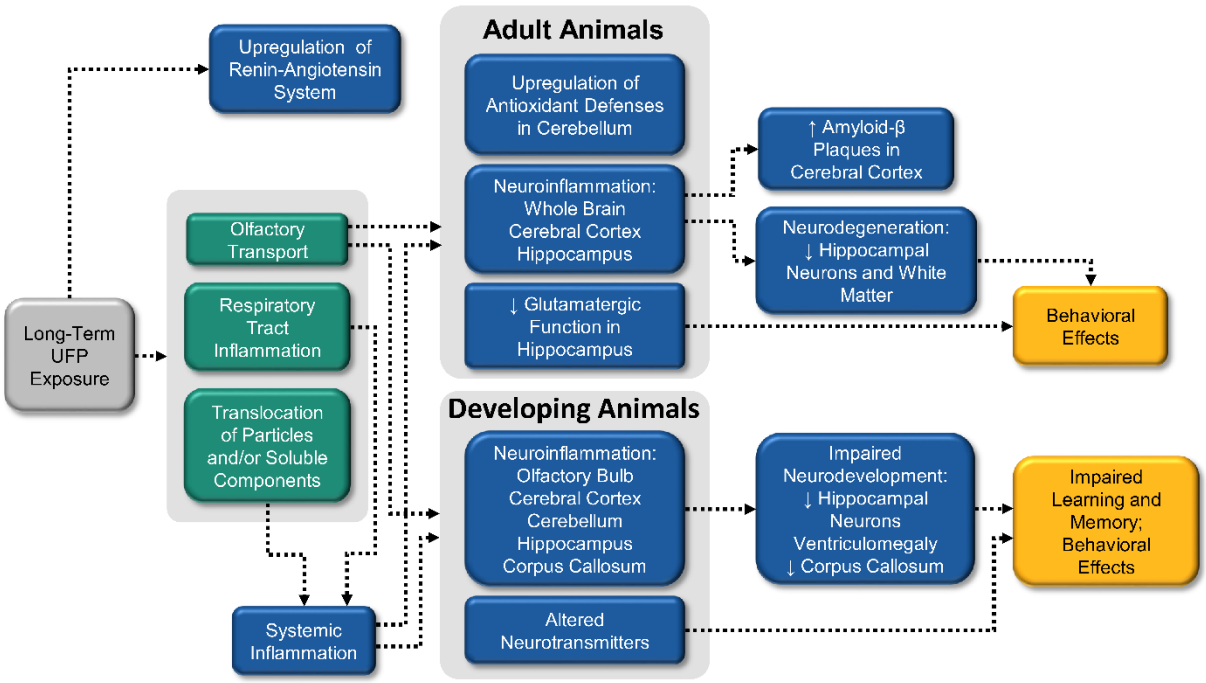
The discussion of long-term UFP exposure and nervous system effects opens with a discussion of biological plausibility (Section 8.1.1) that provides background for the subsequent sections in which groups of related endpoints are presented in the context of relevant disease pathways. These outcome groupings are activation of the SNS and HPA stress axis (Section 8.6.2), brain inflammation and oxidative stress (Section 8.6.3), morphologic changes in the brain (Section 8.6.4), cognitive and behavioral effects (Section 8.6.5) and neurodevelopmental effects (Sections 8.6.6). Finally, the collective body of evidence is integrated across and within scientific disciplines, and the rationale for the causality determination is outlined in Section 8.6.7.

8.6.1 Biological Plausibility

This section describes biological pathways that potentially underlie nervous system effects resulting from long-term exposure to UFP. Figure 8-11 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" long-term exposure to UFP may lead to nervous system effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 8.6.

Once UFP deposits in the respiratory tract, it may be retained, cleared, or solubilized (see Chapter 4). UFP and its soluble components may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate ROS and this capacity is termed "oxidative potential". Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see Chapter 4). Immune system responses due to the presence of particles in the interstitial space may contribute to health effects. Inflammatory mediators may diffuse from the respiratory tract into the systemic circulation and lead to inflammation in extrapulmonary compartments (Section 6.6.1). UFP and its soluble components may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments. A fraction of UFP may deposit on the olfactory epithelium. UFP and its soluble components may be transported via the olfactory nerve to the olfactory bulb of the brain. The extent to which translocation into the systemic circulation or

transport to the olfactory bulb occurs is currently uncertain. For further discussion of translocation and olfactory transport, see Chapter 4.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 8-11 Potential biological pathways for nervous system effects following long-term UFP exposure.

Evidence that long-term exposure to UFP may affect the nervous system generally informs one pathway (Figure 8-11). This pathway begins with pulmonary inflammation and leads to systemic inflammation and to neuroinflammation in both adult and developing animals. Neurodegeneration in adult animals and neurodevelopmental disorders in developing animals may be downstream effects of neuroinflammation and changes in neurotransmitters. Evidence for this pathway is described below.

In addition, there is evidence for two upstream events that support a possible involvement of the RAS and the SNS. Aztatzi-Aguilar et al. (2015) found upregulation of the RAS in the lung and heart in adult animals following long-term exposure to UFP (Section 5.6.3, Section 6.6.4). Allen et al. (2014b)

found increased levels of norepinephrine in the cerebral cortex and decreased levels of serum glucocorticoids in developing animals exposed to UFP postnatally. Given that the changes in RAS were observed in adult animals and the changes in norepinephrine and glucocorticoids were observed in developing animals, the relationship between these events is uncertain.

Inflammation

Deposition of UFP in the respiratory tract may lead to pulmonary inflammation (see Section 5.6.1) and to systemic inflammation (see Section 6.6.1), which in turn may lead to neuroinflammation. Neuroinflammation may be due to peripheral immune activation (Fonken et al., 2011) or to systemic circulation of UFP that results in particle uptake in the brain (Ljubimova et al., 2013). Neuroinflammation may alternatively occur following olfactory transport of poorly soluble particles or their soluble components or to a neuroendocrine stress response resulting from activation of the HPA stress axis (Kodavanti, 2016).

In adult animals, inflammatory responses were seen in whole brain, cerebral cortex, and hippocampus following long-term UFP exposure (Kleinman et al., 2008), (Morgan et al., 2011), (Cacciottolo et al., 2017), and (Tyler et al., 2016). Inflammation was accompanied by upregulation of antioxidant defense enzymes in the cerebellum (Zhang et al., 2012) and decreased markers of glutamatergic function in the hippocampus (Woodward et al., 2017). Neurodegeneration was demonstrated in the hippocampus, as indicated by decreased neurite area and decreased white matter (Woodward et al., 2017) (Cacciottolo et al., 2017). The antioxidant response, the glutamatergic response, and the neurodegeneration response were age-dependent effects that were observed in young adult rodents but not in middle-aged ones. In addition, increased amyloid-β plaques and other markers of Alzheimer's disease were seen in cerebral cortex following exposure to UFP (Cacciottolo et al., 2017). This response was dependent on the presence of several APOE alleles that are known to confer susceptibility to Alzheimer's disease. Neurodegeneration and changes in glutamatergic function occurred in conjunction with behavioral effects in adult mice exposed to UFP (Cacciottolo et al., 2017).

Neuroinflammation was also seen in developing animals exposed to UFP during the postnatal period (Allen et al., 2014a). Brain regions affected included the olfactory bulb, cerebral cortex, cerebellum, and corpus callosum. These changes occurred early after exposure and were persistent, especially in males. Morphologic changes, including ventriculomegaly, reduction in corpus callosum size, and hypomyelination of the corpus callosum were observed, especially in males (Allen et al., 2014a) (Allen et al., 2015). Postnatally-exposed rodents exhibited changes in neurotransmitters that were specific to brain region and sex (Allen et al., 2014a). Impaired learning and memory and behavioral effects were observed in developing mice exposed to UFP postnatally (Allen et al., 2014b), (Allen et al., 2013) and prenatally (Davis et al., 2013). Alterations in morphology and neurotransmitters may contribute to the observed changes in learning, memory, and behavior.

Summary of Biological Plausibility

There is one proposed pathway by which long-term UFP exposure may lead to nervous system effects. It begins with pulmonary inflammation/systemic inflammation or olfactory transport of UFP and leads to neuroinflammation. In adult animals, neuroinflammation may lead to neurodegeneration and the development of Alzheimer's disease, as well as to behavioral effects. In developing animals, neuroinflammation may lead to altered neurodevelopment and neurotransmitters. Both may contribute to impaired learning and memory and to behavioral effects. Animal toxicological and controlled human exposure studies provide the evidence for the upstream and downstream events, and there are no epidemiologic studies that evaluated the relationship between long-term UFP exposure and nervous system effects. This pathway will be used to inform a causality determination, which is discussed later in the chapter (Section 8.6.7).

8.6.2 Activation of the Sympathetic Nervous System and the Hypothalamic-Pituitary-Adrenal (HPA) Stress Axis

In an animal toxicological study, Allen et al. (2014a) investigated changes in neurotransmitters in the brains of weanling mouse pups exposed postnatally to UFP CAPs (Table 8-32). Sex-specific alterations in neurotransmitter levels were observed. In males, glutamate was increased in the hippocampus at PND 14 and 55, dopamine turnover was increased in the midbrain and cortex at PND 14 and 55, and norepinephrine was increased in the cortex at PND 55 ($p < 0.05$). In females, gamma-aminobutyric acid was reduced in the hippocampus, homovanillic acid and dopamine were increased in the midbrain, and serotonin was increased in the hippocampus at PND 14 and 55 ($p < 0.05$). In addition, norepinephrine was increased in the cortex at PND 55 ($p < 0.05$); dopamine turnover was increased in the hippocampus and reduced in the midbrain at PND 14 ($p < 0.05$).

Table 8-32 Study-specific details from an animal toxicological study of long-term exposure to UFP and activation of the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) stress axis.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Allen et al. (2014a) Species: Mouse Sex: male and female Strain: C57BL/6J Age/Weight: weanling Postnatal exposure at PND 4−7, 10−13	CAPs collected in Rochester, NY from a "nearby highly trafficked roadway" using the Harvard University Concentrated Ambient Particle System Particle size: ≤200 nm Control: HEPA-filtered room air	Route: Whole body inhalation Dose/Concentration: Prenatal exposure mean 96.4 μg/m^3 Particle number: 200,000 particles/cm^3 Duration: 4 h/day, 4 days/week Time to analysis: 24 h (PND 14) and 40 days (PND 55) after postnatal exposure or PND 270	Brain tissue—Region-specific neurotransmitter (HPLC) levels

CAPs = concentrated ambient particles; HEPA = high efficiency particulate absorber; HPLC = high performance liquid chromatograph; PND = postnatal day.

8.6.3 Brain Inflammation and Oxidative Stress

Several animal toxicological studies examined inflammatory and oxidative responses in the brains of C67BL/6J mice exposed to re-aerosolized UFP collected near a freeway in Los Angeles, CA. (Table 8-33). Morgan et al. (2011) exposed young mice (3 months) for 10 weeks and examined inflammatory responses in the cerebral cortex and the hippocampus. In the cerebral cortex, increases in mRNA of the innate immune receptor CD14 were observed in addition to increases in mRNA of the microglial marker CD68 and the astrocyte marker GFAP ($p < 0.05$). In the hippocampus, IL−1α and TNFα mRNA were increased ($p < 0.05$). Decreases in protein levels of GluA1, a glutamate receptor, were observed ($p < 0.05$), although levels of GluA2, synaptophysin, and PSD−95 were unchanged in the hippocampus. These findings indicate changes in glutamatergic functions, in addition to microglial and astrocyte activation and increased markers of inflammation.

Similarly, effects of 10-weeks exposure to UFP were studied in both young (3 months) and middle-aged (18 months) C67BL/6J mice (Woodward et al., 2017) (Zhang et al., 2012). In Cacciottolo et al. (2017), microglial activation was assessed by IBA−1 immunostaining and found to be increased in young mice, but not middle-aged mice. These changes were seen in CA1 stratum oriens and DG polymorphic layer areas of the hippocampus ($p < 0.05$) but not in the CA1 stratum radiatum, DG molecular layer, corpus callosum, and alveus. Exposure to UFP decreased by 50% the level of

glutamatergic receptor protein subunit GluA1 and increased by 10−fold TNFα mRNA in the hippocampus of young mice ($p < 0.05$). Other glutamatergic protein subunits were unaffected in young mice. Exposure to UFP had no effect on these parameters in middle-aged mice. However, age alone had an effect, with GluA1 levels decreased by 50% in middle-aged mice compared to young mice ($p < 0.05$). In Zhang et al. (2012), increases in GCLC and GCLM mRNA, as well as protein levels, were found in the cerebellum of young mice (3 months) similarly exposed ($p < 0.05$). Increases in mRNA for NAPDH quinone oxidoreductase and heme oxygenase 1 were also observed ($p < 0.05$). These Phase II regulated detoxifying enzymes are important in defense against oxidative stress. In middle-aged mice (18 months), UFP exposure resulted only in an increase in GCLM mRNA ($p < 0.05$).

Furthermore, Tyler et al. (2016) reported changes in markers related to inflammation in C57BL/6 and ApoE knockout mice exposed to UFP that was generated from motor vehicle exhaust. A 30-day exposure resulted in an increase in mRNA for CCL5 in the hippocampus of C57BL/6 mice and an increase in mRNA for CXCL1, IL−6, and TGF-β in the hippocampus of ApoE knockout mice. Minimal inflammatory effects were seen in BALF, although increased uptake of UFP was seen in bronchial macrophages (see Section 5.6.3). In contrast, exposure to UFP CAPs from Riverside, CA for 2 weeks did not induce any changes in global gene expression in the brain, or expression of Arc and Rac genes and their protein products, in Fischer 344 rats (Ljubimova et al., 2013).

Table 8-33 Study-specific details from animal toxicological studies of long-term exposure to UFP and brain inflammation and oxidative stress.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Ljubimova et al. (2013) Species: Rat Sex: Male Strain: Fisher 344 Age/Weight: 3−7 weeks	CAPs from Riverside, CA (summer) Particle size: <150 nm Control: Filtered air	Route: Whole body inhalation Dose/Concentration: 63 μg/m³ Particle number: 65,000 particles/cm³ Duration: 5 h/day, 4 days/week for 1, 3, and 10 mo	Brain tissue—Immunohistochemistry Gene expression—mRNA
Morgan et al. (2011) Species: Mouse Strain: C57Bl/6J Sex: Male Age: 3 mo	Re-aerosolized collected ambient PM near a freeway Particle sizes: Ultrafine PM <180 nm Control: Re-aerosolized extracts of sham filters	Route: whole body inhalation Dose/concentration: 468 ± 25 μg/m³ 254,000 particles/cm³ Duration of exposure: 5 h/day, 3 days/week for 10 weeks	Expression of hippocampal proteins • GLuA1, GluA2, synaptophysin and PSD95 Glial activation—mRNA of microglial markers CD14 and CD68, astrocyte GFAP cytokines

Table 8-33 (Continued): Study-specific details from animal toxicological studies of long-term exposure to UFP and brain inflammation and oxidative stress.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Cacciottolo et al. (2017) Species: Mouse Strain: C57Bl/6J Sex: Female Age: 3 and 18 mo	Re-aerosolized collected ambient PM near a freeway, mixed with HEPA-filtered air Particle sizes: Ultrafine PM < 180 nm Control: HEPA-filtered air	Route: whole body inhalation Dose/concentration: 468 ± 25 μg/m^3 254,000 particles/cm^3 Duration of exposure: 5 h/day, 3 days/week for 10 weeks	Expression of hippocampal proteins • GLuA1, GluA2, and other synaptic proteins Microglial activation—IBA−1 immunostaining
Tyler et al. (2016) Species: Mouse Strain: C57BL/6 and ApoE knockout Age/Weight: 6−8 weeks	Motor vehicle exhaust (DEE and GEE) passed through a denuder to generate UFP Particle size: 147.1 nm ± 1.3 nm Control: filtered air	Route: Whole body inhalation Dose/Concentration: 371.3 ± 15.6 μg/m^3 Duration: 6 h/day for 30 days	Hippocampal tissue: Cytokine gene expression
Zhang et al. (2012) Species: Mouse Strain: C57BL/6J Sex: Male Age: 3 mo, 18 mo	Re-aerosolized collected ambient PM near a freeway Particle sizes: Ultrafine PM <200 nm Control: Re-aerosolized extracts of sham filters	Route: whole body inhalation Dose/concentration: 300−400 μg/m^3 Duration of exposure: 5 h/day, 3 day/week for 10 weeks	Oxidative stress markers—Cerebellar GCLC, GCLM, heme oxygenase−1, and NADPH quinone oxidoreductase mRNA and protein

ApoE = apolipoprotein E; CAPs = concentrated ambient particles; CD = cluster of differentiation; DEE = diesel engine exhaust; GEE = gasoline engine exhaust; GCLC = glutamate-cysteine ligase catalytic subunit; GCLM = glutamate-cysteine ligase modifier subunit; GFAP = glial fibrillary acidic protein; Glu = glutamate; HEPA = high efficiency particulate absorber; IBA−1 = ionized calcium-binding adapter molecule 1; NADPH = nicotinamide adenine dinucleotide phosphate reduced form; PSD = postsynaptic density protein.

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8.6.4 Morphologic Changes

2 Animal toxicological studies investigated morphologic changes in the brain following long-term
3 UFP exposure (Table 8-34). Effects of a 10-week exposure to UFP collected from a Los Angeles freeway
4 on brain morphology were evaluated in both young (3 months) and middle-aged (18 months) C67BL/6J
5 mice (Cacciottolo et al., 2017). Exposure to UFP decreased neurite area in specific hippocampal regions
6 of young mice (i.e., the stratum oriens and stratum radiatum CA1 regions but not the DG or CA3 regions,
7 $p < 0.05$). No changes in neurite area were seen in the forceps major of the corpus callosum or

hippocampal alveus in young mice or in any of the examined areas in middle-aged mice as a result of UFP exposure. Changes in white matter were assessed by staining for myelin basic protein. Middle-aged mice had decreased myelin basic protein in specific hippocampal regions, (i.e., CA1 stratum oriens and DG polymorphic layer compared with young mice, $p < 0.05$). Exposure to UFP resulted in changes in myelin basic protein in the hippocampal stratum oriens of young mice ($p < 0.05$). No UFP exposure-related changes were seen in middle-aged mice. However, age alone had an effect, with myelin basic protein decreased by 50% in the CA1 striatum oriens and 45% in the DG polymorph layer of the hippocampus of middle-aged mice compared with young mice ($p < 0.05$).

Using the same exposure system, Cacciottolo et al. (2017) examined the effect of UFP exposure and the presence of APOE alleles on the development of pathology related to Alzheimer's disease in mice. In wild type mice, 10-weeks inhalation of UFP resulted in decreased neurite density in the hippocampus at 7 months of age. This involved selective loss of hippocampal CA1 neurons ($p < 0.005$) but not DG neurons. In addition, the density of GluR1 receptor subunits, but not other synaptic proteins involved in hippocampal-based memory, was decreased in the hippocampus of wild type mice ($p < 0.005$). In mice carrying transgenes for human APOE ϵ3 or ϵ4 alleles in combination with five familial AD mutations (EFAD mice), similar changes were observed at 7 months of age following 15-weeks inhalation of UFP ($p < 0.01$). These changes were not dependent on the number of alleles (E3FAD vs E4FAD). However, exposure to UFP resulted in increases in amyloid deposits in the cerebral cortex of E4FAD mice but not E3FAD mice ($p < 0.05$). Similarly, amyloid-β oligomers in soluble extracts of cerebral cortex were increased in E4FAD mice but not E3FAD mice ($p < 0.05$). APOE alleles are known to confer susceptibility to Alzheimer's disease which is characterized by the accumulation of amyloidβ and cognitive effects. APOE ϵ4 confers greater susceptibility to women than men. While EFAD mice are known to accumulate amyloid aggregates at an early age, wild type C67Bl/6J do not develop amyloid aggregates at any age.

Table 8-34 Study-specific details from animal toxicological studies of long-term exposure to UFP and morphologic changes.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Cacciottolo et al. (2017) Strain: C57BL/6J and EFAD mice carrying transgenes for human APOE ϵ3 or ϵ4 alleles in combination with five familial AD mutations Sex: Female Age: 8 weeks	Re-aerosolized collected ambient PM near a freeway Particle sizes: Ultrafine PM <200 nm Control: Re-aerosolized extracts of sham filters	Route: whole body inhalation Dose/concentration: 468 ± 25 μg/m^3 254,000 particles/cm^3 Duration of exposure: 5 h/day, 3 days/week for 15 weeks (transgenic mice) or 10 weeks (wild type mice) Time to analysis: 7 mo of age	Brain tissue—Immunohistochemistry Histochemistry Protein levels Immunoassay
Woodward et al. (2017) Species: Mouse Strain: C57BL/6J Sex: Female Age: 3 and 18 mo	Re-aerosolized collected ambient PM near a freeway, mixed with HEPA-filtered air Particle sizes: Ultrafine PM <180 nm Control: HEPA-filtered air	Route: whole body inhalation Dose/concentration: 342 ± 49 μg/m^3 140,000 particles/cm^3 Duration of exposure: 5 h/day, 3 days/week for 10 weeks	Histochemistry: Hippocampus neurite area and Myelin Basic Protein

AD = Alzheimer's disease; APOE = apolipoprotein E; EFAD = early onset familial Alzheimer disease; HEPA = high efficiency particulate absorber.

8.6.5 Cognitive and Behavioral Effects

An animal toxicological study investigated cognitive and behavioral effects following long-term UFP exposure (Table 8-35). Effects of a 10-week exposure to UFP collected from a Los Angeles freeway were studied in both young (3 months) and middle-aged (18 months) C67BL/6J mice (Cacciottolo et al., 2017). There were no age- or UFP exposure-related changes in short- or long-term memory, as assessed by the novel object recognition test, or in working memory, as assessed by the spontaneous alternation of behavior test. However, UFP exposure decreased exploratory behavior by 30% ($p < 0.01$) in middle-aged mice and activity in both age groups ($p < 0.05$). Middle aged mice also responded to UFP exposure with weight loss ($p < 0.05$) that was reversible upon cessation of exposure and that correlated with changes in locomotor activity ($p < 0.05$).

Table 8-35 Study-specific details from an animal toxicological study of long-term exposure to UFP and cognitive and behavioral effects.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Cacciottolo et al. (2017) Species: Mouse Strain: C57BL/6J Sex: Female Age: 3 and 18 mo	Re-aerosolized collected ambient PM near a freeway, mixed with HEPA-filtered air Particle sizes: Ultrafine PM <180 nm Control: HEPA-filtered air	Route: whole body inhalation Dose/concentration: 468 ± 25 μg/m^3 254,000 particles/cm^3 Duration of exposure: 5 h/day, 3 days/week for 10 weeks	Tests of cognition and activity

HEPA = high efficiency particulate absorber.

8.6.6 Neurodevelopmental Effects

8.6.6.1 Epidemiologic Studies

Sunyer et al. (2015) enrolled students (n = 2,715, 7−10 years old) from 39 schools in Barcelona, Spain in order to study the relationship between cognitive development and traffic related pollutants including UFP (Table 8-36). Schools were selected from high and low pollution areas and matched by school socioeconomic index. The study was longitudinal in design with repeated cognitive testing during an approximately one-year period. The outcomes, validated tests of working memory and attention, were selected because they measure cognitive functions that are typically under development during the lifestages of the children participating (i.e., 7−10 years old). Authors reported a 12 month decrease in both working [−4.9 (95% CI: −10, 0.22) per IQR increase in UFP] and superior working memory [−5 (95% CI: −9.1, −0.96) per IQR Increase in UFP]. A 12 month increase in inattentiveness was also reported [3.9 (0.31, 7.6) per IQR increase in UFP].

Table 8-36 Characteristics of the studies examining the association between long-term exposure to UFP and neurodevelopmental effects.

Study Location/Years	Study Population	Exposure Assessment	Concentration	Outcome	Copollutant Examination
†Sunyer et al. (2015) Barcelona, Spain Jan 2012–March 2013 Longitudinal Cohort	School children 7−10 yr N = 2,715 39 schools	Direct measurement of UFP (10−700 nm) at schools. 2 times during 1-week periods separated by 6 mo to reflect warm and cold seasons	UFP Outdoor: 22,157 particles per cubic cm	Working memory and attention	Copollutant correlations (r): EC outdoors *r* = 0.62 Copollutant model: NR

Mo=month(s); N, n = number of subjects; nm=nanometers; NR=not reported; yr=year(s).

†Studies published since the 2009 PM ISA.

8.6.6.2 Animal Toxicological Studies

Several animal toxicological studies examined the effects of long-term UFP exposure on neurodevelopment (Table 8-37). Davis et al. (2013) measured markers of glutamate receptors, neuronal growth cones, synaptic proteins, kinases, and glial proteins in the hippocampus of young C57BL/6J mice exposed prenatally to UFP collected from a Los Angeles freeway. Dams were exposed to UFP prior to conception, mated with unexposed males, and then exposed to UFP during gestation. Thus, exposure occurred throughout oocyte maturation and gestation. Prenatal exposure to UFP resulted in a decrease in protein levels of JNK1, a protein kinase, in the hippocampus of neonatal offspring ($p \leq 0.05$). Many markers of inflammation and other processes were unchanged. Davis et al. (2013) also investigated internalizing disorders using specific behavioral testing in the offspring. Male offspring exhibited behavioral sequelae, with decreased latency to immobility and increased duration of immobility in the tail-suspension test ($p < 0.05$), a test of propensity for mental health impairment or depression and low resilience to stress; females were refractory to change with these endpoints. Female and male offspring did not display changes in tests of anxiety. Prenatal UFP exposure was associated with changes in internalizing behavior of depression but not anxiety in male offspring; internalizing behavior of female offspring was not affected by prenatal UFP exposure.

Allen et al. (2015); Allen et al. (2014a) investigated the effects of exposure to UFP CAPs in weanling mouse pups during PND 4−7 and PND 10−13. This post-gestational time period, which is considered equivalent to the third trimester in humans, is marked by rapid neuro- and gliogenesis. Mice were sacrificed at PNDs 14, 55, and 270. UFP CAPs exposure altered GFAP immunostaining, an indicator of astrocyte activation, in a sex-specific manner. GFAP immunostaining was reduced in the hippocampus of male mice at PND 14 and in the corpus callosum of male mice at PND 14 and PND 55 ($p < 0.05$). However, GFAP was increased at PND 14 in the amygdala ($p \leq 0.05$). In females, GFAP immunostaining increased in hippocampus, corpus callosum, and anterior commissure on PND 14 ($p < 0.05$), but not on PND 55. UFP CAPs exposure also altered IBA−1 immunostaining, an indicator of glial activation, in a sex-specific manner. In males, IBA−1 immunostaining was increased in the anterior commissure at PND 14 and PND 55, in the hippocampus at PND 55, and in the corpus callosum at PND 270 ($p < 0.05$). No changes were seen in females. Findings of early (astrocyte and microglial) and persistent (microglial) activation, especially in males, suggest that astrocyte and microglial activation may be important mediators of responses to UFP CAPs exposure.

Allen et al. (2014a) and Allen et al. (2015) also examined morphologic changes in the brains of these weanling mouse pups exposed postnatally to UFP CAPs. Ventriculomegaly was observed in PND 14 male ($p \leq 0.05$), but not female mice. This effect in male mice persisted in young adulthood (PND 55) and at PND 270 ($p \leq 0.05$). Ventriculomegaly is related to poor neurodevelopmental outcomes in children, which tend to be higher in males. In addition, exposure to UFP CAPs resulted in a reduction in

the size of the corpus callosum in both sexes at PND 14 ($p \leq 0.05$) and a male-specific decrease in myelination in the corpus callosum at PND 14 ($p \leq 0.05$). Striatal and frontal cortex myelination was unaffected by exposure to UFP CAPs in either sex. Findings of ventriculomegaly, reductions in corpus callosum size, and hypomyelination, especially in males, are consistent with morphologic changes associated with neurodevelopmental disorders such as ASD in humans.

Allen et al. (2013) and Allen et al. (2014b) investigated behavioral effects in male and female mice exposed to UFP CAPs, as described above. Behavioral testing was carried out on PND 71 and animals were sacrificed one month later. Some mice were exposed a second time to UFP CAPs beginning at PND 56 for 4 days. In the first study, Allen et al. (2013) found that postnatal exposure to UFP CAPs resulted in enhanced preference for immediate reward. This was evidenced by changes in fixed ratio overall rate, run rate, inter-response time, fixed ratio resets, and responses per reinforcer ($p < 0.05$). Additionally, interactions were found for fixed ratio overall rate, fixed ratio completion time, and fixed ratio resets ($p < 0.05$) in mice that were exposed both postnatally and as adults. Locomotor activity was evaluated and found to not be altered by exposure to UFP CAPs, indicating that hyperactivity was unlikely to explain the behavioral alterations. In the second study, Allen et al. (2014b) measured initial fixed interval schedule controlled behavior, which is related to preference for immediate reward, and a measure of impulsivity. Novel object recognition, which is an indicator of learning and short-term memory, and locomotor activity were also determined. Postnatal exposure to UFP CAPs resulted in greater impulsivity-linked behavior. In males, postnatal exposure resulted in decreases in overall rate and run rate ($p < 0.05$) while in females, adult exposure resulted in increases in overall rate and run rate ($p < 0.05$). Indices of novel object recognition were decreased by postnatal UFP CAPs exposure in male (change in time with novel object) and female (change in time/approaches to novel object) mice ($p < 0.05$). Interactions resulting from exposure during both the postnatal and adult lifestage were noted for both sets of behavioral tests. Spontaneous locomotor behavior was impaired in both males and females as a result of exposure to UFP CAPs during both lifestages ($p < 0.05$). Furthermore, levels of serum corticosterone and some brain region-specific neurotransmitters were correlated with measures of impulsivity-linked behavior in male mice exposed during the postnatal period and in female mice exposed as adults ($p < 0.05$).

Altogether, these results indicate that prenatal and postnatal exposure to UFP CAPs led to neurotoxic changes which persisted over time. These effects included neuroinflammation, morphologic changes, and behavioral effects.

Table 8-37 Study-specific details from animal toxicological studies of long-term exposure to UFP and neurodevelopmental effects.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Allen et al. (2013) Species: Mouse Sex: male and female Strain: C57BL/6J Age/Weight: weanling Postnatal exposure at PND 4−7, 10−13 Adult exposure at PND 56−60	CAPs collected in Rochester, NY from a "nearby highly trafficked roadway" using the Harvard University Concentrated Ambient Particle System Particle size: ≤200 nm Control: HEPA-filtered room air	Route: Whole body inhalation Dose/Concentration: Prenatal exposure mean 96.4 µg/m^3 Adult exposure mean 67.9 µg/m^3 Particle number: Mean 180,000−200,000 particles/cm^3 Duration: 4 h/day, 4 days/week Time to analysis: 24 h after final exposure-PND 14	Behavioral tests • Preference for immediate reward • Learning/memory—novel object recognition • Locomotion
Allen et al. (2014b) Species: Mouse Sex: male and female Strain: C57BL/6J Age/Weight: weanling Postnatal exposure at PND 4−7, 10−13 Adult exposure at PND 56−60	CAPs collected in Rochester, NY from a "nearby highly trafficked roadway" using the Harvard University Concentrated Ambient Particle System Particle size: ≤200 nm Control: HEPA-filtered room air	Route: Whole body inhalation Dose/Concentration: Prenatal exposure mean 96.4 µg/m^3 Adult exposure mean 67.9 µg/m^3 Particle number: 180,000−200,000 particles/cm^3 Duration: 4 h/day, 4 days/week Time to analysis: PND 71 for behavioral testing 9 mo of age for brain tissue analysis PND 60 and 6 mo of age for blood collection	Behavioral tests Impulsivity—fixed interval schedule-controlled performance Learning/memory—novel object recognition Locomotion Brain tissue—Region specific levels of monoamines, amino acids, GFAP, IBA−1 Blood—corticosterone
Allen et al. (2014a) Species: Mouse Sex: male and female Strain: C57BL/6J Age/Weight: weanling Postnatal exposure at PND 4−7, 10−13	CAPs collected in Rochester, NY from a "nearby highly trafficked roadway" using the Harvard University Concentrated Ambient Particle System Particle size: ≤200 nm Control: HEPA-filtered room air	Route: Whole body inhalation Dose/Concentration: Prenatal exposure mean 96.4 µg/m^3 Particle number: 200,000 particles/cm^3 Duration: 4 h/day, 4 days/week Time to analysis: 24 h (PND14) and 40 days (PND 55) after postnatal exposure or PND 270	Immunostaining—GFAP and IBA−1 Image analysis Brain tissue—Region-specific cytokine (immunoassay) levels
Allen et al. (2015) Species: Mouse Sex: male and female Strain: C57BL/6J Age/Weight: weanling Postnatal exposure at PND 4−7, 10−13	CAPs collected in Rochester, NY from a "nearby highly trafficked roadway" using the Harvard University Concentrated Ambient Particle System Particle size: ≤200 nm Control: HEPA-filtered room air	Route: Whole body inhalation Dose/Concentration: Mean 96 µg/m^3 Particle number: 200,000 particles/cm^3 Duration: 4 h/day, 4 days/week Time to Analysis: PNDs 14, 55, 270	Immunostaining—brain tissue Image analysis—brain tissue

Table 8-37 (Continued): Study-specific details from animal toxicological studies of long-term exposure to UFP and neurodevelopmental effects.

Study/Study Population	Pollutant	Exposure Details	Endpoints Examined
Davis et al. (2013) Species: Mouse Strain: C57BL/6J Sex: Female Age: 3 mo	Re-aerosolized collected ambient PM near a freeway Particle Sizes: Ultrafine PM <180 nm, Control: Re-aerosolized extracts of sham filters	Route: whole body inhalation Dose/Concentration: 350 μg/m^3 Duration of exposure: 5 h/day, 3 day/week for 7 weeks before conception and through gestation up to 2 days before birth Time to analysis: PND 3 for brain tissue 8 mo for behavioral testing	Expression of hippocampal proteins • markers of glutamate receptors, neuronal growth cones, synaptic proteins, kinases and glial proteins Behavioral testing • tail suspension test Preliminary physical assessment

CAPs = concentrated ambient particles; GFAP = glial fibrillary acidic protein; IBA−1 = ionized calcium binding adaptor molecule 1; HEPA = high efficiency particulate absorber; PND = postnatal day.

8.6.7 Summary and Causality Determination

The 2009 PM ISA reported limited animal toxicological evidence of a relationship between long-term exposure to UFP and nervous system effects, without supporting epidemiologic studies. Recent animal toxicological studies substantially add to this evidence base by demonstrating neuroinflammation, Alzheimer's disease-related pathology, neurodegeneration, and altered neurodevelopment. Recent epidemiologic studies are very limited in number. The evidence for the relationship between long-term exposure to UFP and effects on the nervous system is summarized in Table 8-38, using the framework for causality determination described in the Preamble to the ISAs (U.S. EPA, 2015).

Studies of long-term exposure of adult mice to UFP from traffic-dominated sources provide evidence of inflammation and oxidative stress in the whole brain, hippocampus, and cerebral cortex (Cacciottolo et al., 2017; Tyler et al., 2016; Zhang et al., 2012; Morgan et al., 2011; Kleinman et al., 2008). Astrocyte activation and altered glutamatergic functions were also seen in these studies. Neurodegeneration, as indicated by decreased neurite density and white matter, occurred in specific regions of the hippocampus in UFP exposed mice (Cacciottolo et al., 2017). Many responses, including neurodegeneration, were greater in young compared with middle-aged mice. However, one of the measured behavioral effects was altered to a greater degree by UFP exposure in middle-aged mice compared with young mice (Cacciottolo et al., 2017). Pathologic changes characteristic of Alzheimer's disease (i.e., amyloid deposits and amyloid-β oligomers in the cortex) were seen in a mouse model of Alzheimer's disease, but not in wild type mice following exposure to UFP (Cacciottolo et al., 2017).

Prenatal exposure to UFP resulted in altered behavioral indices in adult male, but not female, mice (Davis et al., 2013). Postnatal exposure to UFP CAPs led to developmental neurotoxicity in a group of studies from the same laboratory (Allen et al., 2015; Allen et al., 2014b; Allen et al., 2014a; Allen et al., 2013). Activation of microglia and astrocytes, indicative of inflammation and injury, respectively, was observed along with alterations in brain morphology and neurotransmitters, and changes in serum corticosterone and behavior. Some effects were sex-specific, notably the persistent ventriculomegaly found in male mice (Allen et al., 2015; Allen et al., 2014a). Long-term exposure to UFP was associated with effects on cognitive development in children (Sunyer et al., 2015). However, uncertainties remain as a result of inadequate assessment of potential copollutant confounding, the spatial variation in UFP concentrations, and exposure measurement error.

The strongest evidence is provided by animal toxicological studies showing inflammation, oxidative stress, and neurodegeneration in adult mice and Alzheimer's disease pathology in a susceptible animal model. In addition, pre- and early postnatal exposure to UFP results in behavioral effects, inflammation, and persistent morphologic changes. Epidemiologic studies of UFP were lacking. **Overall, the collective evidence is sufficient to conclude that a causal relationship is likely to exist between long-term UFP exposure and nervous system effects.**

Table 8-38 Summary of evidence for a likely to be causal relationship between long-term UFP exposure and nervous system effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Brain Inflammation and Oxidative Stress			
Consistent evidence from multiple toxicological studies	Evidence of inflammation in whole brain, cerebral cortex, and hippocampus; evidence of oxidative stress in cerebellum	(Kleinman et al., 2008) †(Morgan et al., 2011) †(Cacciottolo et al., 2017) †(Tyler et al., 2016) †(Zhang et al., 2012)	114.2 μg/m^3 468 μg/m^3 342 49 μg/m^3 371.3 μg/m^3 200−400 μg/m^3
Activation of the Sympathetic Nervous System			
Inconclusive evidence	Changes in norepinephrine in cortex but levels in hypothalamus were not determined	†(Allen et al., 2014a)	96.4 μg/m^3

Table 8-38 (Continued): Summary of evidence for a likely to be causal relationship between long-term exposure to ultrafine particulate and nervous system effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Morphologic Changes			
Evidence from animal toxicological studies	Neurodegenerative changes in hippocampus	†(Cacciottolo et al., 2017)	342 µg/m^3
		†(Cacciottolo et al., 2017)	468 µg/m^3
	Alzheimer's disease pathology in cerebral cortex; dependent on APOE alleles	†(Cacciottolo et al., 2017)	468 µg/m^3
Cognitive and Behavioral Effects			
Limited animal toxicological evidence	Behavioral effects in adult mice	†(Cacciottolo et al., 2017)	342 ± 49 µg/m^3
Neurodevelopmental Effects			
Extensive evidence from animal toxicological studies from two different laboratories	Behavioral effects resulting from prenatal and postnatal exposure	†(Davis et al., 2013)	350 µg/m^3
		†(Allen et al., 2014b)	96.4 µg/m^3
	Altered neurotransmitters	†(Allen et al., 2013)	96.4 µg/m^3
		†(Allen et al., 2014a)	96.4 µg/m^3
	Neuroinflammation and morphologic changes including persistent morphology resulting from postnatal exposure	†(Allen et al., 2014b)	96.4 µg/m^3
		†(Allen et al., 2014a)	96.4 µg/m^3
		†(Allen et al., 2015)	96.4 µg/m^3
Overall			
Limited epidemiologic evidence	Associations with increased inattention and decreased scores on tests of memory	†(Sunyer et al., 2015)	22,157 particles/cubic cm
Uncertainty regarding copollutant confounding	No copollutant model results were reported.		
Uncertainty due to exposure measurement error	UFP concentration data for use in epidemiologic studies not frequently available; where available spatial variation of UFP may remain uncharacterized	Section 3.5	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble.

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is characterized.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated (for experimental studies, ≤2 mg/m^3).

†Studies published since the 2009 PM ISA.

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CHAPTER 9 REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

Summary of Causality Determinations for Particulate Matter (PM) Exposure and Male and Female Reproduction and Fertility, and Pregnancy and Birth Outcomes

This chapter characterizes the scientific evidence that supports causality determinations for short- and long-term PM exposure and reproductive and developmental outcomes. The types of studies evaluated within this chapter are consistent with the overall scope of the ISA as detailed in the Preface (Section P.3.1). In assessing the overall evidence, strengths and limitations of individual studies were evaluated based on scientific considerations detailed in the Appendix. The evidence presented throughout this chapter support the following causal conclusions. More details on the causal framework used to reach these conclusions are included in the Preamble to the ISA (U.S. EPA, 2015).

Size Fraction	Causality Determination
Male and Female Reproduction and Fertility	
$PM_{2.5}$	Suggestive of, but not sufficient to infer
$PM_{10-2.5}$	Inadequate to infer
UFP	Inadequate to infer
Pregnancy and Birth Outcomes	
$PM_{2.5}$	Suggestive of, but not sufficient to infer
$PM_{10-2.5}$	Inadequate to infer
UFP	Inadequate to infer

This chapter evaluates the scientific evidence related to the potential effects of PM ($PM_{2.5}$, $PM_{10-2.5}$, and ultrafine particles [UFP]) on reproductive and developmental outcomes in three sections including (1) Male and Female Reproduction and Fertility; (2) Pregnancy and Birth Outcomes; and (3) Developmental Effects. The body of literature characterizing reproductive and developmental effects associated with exposure to PM is large and has grown considerably since the 2009 PM ISA (U.S. EPA, 2009). Well-designed studies with consideration of potential confounding and other sources of bias are emphasized in this section (see APPENDIX 1 for study evaluation guidelines). In order to evaluate and characterize the evidence for the effects of PM on reproductive and developmental effects in a consistent, cohesive and integrated manner, results from both short-term and long-term exposure periods are included in a single section and are identified accordingly in the text and tables throughout this section. Because

the length of gestation in rodents is 18−24 days, on average, animal toxicological studies investigating the effects of PM generally are short-term exposure periods. For comparison, an epidemiologic study that uses the entire pregnancy as the exposure period is considered to have a long-term exposure period (about 40 weeks, on average). A major issue in studying environmental exposures and reproductive and developmental effects (including infant mortality) is selecting the relevant exposure period, since the biological plausibility leading to these outcomes and the critical periods of exposure are not completely understood. Thus, multiple exposure periods are evaluated in many epidemiologic studies, including long-term (months to years) exposure periods, such as entire pregnancy, individual trimesters or months of pregnancy, and short-term (days to weeks) exposure periods such as the days and weeks immediately preceding birth. Thus, the biological plausibility for the effects of PM on reproductive and developmental outcomes will combine short-term and long-term exposures in each particle size class ($PM_{2.5}$, UFP, and coarse PM). Further, infants and fetal development processes may be particularly sensitive to PM exposure, and although the physical mechanisms are not always fully understood the impacts from PM exposure at these critical windows of development may have permanent, lifelong effects.

Separate causality determinations are made for the two sections Male and Female Fertility and Reproduction; Pregnancy and Birth Outcomes. For developmental effects, summaries are included in this section of the ISA and full descriptions as well as causality determinations are found in the specific health endpoint (respiratory, cardiovascular, metabolic and neurological disease) section.

9.1 $PM_{2.5}$ Exposure and Reproductive and Developmental Effects

The body of literature characterizing male and female reproduction and fertility with $PM_{2.5}$ exposure is large and has grown considerably since the 2009 PM ISA (U.S. EPA, 2009). The evidence from the 2009 PM ISA determined that there was a suggestive causal relationship between long-term $PM_{2.5}$ exposure and reproductive and developmental outcomes. Effects of $PM_{2.5}$ exposure on sperm have been studied in both the animal toxicology and the epidemiologic literature. The strongest effects in the epidemiologic literature come from studies on sperm motility with $PM_{2.5}$ associated with impaired motility. The toxicological literature also has $PM_{2.5}$-dependent effects on sperm including impaired spermatogenesis and spermiation. Other studies from epidemiologic literature on sperm morphology have inconsistent results. Studies of female reproduction in association with $PM_{2.5}$ exposure cover estrus, ovulation, reproduction, and fertility. In rodents, ovulation and estrus are affected by $PM_{2.5}$ exposure. In the epidemiologic literature, results on human fertility and fecundity in association with $PM_{2.5}$ exposure is limited, but evidence from IVF shows a modest association of $PM_{2.5}$ concentrations with decreased odds of becoming pregnant. The toxicological evidence provides biological plausibility to these outcomes and shows multiple sensitive windows for PM exposure's effects. In the pregnancy and birth outcomes section of this document, studies on fetal growth, birth weight, preterm birth and preterm rupture of membranes show positive associations with $PM_{2.5}$ exposure in some animal toxicology and epidemiologic studies.

The toxicological evidence gives biological plausibility to these outcomes and shows multiple sensitive windows for PM exposure's effect on pre-term birth and low birth weight. Multiple epidemiologic and toxicological studies of birth defects show that PM is associated with cardiovascular birth defects, albeit of different types. The studies of fetal growth, birth weight, and infant mortality, increased in number in this ISA but generally continue to lack controls for confounding by other air pollutants, and show sensitivity to PM exposure across multiple trimesters of the pregnancy. Studies on sperm had mixed effects with epidemiologic studies of sperm focused on motility and toxicological studies focused on spermatogenesis. Studies of fertility in females showed effects on estrus in animal toxicology studies. Pregnancy outcomes showed mixed effects with $PM_{2.5}$ exposure and gestational diabetes, but when analyzed by trimester, the 2nd trimester showed the strongest effects, especially with gestational diabetes. In animal toxicological studies, the structure and vascularization of the placenta and umbilical cord were affected by $PM_{2.5}$ exposure. Developmental outcomes included cardiovascular, respiratory, and neurological outcomes like autism and are covered in more detail in those respective sections. More detailed information on male and female reproduction and fertility, pregnancy and birth outcomes, and developmental effects follows below.

9.1.1 Male and Female Reproduction and Fertility

9.1.1.1 Biological Plausibility

This section describes biological pathways that potentially underlie reproductive and developmental health effects specific to male and female reproduction and fertility resulting from exposure to $PM_{2.5}$. Figure 9-1 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" exposure to $PM_{2.5}$ may lead to effects on Reproduction and Fertility contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 9.1.

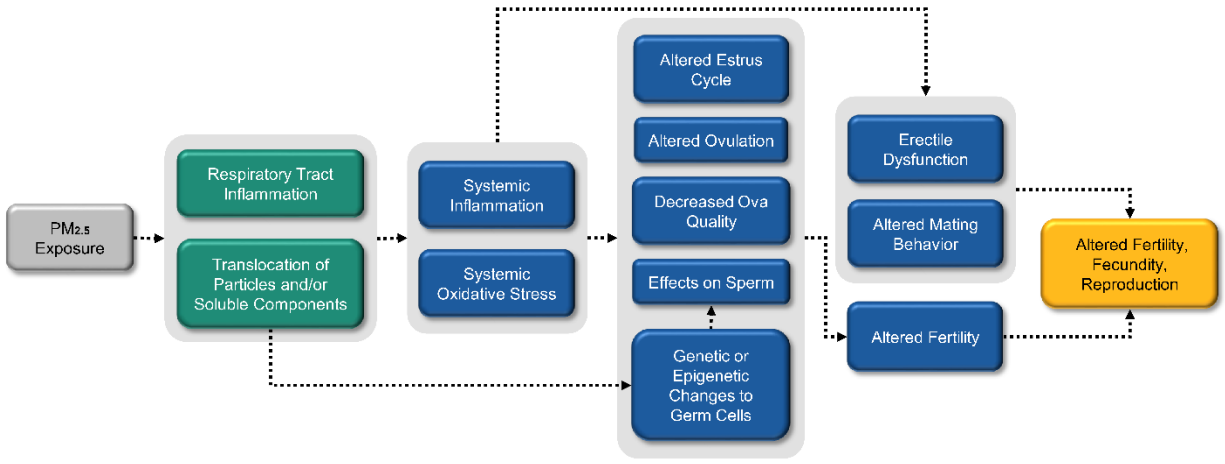


Figure 9-1 Potential biological pathways for male and female reproduction and fertility effects following $PM_{2.5}$ exposure

[a] Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

When considering the available health evidence, there are plausible pathways connecting inhalation of $PM_{2.5}$ to the apical reproductive and developmental events reported in epidemiologic studies (Figure 9-1). The biological plausibility for $PM_{2.5}$-induced effects on reproduction and fertility is supported by evidence from the 2009 PM ISA (U.S. EPA, 2009) and by new evidence. Once these pathways are initiated, there is evidence from experimental and epidemiologic studies that $PM_{2.5}$ inhalation may result in a series of physiological responses that could lead to male and female reproductive effects and altered fertility (e.g., fertility, fecundity, reproduction). The evidence for the initial events (Figure 9-1) that could result in inhalation of $PM_{2.5}$ having on effects fertility and reproduction includes translocation of particles less than 200 nm and/or their soluble components (Chapter 4); and respiratory tract inflammation (Chapter 6). Inhalation of $PM_{2.5}$ can result in translocation of particles or soluble factors from the lungs (see Chapter 5) which then can increase respiratory tract inflammation, which can be followed by systemic inflammation, e.g., C-reactive protein (CRP, see Chapter 5), even increasing CRP during pregnancy (Lee et al., 2011b). Soluble components of $PM_{2.5}$, and poorly soluble particles that are part of the $PM_{2.5}$ fraction and smaller than approximately 200 nm, may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments. Beyond these events, there is also evidence from experimental and epidemiologic studies demonstrating that exposure to $PM_{2.5}$ could result in a coherent series of physiological responses that provide biological plausibility for the associations reported in epidemiologic

and laboratory animal studies including altered fertility, fecundity and reproduction (Veras et al., 2009), (Legro et al., 2010), (Slama et al., 2013).

As depicted in Figure 9-1, these initial events can give rise to intermediate events including systemic inflammation from epidemiologic evidence of increased CRP during pregnancy (Lee et al., 2011b), animal studies of altered estrous cycle (Veras et al., 2009), altered ovulation (Veras et al., 2009), or decreased ova quality (Veras et al., 2009), erectile dysfunction in epidemiologic studies (Tallon et al., 2017) genetic and epigenetic changes to sperm and other effects on sperm in epidemiologic studies(Hammoud et al., 2009), (Radwan et al., 2015), (Hansen et al., 2010), and laboratory animal studies(Pires et al., 2011).

Laboratory animals provide the biological plausibility for effects on female reproduction with $PM_{2.5}$ inhalation. Briefly, inhalation of $PM_{2.5}$ affects the female and altered estrous cyclicity, ova quality and ovulation. After inhalation of $PM_{2.5,}$ there is elongation of the estrous cycle in female rodents that had been exposed to $PM_{2.5}$ for two generations (Veras et al., 2009), which reduced the total number of estrous cycles over a set time period (Veras et al., 2009). In laboratory animals the inhalation of $PM_{2.5}$ also decreased numbers of ovarian follicles at the antral stage with fewer follicles reaching this terminal stage just before ovulation in 2nd generation offspring (Veras et al., 2009). Also, ova quality is decreased (Veras et al., 2009).

Then there are intermediate effects on sperm after $PM_{2.5}$ inhalation, decreasing sperm quality (Hammoud et al., 2009) or motility(Radwan et al., 2015) in epidemiologic studies, or in rodents decreasing the number of sperm (Pires et al., 2011), affecting spermiation (Pires et al., 2011) or induction of genetic and epigenetic changes to sperm of rodents exposed to $PM_{2.5}$ (Yauk et al., 2008). Sertoli cells, which are important for the process of spermatogenesis, are decreased in laboratory animals after prenatal $PM_{2.5}$ exposure (Pires et al., 2011) and testicular weight and volume are decreased with prenatal $PM_{2.5}$ exposure (Pires et al., 2011). Epidemiologic studies show $PM_{2.5}$ exposure is associated with erectile dysfunction (Tallon et al., 2017).

In laboratory animal studies, parental (male and female) inhalation of $PM_{2.5}$ altered fertility and altered fecundity in the 1st (F1) and 2nd generation (F2) offspring after continuous inhalation of $PM_{2.5}$ from preconception (Veras et al., 2009). Inhalation of $PM_{2.5}$ by laboratory animals resulted in increased time required for a successful mating and fertility and pregnancy indices were significantly changed due to $PM_{2.5}$ inhalation (Veras et al., 2009). In these same animals with inhalation of $PM_{2.5,}$ there was a significant increase in rate of the post-implantation loss in G1 and G2 animals (Veras et al., 2009). In epidemiologic studies, increased $PM_{2.5}$ exposure in the month prior to conception was associated with reduced fecundability (Slama et al., 2013) and increased $PM_{2.5}$ during ovulation induction was associated with decreased odds of achieving pregnancy by IVF (Legro et al., 2010). Together, these mechanisms provide plausible pathways by which inhalation of $PM_{2.5}$ could progress from the initial events noted above to altered fertility, fecundity, and reproduction. A schematic characterizing the biological plausibility of $PM_{2.5}$ on reproduction and fertility is shown in Figure 9-1.

$PM_{2.5}$ inhalation could lead to reproductive and developmental health effects on male reproduction, female reproduction or fertility following multiple pathways. Pathways leading to effects in female fertility could begin with particle translocation or solubility of particle contents and inflammation, and oxidative stress that may lead to changes along the female reproduction pathway that impact estrus, ova quality, and ovarian follicle formation. Male reproductive outcomes affected by $PM_{2.5}$ exposure and translocation or solubilization of particle contents can involve inflammation or oxidative stress as well as genetic and epigenetic changes that can contribute to impacts on male reproduction including effects on sperm in laboratory animals and epidemiologic studies and erectile dysfunction in humans. Effects on fertility can begin with the initial particle translocation and solubility, oxidative stress and inflammation, with effects on overall fertility including an increase in rate of the post-implantation loss in laboratory animals as well as epidemiologic evidence of reduced fecundability and decreased odds of achieving pregnancy. While experimental studies involving animals contribute most of the evidence of upstream effects, epidemiologic studies found associations between $PM_{2.5}$ exposure and various outcomes. Together, these proposed pathways provide biological plausibility for epidemiologic results of reproductive and developmental health effects and will be used to inform a causality determination, which is discussed later in the chapter (Section 9.1.5).

9.1.1.2 Male Reproduction

Epidemiologic Evidence of Male Reproductive Function

A limited amount of research has been conducted to examine the association between $PM_{2.5}$ and male reproductive outcomes. In the studies of sperm parameters, there is some evidence for decreased motility (Hammoud et al., 2009), including after adjustment for some copollutants (i.e., NO_X, CO) (Radwan et al., 2015), and evidence for association with abnormal morphology is inconsistent, with a study finding higher percent abnormal sperm with higher $PM_{2.5}$ levels (Radwan et al., 2015) and a U.S. study reporting no evidence of associations between $PM_{2.5}$ exposure and sperm morphology (Hansen et al., 2010). Among participants in the National Social Life, Health, and Aging Project (NSHAP), Tallon et al. (2017) observed positive associations between exposure to annual $PM_{2.5}$ concentrations and erectile dysfunction in men aged 57−85 years (OR: 1.26; 95% CI: 0.81, 1.96)[75]. Effect estimates were similar in magnitude and precision when $PM_{2.5}$ concentrations were averaged over 1, 2, 3, 4, 5, 6, or 7 years. In summary, there are some association between $PM_{2.5}$ exposure and some sperm parameters, though the number of studies is limited.

[75] As detailed in the Preface, risk estimates are for a 5 µg/m3 increase in $PM_{2.5}$ concentrations unless otherwise noted.

Toxicological Evidence of Male Reproductive Function

The role of particulate matter exposure on male reproductive function has been explored in a limited number of animal toxicology studies evaluating endpoints including daily sperm production, male reproductive success, male reproductive organ histology and weight or hormonal concentrations and are separated below based on early life PM exposure or adult PM exposure. The results from these studies are summarized in Table 9-1. The 2009 PM ISA (U.S. EPA, 2009) did not include male reproductive studies that are in scope for the current ISA.

In recent work, spermatogenesis was affected in adult animals after prenatal and/or early postnatal exposure of mice to $PM_{2.5}$ (ambient air versus filtered air) from high traffic areas of Sao Paulo, Brazil. Pires et al. (2011) assessed germ cell count, rates of proliferation and apoptosis, spermatid retention and spermatogenic cycle timing. Animals were exposed 24 hour/day for 120 days prior to mating and then throughout pregnancy (prenatal) or for 10 days after birth (postnatal) to ambient or filtered Sao Palo air. Prenatal exposure to ambient air resulted in reduced body weights ($p < 0.001$) and reduced testicular weights ($p = 0.012$) and volume ($p = 0.013$), decreased tubular diameter ($p = 0.004$), and decreased number of elongated spermatids in pre- and postnatal-exposed animals versus filtered air controls. When compared to any other single exposure or the control animals, pre- and postnatal exposure caused significantly higher spermatid head retention at stages VIII−XII, a marker of defective spermiation ($p = 0.004$). No significant changes were detected in Leydig cell, Sertoli cell, spermatogonia, spermatocyte, or round spermatid numbers, or germ cell proliferation, apoptosis, or frequency of spermatogenic stages. The particulate portion of ambient air exposure was responsible for multiple decrements in spermatogenesis in adult animals after early life $PM_{2.5}$ exposure.

Table 9-1 Recent toxicological studies of male reproduction.

Study	Study Population	Exposure Details	Endpoints Examined
(Pires et al., 2011)	Balb/c pregnant mice and male offspring, N = 60, prenatal and postnatal exposure to ambient PM until 90 days of age.	Pregnant dams and male offspring, 120 days (premating through PND 90). $PM_{2.5}$ conc: 16.61 μg/m^3 nonfiltered air, 2.29 μg/m^3 filtered air. $PM_{2.5}$ levels were measured gravimetrically by collecting $PM_{2.5}$ particles from cellulose filters obtained using a Harvard impactor.	Effects of pre- and postnatal ambient $PM_{2.5}$ exposure on offspring testis weights, germ cell proliferation, testis morphology, apoptotic germ cells.

In conclusion, mixed effects were seen for associations of $PM_{2.5}$ exposure with male reproductive outcomes. Prenatal and/or early postnatal exposure of mice to $PM_{2.5}$ reduced testicular weight, volume

and tubular diameter, decreased number of elongated spermatids and affected spermiation. Epidemiologic evidence showed positive associations of $PM_{2.5}$ with sperm motility and erectile dysfunction.

9.1.1.3 Female Reproduction

Infertility affects approximately 11% of all women ages 15−44 in the U.S. (Chandra et al., 2013), and can have negative psychological impacts and affect quality of life; infertility and subfertility may also potentially signal poorer physiological health. For example, those with fertility problems are more likely to experience adverse pregnancy and birth outcomes if they do become pregnant (Hansen et al., 2005; Helmerhorst et al., 2004; Jackson et al., 2004). Outcomes evaluated in this section include fecundity, the biologic capacity to reproduce, and fertility, the ability to conceive or induce conception. Researchers may also investigate potential mechanistic links between pregnancy conditions and biomarkers and later birth outcomes; such as pregnancy related hypertension, which is a leading cause of perinatal and maternal mortality and morbidity (Lee et al., 2012b).

Epidemiologic Evidence for Female Reproductive Function

Epidemiologic studies related to fecundity or fertility were not identified for inclusion in the 2009 PM ISA (U.S. EPA, 2009). Recent studies of female reproductive function frequently use populations undergoing assisted reproductive treatment, as these populations have a large amount of data collected on them during treatment and defined menstrual cycles and start points. However, populations undergoing assisted reproductive treatment may be less healthy than the general population of reproductive age. In cohorts recruited from the general population, exact timing can be difficult to determine due to reliance on participant recall, particularly if they are surveyed well after initiation of pregnancy attempts. Many pregnancies are unplanned, which also adds a level of complication to quantifying fertility. Overall, a limited body of evidence provides modest evidence that both short- and long-term $PM_{2.5}$ exposure is associated with decreased fecundability, but did not observe associations between $PM_{2.5}$ exposure and fertility.

Several recent epidemiologic studies examined the association between exposure to air pollutants and the reproductive function or fertility. Gametes (i.e., ova and sperm) may receive higher exposures while outside of the human body, as occurs with assisted reproduction. A recent study estimated daily concentrations of criteria pollutants at addresses of women undergoing their first in vitro fertilization (IVF) cycle and at their IVF labs from 2000 to 2007 in the northeastern U.S. (Legro et al., 2010). Increasing $PM_{2.5}$ concentration estimated at the patient's address during ovulation induction (short-term exposure, ~12 days) was associated with a decreased odds of achieving pregnancy (determined by serum pregnancy test; OR: 0.90; 95% CI: 0.82, 0.99) or an intrauterine pregnancy (determined by ultrasound; OR: 0.90; 95% CI: 0.82, 0.99). These authors observed generally null associations with odds of a live birth after pregnancy was established when $PM_{2.5}$ concentrations were averaged over a number of

exposure periods during pregnancy. The results of this study indicate that short-term $PM_{2.5}$ exposure during ovulation was detrimental and reduced the likelihood of becoming pregnant. Among the general population in the Czech Republic, increased $PM_{2.5}$ exposure in the 30 days before initiation of unprotected intercourse also was associated with reduced fecundability [fecundability ratio: 0.93 (95% CI: 0.88, 0.98), (Slama et al., 2013)].

In an analysis of the Nurses' Health Study II Mahalingaiah et al. (2016), observed null associations with infertility and long-term $PM_{2.5}$ exposure using national spatiotemporal models. They also found no evidence of association with endometriosis, a condition potentially linked to infertility (i.e., attempting to get pregnant for at least one year without success) (Mahalingaiah et al., 2014). Interpolation methods were used to estimate monthly $PM_{2.5}$ concentrations before 1999 in both of these analyses. Of the other recent studies, a cross-sectional study in Spain also reported null associations with fertility rates based on number of live births per 1,000 women aged 15−44 years (Nieuwenhuijsen et al., 2014), while a study of almost 2,000 couples in the Czech Republic found increased $PM_{2.5}$ exposure in the 60 days before initiation of unprotected intercourse was associated with reduced fecundity (Slama et al., 2013). Slama et al. (2013) also examined exposure in the 30 days post-conception as a negative control and observed no evidence of association between $PM_{2.5}$ and fecundity in this period, providing greater certainty for the observed effect of $PM_{2.5}$ exposure on fecundity in their study.

In summary, recent epidemiologic studies showed short-term $PM_{2.5}$ exposure during ovulation was detrimental and reduced the likelihood of becoming pregnant in women undergoing IVF, and in a separate study increased $PM_{2.5}$ exposure in the 30 days before initiation of unprotected intercourse also was associated with reduced fecundability. Little evidence exists in the literature for laboratory animal studies on this outcome. Overall, there appears to be some association between $PM_{2.5}$ exposure and reproductive function (i.e., fecundity outcomes), though the number of studies is limited. In addition, each of these studies account for fertility or fecundity in a different manner, making it difficult to directly compare results across studies. Studies of female reproductive function are summarized in Supplemental Table S9-1 (U.S. EPA, 2018).

Animal Toxicological Evidence for Female Reproduction

Multiple animal toxicological studies of female fertility and estrus from the 2009 PM ISA (U.S. EPA, 2009) reported altered estrous cycles, increased time necessary for mating, smaller litter sizes with increased resorptions and fetal deaths, decreased fertility index, and increased pregnancy index in rodents exposed to $PM_{2.5}$, often ambient air in Sao Paulo, Brazil (Veras et al., 2009). $PM_{2.5}$ inside both chambers and in the outside environment was determined gravimetrically using Harvard impactors.

$PM_{2.5}$ exposure preconception, during gestation or in utero can potentially affect litter size by changing the number of pups conceived or by inducing pup loss during pregnancy or decreasing the number of fertilizations or implantation sites. The 2009 PM ISA (U.S. EPA, 2009) reported significant

changes to litter size with $PM_{2.5}$ exposure. In recent work, litter size was not affected by prenatal exposure of B6C3F1 hybrid mice to Sterling Forest, NY $PM_{2.5}$ CAPs (Klocke et al., 2017) 6 hour each day for most of gestation. Across multiple studies, preconception plus gestational exposure of dams to $PM_{2.5}$ significantly decreased litter size, but paternal exposure plus gestational exposure or gestational exposure alone were not sufficient to affect litter size. More details of these studies are in Table 9-2 below.

Table 9-2 Key toxicological studies of effects of $PM_{2.5}$ on female reproductive function.

Study	Population	Exposure Details	Endpoints Examined
(Klocke et al., 2017)	Male and female B6C3F1 mice (8−10 weeks old) were mated and then dams were exposed to Sterling Forest CAPs.	Prenatal exposure to filtered air or Sterling Forest CAPs for 6 hours/day during gestation (GD0.5 to GD 16.5). Mean CAPs concentration over the exposure period averaged 92.696±19.16 (mean ± SD) μg/m^3 compared to 3.526±0.87 μg/m^3 for FA controls. CAPs exposure levels ranged from 32.95 to 184.43 μg/m^3 over the duration of the exposure period.	Reproductive success.

In conclusion, a recent study exists on animal reproductive success (litter size) with null findings, but no other new studies in the animal toxicology literature on female fertility or estrous cycle have been published since the 2009 PM ISA (U.S. EPA, 2009). The recent epidemiologic literature contains studies on infertility with a U.S. study showing null associations with $PM_{2.5}$ and a Czech study showing positive associations of infertility with $PM_{2.5}$. Epidemiologic associations between $PM_{2.5}$ and endometriosis were null.

9.1.2 Pregnancy and Birth Outcomes

9.1.2.1 Biological Plausibility

This section describes biological pathways that potentially underlie reproductive and developmental health effects of pregnancy, birth weight, and birth outcomes resulting from exposure to $PM_{2.5}$. Figure 9-2 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" exposure to $PM_{2.5}$ may lead to reproductive and developmental health effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 9.1.2.

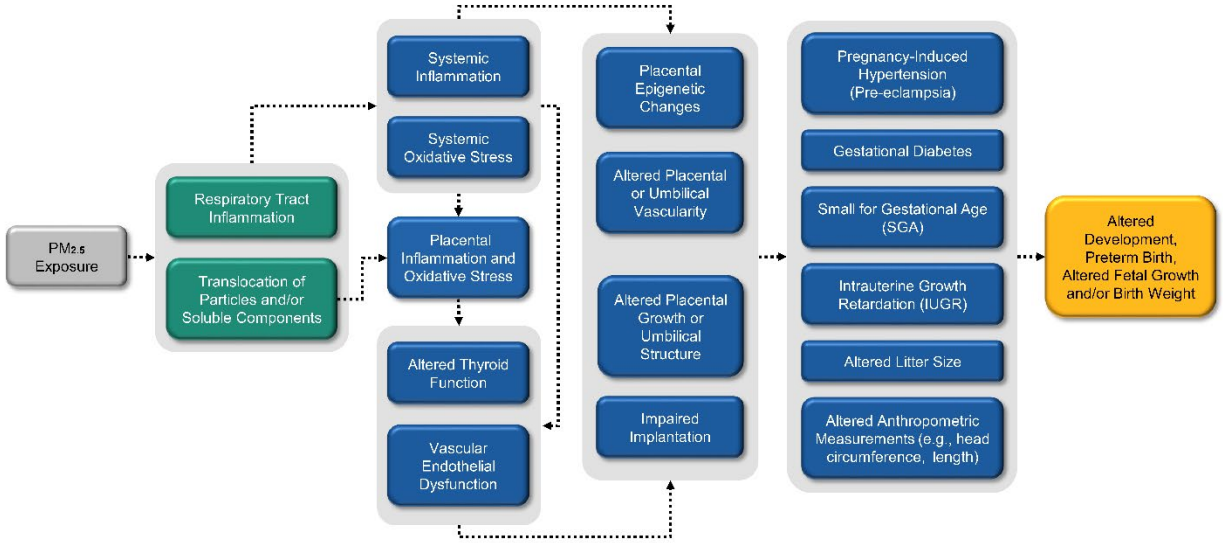


Figure 9-2 Potential biological pathways for pregnancy and birth outcomes following $PM_{2.5}$ exposure

[a] Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Evidence is accumulating that $PM_{2.5}$ exposure may affect pregnancy and birth outcomes. The evidence from the 2009 PM ISA (U.S. EPA, 2009) and new evidence indicates multiple initial events after $PM_{2.5}$ inhalation contribute to effects on pregnancy and birth outcomes including translocation of particles/soluble components (Valentino et al., 2016); systemic inflammation or oxidative stress. Beyond these initial events, there is also evidence from experimental and epidemiologic studies demonstrating that $PM_{2.5}$ inhalation could result in a coherent series of physiological responses that provide biological plausibility for the associations reported in epidemiologic studies and animal toxicological studies that contribute to the apical endpoint of altered development, preterm birth, altered fetal growth or birth weight. The initial event of systemic oxidative stress is demonstrated in the epidemiologic literature with $PM_{2.5}$-dependent increased odds of elevated c-RP levels during pregnancy (Lee et al., 2011b) or in nonpregnant individuals (Devlin et al., 2014). $PM_{2.5}$-dependent reproductive organ specific inflammation includes placental oxidative stress and intrauterine inflammation (Nachman et al., 2016; Saenen et al., 2016), altered umbilical cord blood lymphocyte distribution (Herr et al., 2010), and increased inflammation along the lipoxygenase pathway in cord blood (5-LOX, 12/15 LOX pathways) (Martens et al., 2017). With increased $PM_{2.5}$ exposure intermediate endpoints emerge with the epidemiologic literature showing altered fetal thyroid function (Janssen et al., 2016; Lavigne et al., 2016a) and altered fetal metabolism (Janssen et al., 2016; Lavigne et al., 2016a). With increased $PM_{2.5}$ exposure, changes to metabolism are seen with increased risk of gestational diabetes (Hu et al., 2015) during the second

trimester. Impaired fetal or maternal thyroid function during a pregnancy can impact the pregnancy, birth outcomes and development. As shown in Figure 9-2, the initial mechanisms can contribute to downstream intermediate effects in laboratory animals including placental or umbilical cord vascularity changes (Veras et al., 2012), endothelial dysfunction (Veras et al., 2012), altered thyroid function (Janssen et al., 2016; Lavigne et al., 2016a) or altered umbilical cord structure (Veras et al., 2012), and in epidemiologic studies of placental genetic or epigenetic changes (Janssen et al., 2013), altered placental growth (Saenen et al., 2015) and impaired implantation (Saenen et al., 2015). One pathway shows impaired placental development including epidemiologic evidence of increased placental inflammation (Saenen et al., 2016), altered expression of placental genes (decreased placental tissue *Bdnf* and *Syn1*) (Saenen et al., 2015), and at the epigenetic level, and human placenta global hypo-methylation with $PM_{2.5}$ exposure (Janssen et al., 2013). Laboratory animal evidence includes altered placental vascularity (Veras et al., 2008), decreased blood vessel diameter on maternal side of placenta and increased capillary surface area on fetal side of placenta (Veras et al., 2008), and decreased placental weight (Veras et al., 2008) (Blum et al., 2017). The line of evidence for effects on the umbilical cord shows $PM_{2.5}$-dependent impairment of the umbilical cord with the epidemiologic literature showing altered cord lymphocyte distribution (Saenen et al., 2016), increased cord blood inflammatory markers (e.g., upregulation of the 5-LOX pathway) (Martens et al., 2017), and laboratory animal evidence of impaired cord artery vascularity (increased endothelin receptor A levels and cord endothelial dysfunction) (Veras et al., 2012), and decreased cord tensile strength (Veras et al., 2012). Decreased fetal growth (Jedrychowski et al., 2010), decreased birth weight (Jedrychowski et al., 2010) and preterm birth (Brauer et al., 2008), (Salihu et al., 2012), (Ha et al., 2014) (Blum et al., 2017) have the strongest evidence in association with $PM_{2.5}$ inhalation and these aforementioned upstream biomarkers provide biological plausibility for these associations. $PM_{2.5}$ exposure has been shown to be associated with pregnancy induced hypertension or pre-eclampsia, gestational diabetes, anthropometric measurements (crown to rump length), IUGR or SGA (Section 9.1.1). There are plausible mechanisms by which inhalation of $PM_{2.5}$ could progress from the initial events noted above to altered growth and development, birth weight, or preterm birth. Supporting evidence is included in Figure 9-2. Together, these proposed pathways provide biological plausibility for epidemiologic results of reproductive and developmental health effects and will be used to inform a causality determination, which is discussed later in the chapter (Section 9.1.5).

In conclusion, decreased fetal growth, decreased birth weight and preterm birth have the strongest evidence in association with $PM_{2.5}$ exposure and these upstream biomarkers provide biological plausibility for these associations. There are plausible mechanisms by which inhalation exposure to $PM_{2.5}$ could progress from the initial events noted above to altered growth and development, birth weight, or preterm birth. Supporting evidence is included in Figure 9-2.

9.1.2.2 Maternal Health during Pregnancy

Epidemiologic Evidence for Effects on Maternal Health during Pregnancy

Studies of maternal health during pregnancy include a number of outcomes, but primarily focus on gestational hypertension disorders and gestational diabetes. Pregnancy-associated hypertension is a leading cause of perinatal and maternal mortality and morbidity. A large body of research has linked changes in blood pressure to ambient air pollution; however, evidence is inconsistent for $PM_{2.5}$ (Section 6.2.6 and Section 6.3.7). A few recent studies have examined whether increases in $PM_{2.5}$ concentrations are associated with hypertensive disorders of pregnancy including preeclampsia (see Supplemental Table S9-1(U.S. EPA, 2018) for study details). The results of these studies were not consistent. The methods by which exposure was assigned in these studies may contribute to the heterogeneity in associations observed across these studies. For example, examination of a cohort from Orange and Los Angeles counties in California revealed that the direction of the association between a composite outcome of gestational hypertensive disorders and $PM_{2.5}$ changed based on how concentrations were determined, either using the CALINE4 model (positive association; OR 1.47; 95% CI: 1.24, 1.68) or the nearest monitor (negative association; OR 0.90; 95% CI: 0.53, 1.54) (Wu et al., 2011; Wu et al., 2009). A cohort study conducted across the U.S. that estimated $PM_{2.5}$ concentrations using a modified CMAQ model across hospital catchment areas reported no evidence of association with preeclampsia for women with or without asthma (Mendola et al., 2016b). A study of around 3,500 women in Washington State observed no associations between preeclampsia and exposure to $PM_{2.5}$ in the seven months following conception when using a LUR exposure model (Rudra et al., 2011). While a larger cohort from Jacksonville, FL, using monitors within 20 km for assignment and with similar average $PM_{2.5}$ concentrations, reported positive odds ratios with any hypertensive disorder and $PM_{2.5}$ exposure in the first and second trimesters (OR: 1.09; 95% CI: 0.99, 1.20; OR: 1.24; 95% CI: 1.11, 1.39, respectively) (Xu et al., 2014). Two meta-analyses have estimated positive odds ratios (ORs 1.15−1.47) for $PM_{2.5}$ and preeclampsia, however both had large heterogeneity scores, and therefore a combined effect may be inappropriate (Hu et al., 2014; Pedersen et al., 2014).

Several studies evaluated the association between short- and long-term $PM_{2.5}$ exposure and gestational hypertension. Two long-term exposure studies of blood pressure report inconsistent effects, with a Pittsburgh study observing null associations (Lee et al., 2012b) and a Polish study reporting positive associations between second trimester $PM_{2.5}$ exposure and blood pressure measured in the third trimester (Jedrychowski et al., 2012). In addition, a study that evaluated short-term $PM_{2.5}$ exposure and blood pressure observed higher blood pressure associated with increased $PM_{2.5}$ in hours 0−4 before delivery in women with gestational hypertension and preeclampsia, but not among normotensive women or women with chronic hypertension (Männistö et al., 2014).

All of the recent studies of gestational diabetes were conducted in areas with average $PM_{2.5}$ concentrations less than 12 $\mu g/m^3$ and provide limited evidence for an association between $PM_{2.5}$ exposure and gestational diabetes. In a nationwide cohort using a specialized CMAQ model and hospital catchment area for exposure, Robledo et al. (2015) reported null associations with $PM_{2.5}$ exposure in the preconception period (OR: 0.97; 95% CI: 0.94, 1.02) and first trimester (OR: 0.98; 95% CI: 0.94, 1.03). In a Florida based study using a hierarchical Bayesian exposure modeling approach, Hu et al. (2015) observed similar results after adjustment for ozone for the first trimester, and also observed increased odds of gestational diabetes with second trimester exposures. These studies were both large, with hundreds of thousands of women in each. In a study of around 2,000 women that compared exposure assignment with monitor values to that with satellite derived concentrations, Fleisch et al. (2014) observed positive associations with impaired glucose tolerance and $PM_{2.5}$ exposure in the second trimester, but null associations with gestational diabetes. In a larger cohort using only satellite derived concentrations Fleisch et al. (2016) again observed no evidence of association between $PM_{2.5}$ in the first or second trimesters and gestational diabetes.

In other outcomes related to pregnancy, $PM_{2.5}$ exposure has been associated with increased odds of high C-reactive protein (Lee et al., 2011b) and altered umbilical cord lymphocyte distributions (Herr et al., 2010), both potentially linked to inflammatory mechanisms for PM, and decreased placental gene expression potentially related to neurodevelopment (Saenen et al., 2015). Recently, $PM_{2.5}$ exposures have also been found to be associated with placental stress measures and intrauterine inflammation (Nachman et al., 2016; Saenen et al., 2016), along with fetal metabolic and fetal thyroid function (Janssen et al., 2016; Lavigne et al., 2016a). Examining short-term $PM_{2.5}$ exposure, Lee et al. (2011b) report elevated ORs for abnormal C-reactive protein levels. The small body of evidence across various pregnancy-related endpoints limits the ability to judge coherence and consistency across these studies, though the positive associations observed in these studies demonstrate that $PM_{2.5}$ exposure could result in physiological responses that contribute to adverse pregnancy outcomes (e.g., preterm birth, altered fetal growth or birth weight).

In summary, there is some evidence for an effect of $PM_{2.5}$ exposure on maternal health during pregnancy. Studies of maternal health during pregnancy are summarized in Supplemental Table S9-1 (U.S. EPA, 2018).

Toxicological Evidence for Effects on Pregnancy

The placenta appears to be a tissue that is sensitive to the downstream effects of $PM_{2.5}$ exposure. The 2009 PM ISA (U.S. EPA, 2009) provided evidence of changes in placental vascularity with $PM_{2.5}$ exposure, including $PM_{2.5}$ dependent decreased placental weight (GD17) with decreased blood vessel diameter on maternal side of placenta and increased capillary surface area on fetal side of placenta (Veras et al., 2008). Recent studies continue to show effects on the placenta in response to $PM_{2.5}$ exposure. Blum et al. (2017) exposed pregnant B6C3F1 hybrid mice to Sterling Forest $PM_{2.5}$ CAPs 6 hours/day and found

that placental weight was significantly decreased with 3rd trimester $PM_{2.5}$ exposure and significantly increased with PM exposure over the entire pregnancy ($p < 0.05$); placental weight was not affected by 1st or 2nd trimester $PM_{2.5}$ exposure. The effect of $PM_{2.5}$ exposure on placental inflammation was followed a 1-hour daily exposure to Sao Palo $PM_{2.5}$ CAPs before and during pregnancy (Blum et al., 2017). Rats were exposed prior to mating and gestational exposure was started at implantation on GD6 and continued through GD19. Animals were exposed for 1 hour/day to CAPs or to HEPA filtered air (de Melo et al., 2015). Placental IL-4 was significantly increased on the fetal side of the placenta ($p < 0.05$) when the dam had combined CAPs exposure before pregnancy and during pregnancy only; none of the other cytokines assessed (IL-1b, IL-4, IL-6, IL-10, INF-g, TNF-a, and Toll-like receptor 4) in both placenta and serum were significantly increased by $PM_{2.5}$ exposure; also, no other exposure paradigms induced significant changes in cytokines. IL-4 protein levels are significantly increased in the fetal portion of the placenta with PM exposure before and during pregnancy, indicating placental inflammation after PM exposure.

More recent work has evaluated the effects of $PM_{2.5}$ on the mouse umbilical cord structural anatomy, microscopic vascular morphology, and markers of oxidative stress (Veras et al., 2012). Dams were exposed to $PM_{2.5}$ (filtered or unfiltered ambient air, Table 9-3 below). The reproductive and developmental outcomes from these animals were reported in previous publications and were covered in the 2009 PM ISA (Veras et al., 2009; Veras et al., 2008). The mean cross-sectional area of umbilical cords from $PM_{2.5}$-exposed group was significantly lower than the filtered air group ($p < 0.001$). The smaller cross-sectional area was due to a significant 28% decrease in total volume of porous mucoid connective tissue (MCT) of the umbilical cord ($p = 0.002$) and the decrease MCT was attributed to a significant 60% loss of collagen in the MCT ($p = 0.002$). PM-exposure resulted in increased oxidative stress or greater levels of immunostaining for 15-F2t-isoprostane in the walls of cord arteries and veins ($p < 0.0001$). Additionally, $PM_{2.5}$ exposure resulted in increased endothelin receptor A levels in cord arteries and veins ($p < 0.0001$), and no changes in endothelin receptor B. Collectively, the results suggest that the reduced birth weights previously reported following particulate exposures may be associated with decreased tensile properties of the umbilical cord due to loss of collagen and with altered blood flow to the fetus.

These studies demonstrate that gestational exposure to $PM_{2.5}$ alters murine umbilical cords and their vessels as well as the placenta, which could potentially deregulate vascular tone, an important contributor to proper fetal development. A summary of the animal toxicological studies of $PM_{2.5}$ exposure is included below in Table 9-3.

Table 9-3 Key toxicological studies of $PM_{2.5}$ exposure and pregnancy and birth outcomes.

Study	Study Population	Exposure Details	Endpoints Examined
(Veras et al., 2012)	BalbC mice (n = 12 dams, per group, fetuses examined in each group). Exposure to ambient air in São. Paulo near high traffic density. Conducted June to November 2006.	Dams were exposed to filtered or unfiltered air (average $PM_{2.5}$ levels, 6.4 µg/m^3 or 32.8 µg/m^3, respectively).	Mouse umbilical cord structural anatomy, microscopic vascular morphology, and markers of oxidative stress.
(de Melo et al., 2015)	Pregnant Female Wistar Rats	Rats were exposed 5 times per week during the 3 weeks before pregnancy and/or 1 time per day each day during pregnancy, starting on GD6 and though GD19. Animals were exposed to $PM_{2.5}$ (ambient $PM_{2.5}$ concentration of 600 mg/m^3 for 1 h). There were 4 exposure paradigms including filtered air (FA) before and during pregnancy (control), PM CAPs before pregnancy +FA during pregnancy, FA before pregnancy + CAPs during pregnancy, or CAPs both before and during pregnancy.	Placental development and systemic inflammation (cytokines, TLR4), pregnant dam blood counts.
(Blum et al., 2017)	Pregnant B6C3F1 hybrid mice, n = 8−17 dams per exposure.	Mice were exposed 6 hours/day to Sterling Forest CAPs during the pregnancy (entire pregnancy or 1st trimester, 2nd trimester, or 3rd trimester). Average daily CAPS concentration ranged from 113 to 192.5 µg/m^3.	Placental weight

9.1.2.3 Fetal Growth, Birth Weight, and Body Length at Birth

Fetal growth can be difficult to quantify; typically, small for-gestational age (SGA) or intrauterine growth restriction (IUGR) are used as dichotomous metrics to characterize suboptimal fetal growth. SGA represents a statistical description of a small neonate, whereas the term IUGR is reserved for those with clinical evidence of abnormal growth. SGA is defined as infants with a birth weight below the 10th percentile for gestational age, usually with consideration for sex and race as well, and is often used interchangeably with IUGR. There are a number of limitations in using SGA/IUGR as a metric of poor fetal growth. One is that a percentile based measure will always quantify a certain percentage of the infant population as growth restricted whether or not this is truly the case (Wollmann, 1998). For example, in term infants, it is unlikely that 10% are actually growth restricted. Whereas in preterm infants, it is likely that more than 10% are growth restricted; therefore, SGA cases would be overestimated in term infants and underestimated in preterm infants. In addition, exact definitions shift between studies and some studies use alternate definitions of SGA/IUGR. For example, some studies use the birth weight distribution of their study population for defining SGA, which will naturally not be identical for every

study population, and others use country standards, which are likely to be more stable, although they may need to be updated with time (Salihu et al., 2012; Brauer et al., 2008).

Birth weight is a measure of fetal growth and an important indicator of future infant and child health. Birth weight is determined by gestational age and intrauterine growth, as well as maternal, placental, fetal and environmental factors. Environmental insults affecting birth weight may occur throughout pregnancy. Implantation or formation of the placenta may be disrupted in the earliest weeks of pregnancy, leading to decreased nutrition throughout pregnancy; or inflammation might result in arterial resistance within the umbilical cord during the later trimesters resulting in poor fetal nutrition. As the largest gains in birth weight occur during the last weeks of gestation, this may be a particularly vulnerable period for birth weight outcomes. Information on birth weight is routinely collected for vital statistics; given that measures of birth weight do not suffer the same uncertainties as gestational age or growth restriction, it is one of the most studied outcomes within air pollution and reproductive health. Birth weight may be examined as a continuous outcome or dichotomous outcome as low birthweight (LBW) (less than 2,500 g or 5 lbs, 8 oz).

There are many methodological issues relating to the study of outdoor air pollution and adverse birth outcomes; and several articles reviewing these methods characterize these challenges (Chen et al., 2010; Woodruff et al., 2009; Ritz and Wilhelm, 2008; Slama et al., 2008). Some of the key challenges to interpretation of birth outcome study results include: the difficulty in assessing exposure as most studies use existing monitoring networks to estimate individual exposure to ambient air pollution; the need for detailed exposure data, and potential residential movement of mothers during pregnancy; the inability to control for potential confounders such as other risk factors that affect birth outcomes (e.g., smoking, correlated air pollutants); evaluating the exposure window (e.g., trimester) of importance; and limited evidence on the physiological modes of action for these effects (Ritz and Wilhelm, 2008; Slama et al., 2008). Some studies have specifically investigated the effects of residential mobility during pregnancy, generally finding movement to similar areas and limited to no effects on PM exposure levels and effect estimates (Pereira et al., 2016; Chen et al., 2010), though a review reported that there may be differences by covariates (Bell and Belanger, 2012). Recently, an international collaboration was formed to better understand the relationships between air pollution and adverse birth outcomes and to examine some of these methodological issues through standardized parallel analyses of data sets across countries (Woodruff et al., 2010) with a study of term birth weight from this collaboration is included in this assessment (Dadvand et al., 2013b). Some of the key challenges to interpretation of these study results include the difficulty in assessing exposure as most studies use existing monitoring networks to estimate individual exposure to ambient PM; the inability to control for potential confounders such as other risk factors that affect birth outcomes; evaluating the exposure window of importance; uncertainty surrounding exposure measurement error, spatial and temporal heterogeneity and limited evidence on the physiological mechanism of these effects. Study of these outcomes can be difficult given the need for detailed data and potential residential movement of mothers during pregnancy. Another uncertainty is whether PM effects differ by the child's sex.

Epidemiologic Evidence for Fetal Growth, Birth Weight, and Body Length at Birth

Studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) generally observed positive associations between $PM_{2.5}$ exposure averaged over the first or second trimester and growth restriction. Among recent studies examining SGA, the evidence is less consistent, with some studies reporting no evidence that increases in $PM_{2.5}$ were associated with increases in odds of SGA (Ha et al., 2017; Stieb et al., 2015; Hannam et al., 2014; Lee et al., 2013), while several others observed that increases in $PM_{2.5}$ were associated with increases in odds of SGA, though magnitude and precision of effects varied (Hyder et al., 2014; Salihu et al., 2012; Rich et al., 2009; Brauer et al., 2008). In the single study of infant anthropometrics and $PM_{2.5}$, small decrements in length and head circumference with log-increases in $PM_{2.5}$ were observed (Jedrychowski et al., 2010).

The 2009 PM ISA (U.S. EPA, 2009) concluded that a limited number of studies conducted in the U.S. observed positive associations between $PM_{2.5}$ exposure and LBW, but that the evidence from studies conducted outside of the U.S. was inconsistent. Many recent studies evaluate the association between $PM_{2.5}$ exposure and birth weight, including studies of LBW and birth weight as a continuous measure. Similar to the results reported in the 2009 PM ISA (U.S. EPA, 2009), when examining the entire body of available literature as a whole, the evidence for an effect of $PM_{2.5}$ on birth weight remains inconsistent. For example, among studies that examine LBW, many report positive associations (i.e., increased odds of LBW) with $PM_{2.5}$ exposure (Ha et al., 2017; Cândido da Silva et al., 2014; Dadvand et al., 2014; Ha et al., 2014; Harris et al., 2014; Hyder et al., 2014; Laurent et al., 2014; Dadvand et al., 2013b; Pedersen et al., 2013; Trasande et al., 2013; Ebisu and Bell, 2012; Salihu et al., 2012; Morello-Frosch et al., 2010). A number also report null or negative effect estimates (Ha et al., 2017; Lavigne et al., 2016b; Brown et al., 2015; Stieb et al., 2015; Fleischer et al., 2014; Fleischer, 2014; Gray et al., 2014; Vinikoor-Imler et al., 2014; Laurent et al., 2013; Madsen et al., 2010; Brauer et al., 2008; Parker and Woodruff, 2008). Similar results are reported for studies that examine change in the continuous measure of birth weight, with some reporting associations between $PM_{2.5}$ exposure and decreases in birth weight (Erickson et al., 2016; Tu et al., 2016; Stieb et al., 2015; Gehring et al., 2014; Hyder et al., 2014; Pedersen et al., 2013; Kloog et al., 2012; Darrow et al., 2011; Gehring et al., 2011; Gray et al., 2011; Gray et al., 2010; Morello-Frosch et al., 2010), and others reporting null associations or showing increases in birth weight (Tu et al., 2016; Fleisch et al., 2015; Lakshmanan et al., 2015; Hannam et al., 2014; Vinikoor-Imler et al., 2014; Laurent et al., 2013; Geer et al., 2012; Darrow et al., 2011; Gehring et al., 2011; Bell et al., 2010; Jedrychowski et al., 2010; Madsen et al., 2010; Slama et al., 2010; Parker and Woodruff, 2008). The entire body of available studies are characterized in Supplemental Table S9-2 (U.S. EPA, 2018).

When evaluating studies of $PM_{2.5}$ exposure and fetal growth or birth weight conducted in North America, where the most consistent associations were observed in the 2009 PM ISA (U.S. EPA, 2009), the results of recent studies are less consistent. There are several studies examining fetal growth and birthweight condected in North America with reported mean $PM_{2.5}$ concentrations less than 12 $\mu g/m^3$ (Table 9-4). For example, Brauer et al. (2008) investigated SGA (defined to the cohort) and LBW using

both inverse distance weighting (IDW) from monitors and LUR exposure metrics in Vancouver. Increases in $PM_{2.5}$ over the whole pregnancy period were associated with increased odds of SGA with both exposure metrics, though confidence intervals were wider with the IDW method (OR IDW = 1.10 [0.90, 1.28], OR LUR = 1.10 [1.00, 1.16]) (Brauer et al., 2008). For LBW, ORs for the different exposure metrics were divergent, with a negative association when using IDW and a positive OR when using LUR to assign exposure, though both sets of CIs were wide (Brauer et al., 2008). Another study set across 24 cities in Canada using LUR methods involving both monitors and satellite data reported near null odds ratios for SGA and LBW with $PM_{2.5}$ across the full pregnancy period in fully adjusted models; mean changes in birth weight were negative with increasing $PM_{2.5}$ in the fully adjusted model (Stieb et al., 2015).

Table 9-4 Epidemiologic studies of $PM_{2.5}$ exposure and effects on fetal growth and birth weight.[a]

Study	Study Population	Exposure Assessment	Mean µg/m^3	Odds Ratio (95% CI)[b]
†Brauer et al. (2008) Vancouver, BC Follow-up: 1999−2002 Birth Cohort Study	70,249 live births in study area with data on residential history	IDW based on ground-monitors (n = 7) assigned to postal codes LUR (R^2 = 0.52), cross-validation revealed poor performance of $PM_{2.5}$ LUR model	IDW: 5.1 LUR: 4.0	Term LBW; entire pregnancy IDW: 0.91 (0.68, 1.25) LUR: 1.10 (0.97, 1.25) SGA; Entire pregnancy IDW: 1.09 (0.91, 1.25) LUR: 1.07 (1.00, 1.10)
†Stieb et al. (2015) Multicity, Canada Follow-up: 1999−2008 Birth Cohort Study	3 million singleton live births; 1.57% term LBW and 8.31% SGA	Hybrid of ground monitors, LUR and remote sensing (satellite images) described in Beckerman et al. (2013)	8.4	Term LBW; entire pregnancy 1.01 (0.94, 1.08) Term BW; entire pregnancy −20.5 (−24.7, −16.4) grams SGA; entire pregnancy 1.04 (1.01, 1.07)
†Salihu et al. (2012) Hillsborough County, FL Follow-up: 2000−2007 Birth Cohort Study	103,961 singleton live births; 6.4% LBW and 8.4% SGA	6-day concentrations from 14 ground monitors; maternal residential ZIP code centroid linked to nearest monitor, based on centroid of ZIP code in which monitor was located; exposure dichotomized at median	Median: 11.28	ORs for exposure above median compared to below median LBW; entire pregnancy 1.07 (1.01, 1.12) Very LBW; entire pregnancy 1.14 (1.01, 1.29) SGA; entire pregnancy 1.06 (1.01, 1.11)
†Ha et al. (2014) Florida, US Follow-up: 2004−2005 Birth Cohort Study	423,719 singleton live births; 2.4% term LBW	HBM CMAQ predictions for 2003−2005 at maternal residence	Entire pregnancy: 9.9 T1: 9.7 T2: 9.9 T3: 10.2	Term LBW Entire pregnancy: 1.04 (0.97, 1.11) T1: 1.01 (0.96, 1.07) T2: 1.07 (1.01, 1.12) T3: 1.01 (0.96, 1.06)

Table 9-4 (Continued): Epidemiologic studies of $PM_{2.5}$ exposure and effects on fetal growth and birth weight.[a]

Study	Study Population	Exposure Assessment	Mean µg/m³	Odds Ratio (95% CI)[b]
†Ha et al. (2017) Multicity, U.S. Follow-up: 2002−2008 Birth Cohort Study	220,572 births, 11.2% SGA; 2.2% term LBW	Population-weighted CMAQ predictions corrected using IDW to local monitors	Entire Pregnancy: 11.8 T1: 11.9 T2: 11.8 T3: 11.9	SGA Entire pregnancy: 1.01 (0.96, 1.07) T1: 1.00 (0.97, 1.04) T2: 1.02 (0.99, 1.06) T3: 1.00 (0.97, 1.03) Term LBW Entire pregnancy: 1.10 (0.97, 1.26) T1: 1.08 (0.99, 1.17) T2: 1.01 (0.93, 1.10) T3: 0.93 (0.86, 1.01)
†Hyder et al. (2014) CT and MA, U.S. Follow-up: 2000−2006 Birth Cohort Study	662,921 births, 2% term LBW, 10% SGA	Weekly averages from closest ground monitors within 50 km of maternal residence Satellite-based predictions from calibration and modeling approach [see (Lee et al., 2012a; Lee et al., 2011a)]	Monitors Entire Pregnancy: 11.9 T1: 12.0 T2: 11.9 T3: 11.8 Satellite (1) Entire Pregnancy: 11.2 T1: 11.2 T2: 11.2 T3: 11.1	Term LBW; entire pregnancy Monitor: 1.02 (0.96, 1.08) Satellite 1: 1.13 (0.94, 1.36) Satellite 2: 1.17 (1.02, 1.36) Term BW; entire pregnancy Monitor: −12.9 (−16.4, −9.5) Satellite 1: −32.6 (−42.5, −22.4) Satellite 2: −93.4 (−47.7, −30.9) SGA; entire pregnancy Monitor: 1.06 (1.02, 1.08) Satellite 1: 1.13 (1.06, 1.22) Satellite 2: 1.17 (1.08, 1.24)
†Kloog et al. (2012) Massachusetts, U.S. Follow-up: 2000−2008 Birth Cohort Study	634,844 singleton live births from MA Birth Registry	Satellite-based predictions from modeling approach [see (Kloog et al., 2011; Lee et al., 2011a)]	9.6	Term BW Entire pregnancy: −4.40 (−5.16, −2.22) 30 days before birth: −4.6 (−7.5, −1.65) 90 days before birth: −7.9 (−10.55, −3.03)
†Lakshmanan et al. (2015) Boston, MA Follow-Up: 2002−2009 Pregnancy Cohort Study	955 singleton births to mothers enrolled in Asthma Coalition on Community, Environment, and Social Stress (ACCESS) cohort	Satellite-based predictions from modeling approach [see (Kloog et al., 2011)] averaged over entire pregnancy	11.0	Birth Weight for Gestational Age (BWGA) z-score; entire pregnancy 0.16 (−0.33, 0.63)

Table 9-4 (Continued): Epidemiologic studies of $PM_{2.5}$ exposure and effects on fetal growth and birth weight.[a]

Study	Study Population	Exposure Assessment	Mean µg/m³	Odds Ratio (95% CI)[b]
†Fleisch et al. (2015) Boston, MA Follow-up: NR Pregnancy Cohort	2,115 singleton live births to mothers enrolled in Project Viva cohort study	Satellite-based predictions from modeling approach [see (Kloog et al., 2011)] averaged over third trimester	11.7	Birth Weight for Gestational Age (BWGA) z-score; third trimester Q1: 1.00 (referent) Q2: −0.02 (−0.14, 0.10) Q3: 0.03 (−0.09, 0.15) Q4: −0.08 (−0.2, 0.04)
†Laurent et al. (2013) Los Angeles, CA 1997−2006 Birth Cohort Study	61,623 term births from network of four hospitals in LA and Orange counties	Ground monitors (closest monitor), CALINE 4 dispersion model; averaged for each month	Monitor: 17.5 CALINE: 4.25	Ground monitor Term LBW Entire pregnancy: 0.93 (0.84, 1.02) birth weight Entire pregnancy: 26.83 (21.56, 32.11) CALINE Term LBW Entire pregnancy: 0.96 (0.74, 1.24) birth weight Entire pregnancy: 21.8 (15.78, 35.18)

[a]This table includes studies conducted in North America in locations where the annual average $PM_{2.5}$ concentration was 20 µg/m³ or less; a complete list of all fetal growth and birth weight studies is included in Supplemental Table S9-2 (U.S. EPA, 2018).

CMAQ = community multiscale air quality modeling system, C-RP = C-reactive protein, EP = entire pregnancy, FR = fecundity ratio M1 = 1st month of pregnancy, IRR = incidence rate ratio, M7 = 7th month of pregnancy, OR = odds ratio, RR = risk or rate ratio, T1 = 1st trimester of pregnancy, T2 = 2nd trimester of pregnancy, T3 = 3rd trimester of pregnancy.

[b]All estimates reported per 5 µg increase in $PM_{2.5}$ unless otherwise stated.

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

In the U.S., a Florida study of over 100,000 births using nearest monitor reported $PM_{2.5}$ exposure averaged across the whole pregnancy period to be associated with increased odds of SGA (defined by national standards) and LBW (Salihu et al., 2012). Another Florida cohort study on LBW, using the EPA's Hierarchical Bayesian Prediction Model output for $PM_{2.5}$ and ozone, reported increased ORs with increasing $PM_{2.5}$ exposure for all trimesters after adjustment for ozone (Table 9-4); ORs with the highest magnitude were observed with exposures during the 2nd trimester (Ha et al., 2014). Hyder et al. (2014) investigated associations between $PM_{2.5}$ and fetal growth using exposure assignment for the entire pregnancy period though monitors or through two different satellite models in a Connecticut cohort. They reported increased odds ratios for SGA all methods, though odds ratios from the satellite based methods were of higher magnitude (Hyder et al., 2014). ORs for LBW were elevated for satellite methods, but near null for analyses using monitors, and change in birth weight was negative for all methods, with larger magnitude in satellite analyses (Hyder et al., 2014). Kloog et al. (2012) used a satellite model for $PM_{2.5}$ across the last 30 and 90 days of pregnancy, as well as the full pregnancy period, and observed decreases in birth weight with increasing $PM_{2.5}$ concentrations in Massachusetts. Lakshmanan et al. (2015)

investigated birth weight in a small Boston cohort (n = 670) using modeled air pollution data involving satellite data and LUR across the full pregnancy period. A slightly larger (n = 2,114) study conducted in eastern Massachusetts, also using modeled satellite data for $PM_{2.5}$ exposure in the third trimester, observed an association with lower birth weight only at the highest quartile of exposure (Fleisch et al., 2015). In a southern California study using both monitors and CALINE4 model output (mean $PM_{2.5}$ = 4.25 $\mu g/m^3$), Laurent et al. (2013) report null associations with LBW and increases in birth weight with increases in $PM_{2.5}$ for the entire pregnancy period.

In summary, many recent studies evaluated the relationship between $PM_{2.5}$ exposure and fetal growth and birth weight, and some provide evidence for a positive association for these outcomes. Similar to the results of the 2009 PM ISA (U.S. EPA, 2009), studies in North America generally report detrimental effects on fetal growth with $PM_{2.5\ exposure}$, including a study that adjusted for ozone as a copollutant (Ha et al., 2014). However, recent studies have provided limited evidence to inform uncertainties identified in the last review, including uncertainties related to potential copollutant confounding, the critical window of exposure and plausible biological mechanisms by which $PM_{2.5}$ exposure could result in reduced fetal growth (Section 9.1.2). Studies of fetal growth and birth weight are summarized in Supplemental Table S9-2(U.S. EPA, 2018).

Toxicological Evidence for Fetal Growth, Birth Weight, and Body Length at Birth

Recent studies have examined the effects of $PM_{2.5}$ on fetal growth and birth weight. A summary of these data is included in Table 9-5. The 2009 PM ISA (U.S. EPA, 2009) provided evidence of decreased birth weight with $PM_{2.5}$ exposure during the first week of gestation. Near term C-section birth weight of the pups was significantly decreased when dams were exposed daily to $PM_{2.5}$ (ambient Sao Paulo, Brazil, air for 6 hours/day during the first week of gestation versus filtered air) (Rocha et al., 2008). Multiple recent studies examined effects of PM exposure on birth weight and pup length at birth with mixed findings, possibly due to different exposure windows. Pregnant FVB mice were exposed for 6 hours/day to Columbus, OH, CAPS and bore pups with significantly decreased birthweight ($p = 0.012$) (Gorr et al., 2014). In a separate study, average birth weight and crown-rump length were not affected by prenatal exposure [6 hours/day, of B6CF1 mice to Sterling Forest CAPs for 6 hours/day during most of gestation (Klocke et al., 2017)]. In another study of B6CF1 mice exposed to Sterling Forest CAPs or to filtered air for 6 hours/day had low birth weight associated with PM exposure during the 1st and 2nd trimester or exposure over the entire pregnancy ($p < 0.05$) (Blum et al., 2017). Fetal growth was also assessed in pups collected near term by C-section at GD17 (length, body weight, placental weight) (Blum et al., 2017). Third trimester PM exposure or exposure during the entirety of pregnancy was associated with decrements in fetal growth (weight and body length, [$p < 0.05$]); body length was also significantly decreased with 1st trimester PM exposure ($p < 0.05$). Placental weight was significantly decreased with 3rd trimester PM exposure and significantly increased with PM exposure over the entire pregnancy ($p < 0.05$) (Blum et al., 2017). Birth length was significantly decreased with PM exposure for any period

of PM exposure during pregnancy including 1st, 2nd, or 3rd trimester or the entire pregnancy (Blum et al., 2017). The multiple studies mentioned above assessed birth weight or length in pups after prenatal $PM_{2.5}$ exposure and the majority of these animal toxicology studies show that PM exposure is associated with decreased birth weight of pups or decreased body length at birth (Table 9-5).

Table 9-5 Recent animal toxicological studies of $PM_{2.5}$ exposure and effects on fetal growth and birth weight.

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Blum et al., 2017)	Pregnant B6C3F1 hybrid mice, n = 8−17 dams per exposure.	Mice were exposed 6 h/day to Sterling Forest CAPs during the pregnancy (entire pregnancy or 1st trimester, 2nd trimester, or 3rd trimester). Average daily CAPS concentration ranged from 113 to 192.5 μg/m^3.	Fetal growth at GD17 (body length, body weight)
(Gorr et al., 2014)	Pregnant and lactating FVB mice	Ohio OASIS-1 aerosol concentration system was used to expose dams and pups placed in exposure chambers from GD1 through weaning offspring at 3 weeks. Male offspring at 3 mo of age were then isolated for assessments.	Birth weight
(Klocke et al., 2017)	Male and female B6C3F1 mice (8−10 weeks old) were mated and then dams were exposed to Sterling Forest CAPs.	Prenatal exposure to filtered air or Sterling Forest CAPs for 6 h/day during gestation (GD0.5 to GD 16.5). Mean CAPs concentration over the exposure period averaged 92.696 ± 19.16 (mean ± SD) μg/m^3 compared to 3.526 ± 0.87 μg/m^3 for FA controls.	Birth weight and crown-rump length

Toxicology Evidence for Changes in Anogenital Distance

Measurements of anogenital distance, a marker of androgenization using measurement of the perineum, were collected in pups at PND10 and PND21 (Blum et al., 2017). Pregnant animals were exposed to Sterling forest CAPS for 6 hours/day during one-third of pregnancy or a trimester (1st, 2nd, or 3rd) or during the entirety of pregnancy. In female offspring, significantly decreased AGD was reported with $PM_{2.5}$ exposure in the 1st trimester (PND10 and PND21) and with $PM_{2.5}$ exposure over the entire pregnancy (PND21). Shorter AGD in female rodents is associated with variation in reproductive traits in adulthood (1st estrus, timing of vaginal opening, lordosis) (Zehr et al., 2001). In male pups, AGD mirrored that of female pups at PND21 but not at PND10 (Blum et al., 2017). Both males and females had shortened AGD with 1st trimester CAPs exposure or exposure for the entire pregnancy. AGD length was also sensitive to 2nd trimester in male offspring. The effect of $PM_{2.5}$ exposure in decreasing the AGD is consistent with an anti-androgenic effect of PM exposure on pups.

Toxicological Evidence for Altered Sex Ratio in Litters at Birth

Sex ratio, the ratio of males to females in a litter of animals, is often measured to try to understand if an environmental exposure can contribute to a shift in the ratio of sexes of animals born, an effect that is known to be modulated by stress or other environmental exposures. In a recent study where B6CF1 mice were exposed to Sterling Forest CAPs or to filtered air for 6 hours/day, sex ratio was unaffected by PM exposure at multiple gestational exposure windows (1st, 2nd, or 3rd trimester) and the entirety of pregnancy (Blum et al., 2017).

9.1.2.4 Preterm Birth

Preterm birth (PTB), delivery that occurs before 37 weeks of completed gestation, is a marker for fetal underdevelopment and is related to subsequent adverse health outcomes (e.g., infant mortality, neurodevelopmental problems, growth issues) (Mathews and MacDorman, 2010; Saigal and Doyle, 2008; IOM, 2007; Gilbert et al., 2003). PTB is characterized by multiple etiologies (spontaneous, premature rupture of membranes, or medically induced), and identifying exact causes of PTB is difficult. It is likely that some mechanistic pathways are shared between the three groups; however, isolated causes are also likely to exist. Few, if any, studies distinguish between these three groups in examining associations between air pollution and PTB, though some investigations of premature rupture of membrane (PROM) have been conducted. There is substantial uncertainty surrounding the biological mechanisms leading to PTB, and multiple mechanisms may exist simultaneously.

Epidemiologic Evidence for Preterm Birth and Premature Rupture of Membranes (PROM)

The 2009 PM ISA (U.S. EPA, 2009) included limited number studies evaluating the relationship between $PM_{2.5}$ exposure and PTB, each of which reported a positive association. A number of uncertainties affecting interpretation of the evidence for an association between $PM_{2.5}$ exposure and PTB were identified in the 2009 PM ISA (U.S. EPA, 2009), such as identifying the relevant exposure period. The number of studies evaluating the relationship between $PM_{2.5}$ exposure and PTB has grown considerably in the last decade, and the majority of recent studies report positive associations between $PM_{2.5}$ exposure and PTB, frequently for exposures averaged over the entire pregnancy period (Defranco et al., 2016; Hao et al., 2016; Laurent et al., 2016; Lavigne et al., 2016b; Mendola et al., 2016a; Pereira et al., 2015; Ha et al., 2014; Padula et al., 2014; Pereira et al., 2014a; Chang et al., 2013; Lee et al., 2013; Kloog et al., 2012; Salihu et al., 2012; Warren et al., 2012; Gehring et al., 2011; Wilhelm et al., 2011; Wu et al., 2011; Wu et al., 2009; Brauer et al., 2008). However, while the body of literature has grown considerably since the last review, the evidence from these studies is less consistent than reported in the 2009 PM ISA (U.S. EPA, 2009). Several recent studies report null (Giorgis-Allemand et al., 2017; Mendola et al., 2016a; Hannam et al., 2014; Hyder et al., 2014; Pereira et al., 2014a; Salihu et al., 2012;

Gehring et al., 2011; Rudra et al., 2011; Darrow et al., 2009) or negative (Johnson et al., 2016; Mendola et al., 2016a; Stieb et al., 2015; Pereira et al., 2014a) effect estimates. All of these studies are characterized in Supplemental Table S9-3 (U.S. EPA, 2018).

Many of the studies of $PM_{2.5}$ and preterm birth are conducted in North America, where annual average $PM_{2.5}$ concentrations have decreased considerably in the last decade, and are summarized in Table 9-6. All of the studies included in the 2009 PM ISA (U.S. EPA, 2009) relied on fixed-site monitors to assign exposure $PM_{2.5}$. While many more recent studies have used satellite-based methods or statistical models to assign $PM_{2.5}$ exposure, several recent studies estimated $PM_{2.5}$ concentrations from fixed-site monitors in order to assign exposure. In a study of a cohort from Hillsborough county Florida, Salihu et al. (2012) report ORs elevated from the null with $PM_{2.5}$ exposure using nearest monitor to assign entire pregnancy exposure. In a longitudinal cohort from Rochester NY, which followed 3,264 women over 7,121 pregnancies, positive effect estimates were reported for all trimester exposures, with the highest magnitude with exposures in the first trimester (OR: 1.69, 95% CI: 1.22, 2.29) (Pereira et al., 2015). Effect estimates from this study, which used nearest monitor for exposure assignment, were similar for all buffer distances around monitors (Pereira et al., 2015). Brauer et al. (2008) reported positive ORs using both LUR and IDW in a Vancouver cohort with entire pregnancy exposure (OR: 1.34, 95% CI: 1.05, 1.69). A small Washington state study using LUR to estimate $PM_{2.5}$ exposure over the last 3 months of pregnancy, and a study in New York City utilizing combinations of fixed-site monitoring data and air survey data reported null associations (Johnson et al., 2016; Rudra et al., 2011).

Some recent studies used statistical models or satellite-based methods to estimate exposure to $PM_{2.5}$ when evaluating associations with PTB. In a California-based population, (Wu et al., 2011) observed increased odds of PTB with higher levels of $PM_{2.5}$ estimated with the CALINE 4 dispersion model and averaged over the entire pregnancy period. They also observed higher magnitude effect estimates with very PTB (<30-weeks gestational age) compared to moderate PTB (<35-weeks gestational age) or PTB (<37-weeks gestational age). In a study of a Florida cohort, using the EPA's hierarchical Bayesian CMAQ model output for $PM_{2.5}$ concentrations, Ha et al. (2014) reported positive ORs across all trimesters and for entire pregnancy exposures (entire pregnancy OR: 1.14, 95% CI: 1.10, 1.18). The magnitude of the estimate effects was increased after adjustment for ozone in exposure for first and second trimesters and entire pregnancy (entire pregnancy OR after adjustment for ozone: 1.29, 95% CI: 1.20, 1.38), while those for the third trimester remained positive, but were somewhat attenuated (Ha et al., 2014). Hao et al. (2016) reported a positive association with PTB using fused CMAQ model estimates of $PM_{2.5}$ concentrations in Georgia (U.S.) Lavigne et al. (2016b) and Kloog et al. (2012) observed increased ORs for entire pregnancy exposure to $PM_{2.5}$ estimated with satellite-based models for a cohort of more than 800,000 women in Ontario, Canada and a large Massachusetts cohort, respectively.

Several recent studies evaluated the association between $PM_{2.5}$ exposure and PTB using both fixed-site monitoring data and satellite-based methods to assign exposure. In a cohort set in both Massachusetts and Connecticut, Hyder et al. (2014) reported null associations between PTB and $PM_{2.5}$

exposure over the entire pregnancy period; this study used fixed-site monitors and two separate satellite-based models to estimate exposures; results were consistently null or negative across exposure assignment metrics. Finally, a study of over 2.78 million births across Canada, using a both fixed-site monitor and satellite-based LUR metrics to estimate exposures over the entire pregnancy period, reported inverse ORs with increasing $PM_{2.5}$ exposure (Stieb et al., 2015).

There were no studies included in the 2009 PM ISA (U.S. EPA, 2009) that examined the relationship between $PM_{2.5}$ exposure and PROM. Recent studies evaluate the relationship between both short- and long-term $PM_{2.5}$ exposure and PROM. Effect estimates are inconsistent across recent studies of PROM for long-term $PM_{2.5}$ exposure. An Australian cohort reported elevated ORs with exposure to $PM_{2.5}$ in the second and third trimesters (Pereira et al., 2014b). A U.S. cohort reported relative risks below the null for both PROM and preterm PROM (Wallace et al., 2016), and a small Rochester, NY cohort (n = 3,264) followed over multiple pregnancies reported null associations (Pereira et al., 2015).

Several recent studies examined the association between short-term $PM_{2.5}$ exposure and PTB. Darrow et al. (2009) report null associations using a time-series design with 1-week lagged exposures. Also, using a time-series design, Arroyo et al. (2015) observed positive associations with a 1-day lagged $PM_{2.5}$ exposure, and exposure during week 17 of gestation (Arroyo et al., 2016). Symanski et al. (2014) and Rappazzo et al. (2014) separated PTB into multiple categories based on gestational age. Both observed positive and negative associations depending on combined exposure and outcome period, Symanski et al. (2014) with 4-week exposures, and Rappazzo et al. (2014) with exposures during individual weeks of pregnancy. Warren et al. (2012) also examined exposures at individual weeks of pregnancy, observing elevated associations through week 22 of pregnancy. An additional U.S. study observed positive associations with PROM and $PM_{2.5}$ concentrations estimated from a modified CMAQ model in the 5 hours before hospital admission (Wallace et al., 2016).

In summary, a number of recent studies expand and extend the evidence included in the 2009 PM ISA (U.S. EPA, 2009) for relationship between $PM_{2.5}$ exposure and PTB, though the larger body of literature is somewhat less consistent than the small body of evidence in the 2009 PM ISA. Among studies conducted in North America, where mean $PM_{2.5}$ concentrations tended to be below 12 $\mu g/m^3$, generally positive associations were observed between PTB and $PM_{2.5}$ exposure. This pattern of positive associations was consistent across studies that used fixed-site monitors, statistical models, or satellite-based methods to assign exposure. Addressing an uncertainty identified in the 2009 PM ISA (U.S. EPA, 2009), a study that included a copollutant model including $PM_{2.5}$ and ozone reported the positive association between $PM_{2.5}$ exposure and PTB to be robust to adjustment for ozone. However, timing of exposure, another uncertainty identified in the 2009 PM ISA (U.S. EPA, 2009), varies considerably across these studies and remains an uncertainty in interpreting the results of these studies. In addition to PTB, recent studies also evaluated the relationship between short- and long-term $PM_{2.5}$ exposure and PROM, and outcome that was not included in the 2009 PM ISA (U.S. EPA, 2009). These studies report inconsistent results across studies examining both short- and long-term $PM_{2.5}$ exposures.

Table 9-6 Epidemiologic studies of $PM_{2.5}$ exposure and preterm birth.[a]

Study	Study Population	Exposure Assessment	Mean µg/m³	Effect Estimates 95% CI[b]
Long-term Exposure				
†Wu et al. (2011) LA and Orange Counties, CA, U.S. Follow-up: 2000−2006 Birth Cohort Study	81,186 neonatal records from Memorial Health Care System, a four-hospital network; no birth certificate data used	Nearest monitor (n = 10) Modified CALINE4 line-source dispersion model; focus on local traffic-generated pollution within 3 km of residence at delivery; correlation with measured $PM_{2.5}$ = 0.21	Monitor: 17.3 CALINE: 1.8	Preterm birth (<37 weeks) Monitor, LA, EP: 1.04 (0.94, 1.15) Monitor, Orange, EP: 1.09 (1.00, 1.20) Very preterm birth (<30 weeks) Monitor, LA, EP: 1.03 (0.81, 1.30) Monitor, Orange, EP: 1.33 (0.99, 1.77)
†Brauer et al. (2008) Vancouver, BC Follow-up: 1999−2002 Birth Cohort Study	70,249 live births in study area with data on residential history	Nearest monitor (within 10 km) and IDW (within 50 km) based on ground-monitors (n = 7) assigned to postal codes LUR (R^2 = 0.52), cross-validation revealed moderate performance of $PM_{2.5}$ LUR model (R^2 = 0.52)	Nearest: 5.3 IDW: 5.1 LUR: 4.0	Preterm births (PTB) <37 weeks IDW: EP: 1.34 (1.05, 1.69) Preterm births (PTB) <35 weeks IDW: EP: 1.76 (1.10, 2.93) Preterm births (PTB) <30 weeks IDW: EP: 1.84 (0.66, 5.19)
†Salihu et al. (2012) Hillsborough County, FL Follow-up: 2000−2007 Birth Cohort Study	103,961 singleton live births; 9.1% PTB and 1.1% VPTB	6-day concentrations from 14 ground monitors; maternal residential ZIP code centroid linked to nearest monitor, based on centroid of ZIP code in which monitor was located; exposure dichotomized at median	Median: 11.28	Preterm birth Exposed v. unexposed, EP: 1.03 (0.98, 1.07) Very preterm birth (<33 weeks) Exposed v. unexposed, EP: 1.05 (0.93, 1.18)
†Ha et al. (2014) Florida, US Follow-up: 2004−2005 Birth Cohort Study	423,719 singleton live births; 2.4% term LBW	HBM CMAQ predictions for 2003−2005 at maternal residence	EP: 9.9 T1: 9.7 T2: 9.9 T3: 10.2	Preterm birth T1: 1.06 (1.03, 1.08) T2: 1.25 (1.22, 1.28) T3: 1.05 (1.02, 1.07) EP: 1.14 (1.10, 1.18) Very preterm birth (<32 weeks) T1: 1.12 (1.05, 1.20) T2: 1.45 (1.37, 1.54) T3: 1.02 (0.95, 1.09) EP: 1.22 (1.12, 1.32)

Table 9-6 (Continued): Epidemiologic studies of $PM_{2.5}$ exposure and preterm birth.[a]

Study	Study Population	Exposure Assessment	Mean µg/m³	Effect Estimates 95% CI[b]
†Lavigne et al. (2016b) Ontario, Canada Follow-up: 2005−2012 Birth Cohort Study	N = 818,400	Satellite based model, 1 × 1 km	9.2	Preterm birth EP: 1.10 (1.06, 1.15)
†Hao et al. (2016) Georgia, U.S. Follow-up: 2002−2006 Birth Cohort Study	N = 511,658	Model, fused CMAQ	11.44	Preterm birth EP: 1.05 (1.01, 1.09) T1: 1.00 (0.99, 1.03) T2: 1.03 (1.01, 1.05) T3: 1.01 (0.99, 1.03)
†Pereira et al. (2015) Rochester, NY, U.S. Follow-up: 2004−2012 Birth Cohort Study	N = 3,264 women	Monitor, nearest within 40 km	9	Preterm birth EP: 2.19 (1.40, 3.44) T1: 1.69 (1.22, 2.29) T2: 1.54 (1.10, 2.10) T3: 1.34 (1.00, 1.84)
†Kloog et al. (2012) Massachusetts, US Follow-up: 2000−2008 Birth Cohort Study	634,844 singleton live births from MA Birth Registry	Satellite-based predictions from modeling approach [see (Kloog et al., 2011; Lee et al., 2011a)]	9.6	Preterm birth EP: 1.03 (0.54, 0.63)
†Hyder et al. (2014) CT and MA, US Follow-up: 2000−2006 Birth Cohort Study	662,921 births, 2% term LBW, 10% SGA	Weekly averages from closest ground monitors within 50 km of maternal residence Satellite-based predictions from calibration and modeling approach [see (Lee et al., 2012a; Lee et al., 2011a)]	Monitors EP: 11.9 Satellite (1) EP: 11.4 Satellite (2) EP: 11.2	Preterm birth Monitor: 1.00 (0.98, 1.04) Satellite 1: 0.96 (0.86, 1.04) Satellite 2: 1.00 (0.92, 1.08)
†Rudra et al. (2011) Washington, U.S. Follow-up: 1996−2006 Birth Cohort Study	N = 3,509 women	Land use regression	10.8	Preterm birth Last 3 months: 0.74 (0.39, 1.48)

Table 9-6 (Continued): Epidemiologic studies of $PM_{2.5}$ exposure and preterm birth.[a]

Study	Study Population	Exposure Assessment	Mean µg/m³	Effect Estimates 95% CI[b]
†Johnson et al. (2016) New York City, NY, U.S. Follow-up: 2008−2010 Birth Cohort Study	N = 258,294	Combination of NYC community air survey (spatial) and regulatory monitors (temporal), within 300 m	11	Preterm birth T1: 0.98 (0.95, 1.02) T2: 0.97 (0.94, 1.01) Spontaneous preterm birth T1: 0.99 (0.95, 1.04) T2: 0.99 (0.95, 1.04) Medically indicated preterm birth T1: 0.97 (0.92, 1.03) T2: 0.97 (0.92, 1.04)
†Stieb et al. (2015) Canada 1999−2008 Cohort	N = 2,781,940	Land use regression based on monitor and satellite data to postal code	8.33−8.51	Preterm birth EP: 0.95 (0.92, 0.98)
PROM				
†Pereira et al. (2015) Rochester, NY, U.S. 2004−2012 Longitudinal cohort	N = 3,264 women	Monitor, nearest within 40 km	9	Preterm birth EP: 2.19 (1.40, 3.44) T1: 1.69 (1.22, 2.29) T2: 1.54 (1.10, 2.10) T3: 1.34 (1.00, 1.84) Premature rupture of membranes EP: 1.00 (0.86, 1.22) T1: 0.95 (0.82, 1.10) T2: 0.95 (0.82, 1.16) T3: 0.95 (0.73, 1.22)
†Wallace et al. (2016) U.S. Follow-up: 2002−2008 Birth Cohort Study	N = 223,375	Model, specialized CMAQ, bias corrected with monitor data Averaged over delivery hospital referral region Exposures lagged before hour of admission for delivery	11.9	Preterm premature rupture of membranes Adjusted for all pollutants Lag 0 h: 1.04 (1.00, 1.07) Lag 1 h: 1.04 (1.00, 1.07) Lag 2 h: 1.03 (1.00, 1.07) Lag 3 h: 1.03 (1.00, 1.07) Lag 4 h: 1.03 (1.00, 1.06)
†Pereira et al. (2015) Rochester, NY, U.S. Follow-up: 2004−2012 Birth Cohort Study	N = 3,264 women	Monitor, nearest within 40 km	9	Premature rupture of membranes EP: 1.00 (0.86, 1.22) T1: 0.95 (0.82, 1.10) T2: 0.95 (0.82, 1.16) T3: 0.95 (0.73, 1.22)
Short-term Exposure				

Table 9-6 (Continued): Epidemiologic studies of $PM_{2.5}$ exposure and preterm birth.[a]

Study	Study Population	Exposure Assessment	Mean µg/m³	Effect Estimates 95% CI[b]
†Darrow et al. (2009) Atlanta, GA, U.S. 1994−2004 Time-series	N = 1,994 days, 476,789 births	Monitors, daily population weighted spatial averages from 11 monitors	16.4−16.5	Preterm birth (RR) 1-week lag: 0.98 (0.97, 1.00) Within 4 miles of monitor 1-week lag: 1.00 (0.97, 1.02)
†Symanski et al. (2014) Harris County, Texas, U.S. Follow-up: 2005−2007 Birth Cohort Study	N = 171, 923	Monitors County average	NR	Severe preterm birth (<28 weeks) weeks 1−4: 1.37 (1.15, 1.64) weeks 5−8: 0.95 (0.77, 1.15) weeks 9−12: 1.13 (0.93, 1.37) weeks 13−16: 0.84 (0.70, 1.01) weeks 17−20: 1.30 (1.07, 1.58) Moderately preterm birth (29−32 weeks) weeks 1−4: 1.38 (1.20, 1.59) weeks 5−8: 1.04 (0.88, 1.23) weeks 9−12: 1.28 (1.09, 1.51) weeks 13−16: 0.98 (0.84, 1.15) weeks 17−20: 0.96 (0.82, 1.13) weeks 21−24: 0.94 (0.80, 1.10) weeks 25−28: 1.39 (1.20, 1.61) Mildly preterm birth (33−36 weeks) weeks 1−4: 1.08 (1.02, 1.13) weeks 5−8: 1.04 (0.98, 1.10) weeks 9−12: 1.12 (1.06, 1.05) weeks 13−16: 0.98 (0.93, 1.03) weeks 17−20: 1.08 (1.01, 1.14) weeks 21−24: 0.91 (0.86, 0.96) weeks 25−28: 1.05 (0.99, 1.11) weeks 29−32: 1.14 (1.08, 1.21)
†Rappazzo et al. (2014) Pennsylvania, Ohio, New Jersey, U.S. Follow-up: 2000−2005 Birth Cohort Study	N = 1,940,213	Fused CMAQ model, northeastern U.S. specific Exposures over each week of gestation	14.46	Reported as figures
†Warren et al. (2012) Texas, U.S. Follow-up: 2002−2004 Birth Cohort Study	NR	Monitors CMAQ Exposures over each week of gestation	NR	Reported as figures

Table 9-6 (Continued): Epidemiologic studies of $PM_{2.5}$ exposure and preterm birth.[a]

Study	Study Population	Exposure Assessment	Mean µg/m³	Effect Estimates 95% CI[b]
†Wallace et al. (2016) U.S. Follow-up: 2002–2008 Birth Cohort Study	N = 223,375	Model, specialized CMAQ, bias corrected with monitor data Averaged over delivery hospital referral region Exposures lagged before hour of admission for delivery	11.9	Preterm premature rupture of membranes Adjusted for all pollutants Lag 0 h: 1.04 (1.00, 1.07) Lag 1 h: 1.04 (1.00, 1.07) Lag 2 h: 1.03 (1.00, 1.07) Lag 3 h: 1.03 (1.00, 1.07) Lag 4 h: 1.03 (1.00, 1.06)

[a]This table includes studies conducted in North America in locations where the annual average $PM_{2.5}$ concentration was 20 µg/m³ or less; a complete list of all PTB studies is included in Supplemental Table S9-3 (U.S. EPA, 2018).

CMAQ community multiscale air quality modeling system, C-RP: C-reactive protein, EP: entire pregnancy, FR: fecundity ratio M1: 1st month of pregnancy, IRR: incidence rate ratio, M7: 7th month of pregnancy, OR: odds ratio, RR: risk or rate ratio, T1: 1st trimester of pregnancy, T2: 2nd trimester of pregnancy, T3: 3rd trimester of pregnancy.

[b]All estimates reported per 5 µg increase in $PM_{2.5}$ unless otherwise stated.

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Toxicological Evidence for Preterm birth

The 2009 PM ISA (U.S. EPA, 2009) contained no animal studies of preterm birth. A more recent study monitored pup gestational day at birth to determine if pups were born preterm after CAPs exposure (6 hours/day) during specific windows or trimesters of pregnancy. B6CF1 mouse preterm birth was associated with 2nd, 3rd, or entire pregnancy exposure to Sterling Forest CAPs (Blum et al., 2017). $PM_{2.5}$ exposure during certain periods of pregnancy was associated with preterm birth in mouse pups.

9.1.2.5 Birth Defects

Birth defects are structural and functional abnormalities that can cause physical disability, intellectual disability, and other health problems; they are a leading cause of infant mortality and developmental disability in the U.S. Periods of sensitivity to birth defect development are known for many anomaly types; for example, the critical period of cardiac organogenesis, and thus heart defects, is post-conception weeks 3−8. This knowledge of critical periods means that there are fewer uncertainties around timing of exposure for birth defects compared to other birth outcomes. Birth defects as a category are uncommon, occurring in approximately 3% of live births, and low numbers of specific birth defects can lead to wide confidence intervals in epidemiologic studies investigating environmental causes of birth defects.

Epidemiologic Evidence for Birth Defects

The 2009 PM ISA (U.S. EPA, 2009) synthesized small numbers of studies of PM and birth defects; these often focused on PM10 as the exposure of interest. Though overall numbers remain small, there are several new studies of $PM_{2.5}$ and birth defects, typically cardiac or orofacial defects. These studies are primarily conducted within the U.S., and study populations often arise from states with active birth defect registries, where experts will seek out infants with records of birth defects. One study used data from the National Birth Defects Prevention Study, a large multistate initiative with detailed residential histories and information on many potential confounders, and examined associations between both short- (week long) and longer-term exposure periods (average over post-conception weeks 2−8) and cardiac birth defects (Stingone et al., 2014). In Stingone et al. (2014), median $PM_{2.5}$ levels assigned with monitors across the period of interest were 11.6 $\mu g/m^3$; $PM_{2.5}$ exposure was associated with increased odds of some cardiac defects (hypoplastic left heart syndrome, atrioventricular septal defect), decreased for others (atrial septal defects [ASD]), and null for many. This pattern of results is reflected in the general body of literature for cardiac defects, where several studies have shown either null associations or decreased odds of heart defects (including ASD) with $PM_{2.5}$ exposure (Vinikoor-Imler et al., 2015; Schembari et al., 2014; Agay-Shay et al., 2013; Padula et al., 2013c), while others have reported positive odds ratios (Girguis et al., 2016; Zhang et al., 2016; Salemi et al., 2015; Padula et al., 2013b). Studies of orofacial defects have similar issues, and report inconsistent results (Zhu et al., 2015; Padula et al., 2013a; Marshall et al., 2010). Studies of other types of birth defects have reported positive associations with limb defects (Vinikoor-Imler et al., 2013) and abdominal wall defects (Schembari et al., 2014), and negative associations with sperm disomy (Jurewicz et al., 2014). When examining weekly exposure, Stingone et al. (2014) observed increased odds of Tetralogy of Fallot and pulmonary valve stenosis at higher deciles of $PM_{2.5}$ exposure, and Zhu et al. (2015) observed increased odds of cleft lip with or without cleft palate with $PM_{2.5}$ exposure. In a further analysis of the population analyzed in Stingone et al. (2014), Warren et al. (2016) identified different gestational days as critical $PM_{2.5}$ exposure periods for Tetralogy of Fallot and pulmonary valve stenosis.

In summary, results for most birth defects are inconsistent across studies, or have a limited number of studies, hindering the ability to draw conclusions about this body of literature. Studies of birth defects and $PM_{2.5}$ are characterized in Supplemental Table S9-4 (U.S. EPA, 2018).

Toxicological Evidence for Birth Defects

No previous animal toxicology study addressed birth defects with $PM_{2.5}$ exposure. In a recent study, the effect of $PM_{2.5}$ on exacerbating congenital heart defects was evaluated in an animal model (Chen et al., 2016). Elevated homocysteine levels or hyperhomocysteinaemia during pregnancy, is a risk factor for pregnancy complications including congenital heart defects (Verkleij-Hagoort et al., 2006). $PM_{2.5}$ exposure potentiated the adverse fetal cardiovascular outcomes in rodent pups whose dams were hyperhomocysteinaemic during pregnancy (Chen et al., 2016). In this study, animals were exposed to

ambient $PM_{2.5}$ ($PM_{2.5}$, range 8−68 μg/m^3, mean 36 μg/m^3) in Fuzhou China or filtered air (FA) with particles removed (Chen et al., 2016). Pregnant dams were exposed to $PM_{2.5}$ during pregnancy and lactation and were made hyperhomocysteinaemic at the sensitive window for heart development (G8−G10). Various endpoints including morphological changes to the heart, apoptosis of the myocardium, cardiac progenitor transcriptional factor levels, and cytokine concentrations were studied in the offspring. $PM_{2.5}$ exposure potentiated the adverse morphological changes to the heart (atrial, ventral, or septal heart defects) that were induced by HCY. These morphological changes to the heart were accompanied by changes in myocardial apoptosis, expression of cardiac progenitors (GATA4 and Nkx2−5), and changes in cytokines (TNF-a and IL-1B).

9.1.2.6 Fetal and Infant Mortality

Fetal mortality is the intrauterine death of a fetus. Often these deaths are divided into those occurring before 20 weeks of gestation (spontaneous abortion) and those occurring after (miscarriage/stillbirth). In most areas, fetal deaths are only reported after 20 weeks of completed gestation; this may lead to potential bias, as the population at risk of fetal death is any conception but the actual measured population is only those fetuses reaching at least 20 weeks gestational age. Studies therefore tend to focus on the miscarriage/stillbirth fraction of fetal mortality. Infant mortality is a death occurring in the first year of life, and is divided into two periods: neonatal (i.e., death during the first 28 days), and post-neonatal (i.e., death after the first month of life and before the first birthday). The 2009 PM ISA (U.S. EPA, 2009) reported limited evidence for an association between PM_{10} and fetal mortality (measured as stillbirth) and consistent epidemiologic evidence for an association between PM_{10} exposure and infant mortality, especially due to respiratory causes during the post-neonatal period. A limited number of studies included in the 2009 PM ISA (U.S. EPA, 2009) evaluated the association between $PM_{2.5}$ exposure and infant mortality, and none considered infant mortality due to respiratory causes during the post-neonatal period.

In studies of fetal mortality occurring after 20 weeks of gestation, recent studies generally report positive associations, though timing of exposure varies across studies (Defranco et al., 2015; Green et al., 2015; Faiz et al., 2012). Defranco et al. (2015) reported positive associations with high $PM_{2.5}$ exposure (defined as above mean plus IQR) in entire pregnancy and third trimester, but not first or second trimesters. Green et al. (2015) observed positive associations with entire pregnancy exposures (OR 1.03, 95% CI: 0.99, 1.06), though these associations were attenuated after adjustment for NO_2 (OR 0.98, 95% CI: 0.93, 1.05), and stratification by California air basin resulted in associations with higher magnitudes (e.g., Sacramento Valley OR: 1.16, 95% CI: 1.00, 1.35; San Francisco Bay OR: 1.15, 95% CI: 0.97, 1.36). In a New Jersey study, Faiz et al. (2012) observed positive associations in all trimesters, though slightly stronger ones in the first and second trimesters. In a study of short-term exposures, Faiz et al. (2013) reported a positive association with stillbirth and $PM_{2.5}$ exposure averaged over the two previous days previous, though associations were attenuated to the null after copollutant adjustment (i.e., NO_2,

SO_2). Arroyo et al. (2016) also reported a positive association with short-term $PM_{2.5}$ exposure in gestational week 31 and late fetal death (less than 24 hours after birth). Studies of fetal mortality and $PM_{2.5}$ are characterized in Supplemental Table S9-5 (U.S. EPA, 2018).

The two studies of post-neonatal infant mortality reported positive associations for all-cause mortality, respiratory related mortality, and sudden infant death syndrome (SIDS) (Son et al., 2011b; Woodruff et al., 2008). In the U.S.-based study, the association for respiratory-related mortality (OR: 1.08, 95% CI: 0.97, 1.20) remained positive but was attenuated after adjusting for CO (OR: 1.04, 95% CI: 1.04, 0.92, 1.17), and other gaseous pollutants (i.e., SO_2, and O_3), while the association for SIDS moved away from the null after adjusting for CO in copollutant models Woodruff et al. (2008). In a case-crossover study, Yorifuji et al. (2016) report associations between same day $PM_{2.5}$ and post-neonatal death and all-cause deaths, as well as deaths related to respiratory, SIDS, and birth defects. Studies of infant mortality and $PM_{2.5}$ are characterized in Supplemental Table S9-5 (U.S. EPA, 2018).

9.1.3 Developmental Effects

Pregnancy and infancy are periods of rapid development and exposures occurring during these times may have long-lasting effects that do not manifest immediately (i.e., fetal origins or fetal programming hypothesis). Researchers have examined several health outcomes in associations with exposures during the periods of early development including: cancer (Chapter 8), growth (Chapter 9), infection (Chapter 5), eczema (Chapter 5), neurodevelopmental effects including autism (Chapter 8), cardiovascular effects (Chapter 7) and respiratory effects including asthma (Chapter 5). Of these, respiratory and neurodevelopmental outcomes are the most studied. In addition, these studies of early-life exposure provide evidence that long-term $PM_{2.5}$ exposure is associated with developmental effects (Table 9-7). The developmental studies are characterized in more detail in their respective sections elsewhere in the ISA and are presented here as summaries.

Table 9-7 Summary of developmental effects.

Developmental Effects	Summary of Evidence	Cross-link to Study Details	Causal Determination
Respiratory	Epidemiologic evidence: Studies provide evidence of decrements in lung function growth, asthma development, and respiratory infection.	Section 5.2.2.1 Section 5.2.3.1 Section 5.2.2	**Causal relationship is likely** to exist for long-term exposure to $PM_{2.5}$ and respiratory effects
	Toxicological evidence: Early life exposure to particulate matter has the potential to alter the growth or function of the respiratory system.		
Neurodevelopmental	Epidemiologic evidence: Limited body of evidence does not provide consistent evidence of positive associations with cognitive and behavioral effects or autism.	Section 8.2.7.2	**Causal relationship is likely** to exist for long-term exposure to $PM_{2.5}$ and nervous system effects
	Toxicological evidence: Neurodevelopment in laboratory animal toxicology studies is impacted by $PM_{2.5}$ exposure, including the structural change of ventriculomegaly, and brain inflammatory activation.	Section 8.2.7.2	
Cardiovascular	Epidemiologic evidence: $PM_{2.5}$ exposure was associated with increased odds of some cardiac defects, decreased for others, and null for many.	Section 6.2.5 Section 9.1.2.5	**Causal relationship** exists for long-term exposure to $PM_{2.5}$ and cardiovascular system effects
	Toxicological evidence: Early life exposure to PM in animal models has effects on the developing heart, inducing heart failure in adult animals after early life PM exposure.	Section 6.2.5.2 Section 9.1.2.5	

9.1.3.1 Respiratory Developmental Effects

Epidemiologic Evidence of Respiratory Development

Recent studies evaluate the relationship between $PM_{2.5}$ exposure during the prenatal period and/or the first year of life and respiratory health effects and generally observe positive associations. These studies are characterized in Chapter 5, and include studies of lung development (Section 5.2.2.1), lung function (Section 5.2.2.2.1), asthma development (Section 5.2.3.1) and respiratory infection (Section 5.2.6). Evidence from these studies inform and contribute to the conclusion that there is likely to be a causal relationship between long-term $PM_{2.5}$ exposure and respiratory effects. In addition, these studies of early life exposure provide evidence that long-term $PM_{2.5}$ exposure is associated with developmental effects (Table 9-7).

Toxicological Evidence for Respiratory Development

Early life exposure to particulate matter has the potential to alter the growth or function of the respiratory system. Multiple lines of evidence support that $PM_{2.5}$ or its soluble components can cross the placenta or the maternal fetal barrier to the fetal circulation with the potential to impact the developing fetus (Valentino et al., 2016; Veras et al., 2008). The existing evidence for the current ISA is summarized below in Table 9-7. The 2009 PM ISA (U.S. EPA, 2009) included a study of mice with impaired lung development and lung function after prenatal plus postnatal exposure to ambient $PM_{2.5}$ (Mauad et al., 2008); pulmonary pressure volume analysis demonstrated significant reductions in inspiratory and expiratory volumes and structural aberration included incomplete alveolarization of the lungs. In addition, Pires-Neto et al. (2006) found secretory changes in the nasal cavity of young mice exposed for 5 months to urban $PM_{2.5}$. These findings are discussed in Section 5.2.2.

In studies of DEP and asthma, prenatal DEP exposure increased susceptibility of animals to adult-induced allergic (ovalbumin [OVA]) asthma (significantly increased lung resistance and airway hyper-responsiveness, increased airway inflammation), shifted TH1 and TH2 responses and increased BAL cell counts all in an Aryl Hydrocarbon Receptor (AHR)-dependent mechanism (Manners et al., 2014). Another recent study showed diesel exhaust particulate exposure in utero and allergen exposure in utero conveyed protection from systemic and airway allergic (Aspergillus-induced) immune responses in adult offspring (Corson et al., 2010); adult offspring had a lower immune response when exposed in utero to DE or DE and Aspergillus fumigatus in combination versus allergen.

In another recent study, gestational and early prenatal exposure to Beijing $PM_{2.5}$ is associated with significant lung pathology (peribronchial and perivascular inflammation), increased oxidant production and a decreased antioxidant pool as well as significant changes to circadian clock gene expression (Song et al., 2017). More details on these studies can be found in Section 5.2.2.

9.1.3.2 Neurodevelopmental Effects

Epidemiologic Evidence of Neurodevelopment

Recent studies evaluate the relationship between $PM_{2.5}$ exposure during the prenatal period and/or the first year of life and neurodevelopmental effects and the limited body of evidence does not provide consistent evidence of positive associations. These studies are characterized in Chapter 8, and include studies of cognitive and behavioral effects (Section 8.2.7.1), and autism (Section 8.2.7.2). Evidence from these studies inform and contribute to the conclusion that there is likely to be a causal relationship between long-term $PM_{2.5}$ exposure and nervous system effects. In addition, these studies of early-life exposure provide evidence that long-term $PM_{2.5}$ exposure is associated with developmental effects (Table 9-7).

Toxicological Evidence of Neurodevelopment

The 2009 PM ISA U.S. EPA (2009) contained no studies on neurodevelopmental animal toxicology outcomes. The current ISA explores the effect of $PM_{2.5}$ exposure on behavioral outcomes that can be included in the autism spectrum or as an attention deficit or hyperactivity and structural changes in the brain that may accompany autism, ADHD or mental illness, e.g., ventricular enlargement. A recent study (Klocke et al., 2017) showed that prenatal exposure to CAPs was associated with ventriculomegaly in male and female offspring and increased numbers of activated microglia in the brain as well as multiple other brain structural changes. Females had significantly increased iron deposition in the CC with prenatal CAPs exposure; males had significantly decreased total number of microglia in the CC with a nonsignificant trend trended in this direction for females. Neurodevelopment in laboratory animal toxicology studies is impacted by $PM_{2.5}$ exposure, including the structural change of ventriculomegaly, and brain inflammatory activation. Key details from these studies is summarized in Table 9-7. These studies are discussed in more detail in CHAPTER 8.

9.1.3.3 Cardiovascular Effects

Since the 2009 PM ISA (U.S. EPA, 2009), new studies have evaluated developmental cardiovascular risk in animal models after PM exposure and are described below. The two new studies of cardiovascular effects found PM-dependent heart failure and exacerbation of existing congenital heart defects (birth defects section of the ISA, Section 9.3.1). This new study is summarized in Table 9-7.

Toxicological Evidence of Cardiodevelopment

Work by Gorr et al. (2014) showed prenatal and lactational $PM_{2.5}$ exposure induced heart failure in adult offspring with anatomy (dilated cardiomyopathy with ventricular volume changes, and ventricular wall thickening), functional measures (impaired pressure-volume loops and deficits in contraction length) and cellular manifestation (delayed calcium reuptake during relaxation and reduced response to B-adrenergic stimulation, increased cardiac collagen deposition) confirming heart failure. In work from the same lab, Tanwar et al. (2017) showed that prenatal exposure alone to ambient air PM was sufficient to produce heart failure in adulthood, looking at similar outcomes as Gorr et al. (2014) and mechanisms including acute inflammation in cardiac tissue at birth, and changes in cardiac epigenetic markers (sirtuins and DNA methyltransferases). Early life exposure to PM in animal models has effects on the developing heart, inducing heart failure in adult animals after early life PM exposure. For more details on these studies, see Chapter 6.

9.1.3.4 Postnatal Growth and Development

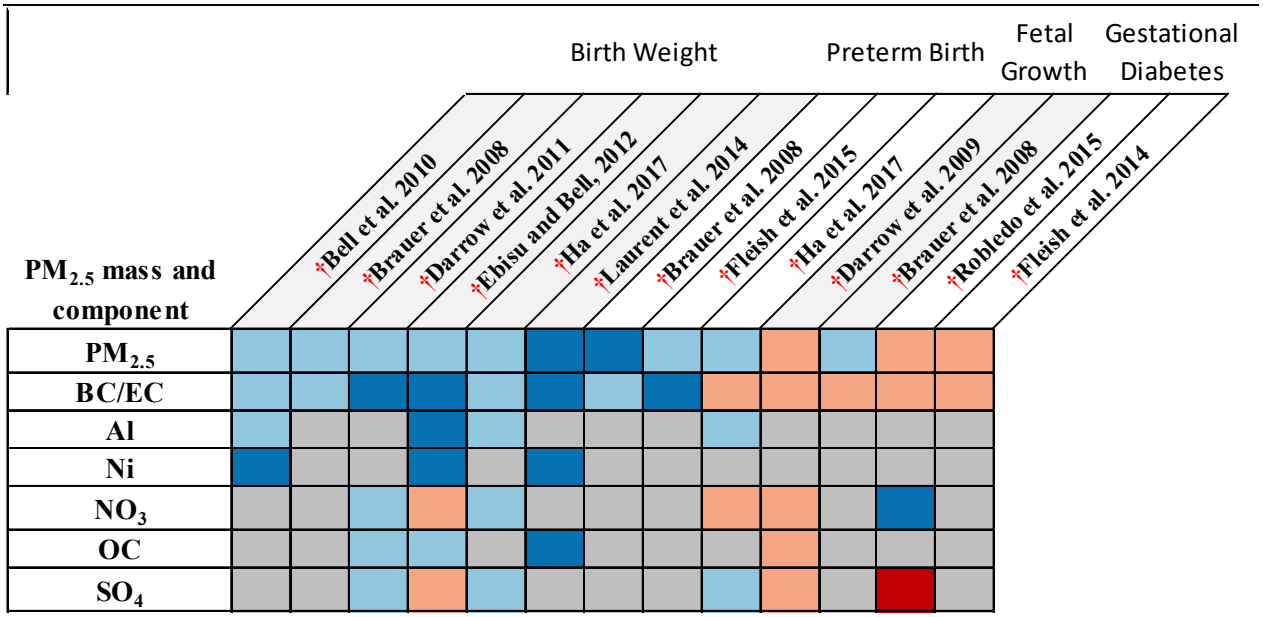
Growth of murine pups in the postnatal period was measured after prenatal exposure to Sterling Forest CAPs. Exposure to CAPs for 6 hours/day during any of the three trimesters of murine pregnancy or during the entire pregnancy was not associated with altered postnatal pup body weight gain in either male or female pups. (Blum et al., 2017).

9.1.4 Associations Between $PM_{2.5}$ Components and Sources and Reproductive and Developmental Effects

In general, few studies have examined associations between $PM_{2.5}$ components and birth outcomes. Elemental carbon (EC) is the component most studied across outcomes, and low birth weight (LBW) is the outcome most commonly evaluated. The evaluation of the association between $PM_{2.5}$ components and reproductive and developmental effects is complicated by the different methods applied across studies. As a result, the systematic standardization of results across studies (i.e., per 5 $\mu g/m^3$ increase), as is the convention throughout this ISA, is not possible when evaluating results for $PM_{2.5}$ components. Overall, the results for individual $PM_{2.5}$ components across studies are generally more imprecise than the results for $PM_{2.5}$ (i.e., much wider confidence intervals, often including the null value), which make the individual results, as well as results across studies, more difficult to interpret. As such, for the purposes of characterizing results with respect to $PM_{2.5}$ components a different convention is employed to evaluate the pattern of associations across studies. Specifically, risk estimates from studies are classified into four categories in Figure 9-3: (1) statistically significant positive associations; (2) positive associations, regardless of width of the confidence interval; (3) null or negative association; and (4) statistically significant negative association. Figure 9-3 demonstrates consistent positive associations for birth weight and preterm birth and exposure to $PM_{2.5}$, BC/EC, OC, and Al, with more studies evaluating $PM_{2.5}$ and BC/EC, and fewer studies examining other components. Based on the pattern of results across this limited number of studies, it is difficult to disentangle the independent effect of any of these components from the effect of $PM_{2.5}$ mass.

Among the studies that examine $PM_{2.5}$ components and LBW, all found positive associations with some components (Ha et al., 2017; Laurent et al., 2014; Ebisu and Bell, 2012; Darrow et al., 2011; Bell et al., 2010). In particular, EC was associated with decrements in birth weight or increased odds of LBW in all studies (Ha et al., 2017; Laurent et al., 2014; Ebisu and Bell, 2012; Darrow et al., 2011; Bell et al., 2010). A four-county cohort in Massachusetts and Connecticut using positive matric factorization to estimate concentrations averaged over the entire pregnancy observed associations with EC, silicon, aluminum, vanadium, and nickel (Bell et al., 2010). Another study included all counties in northeast and mid-Atlantic states with PM composition monitors, reporting positive association between EC, aluminum, calcium, nickel, silicon, titanium, and zinc and LBW or changes in birth weight (Ebisu and Bell, 2012). A study of the five-county Atlanta area reported null associations between $PM_{2.5}$ components and birth

weight in the first month of pregnancy, but both EC and water soluble metals (sum of chromium, copper, iron, manganese, nickel, and vanadium) concentrations were associated with changes in birth weight during the third trimester (Darrow et al., 2011). Laurent et al. (2014), used a spatio-temporal chemical transport model to examine components in Los Angeles county, and observed positive associations between EC, organic carbon, potassium, iron, chromium, nickel, and titanium associated and LBW.



Dark blue = study reported statistically significant positive association; Light blue = study reported a positive association regardless of width of confidence intervals; Light orange = study reported null or negative association; Red = study reported statistically significant negative association; Gray = study did not examine individual component. Only those $PM_{2.5}$ components that were examined in at least three studies are included in this figure.

†$PM_{2.5}$ component studies published since the 2009 PM ISA (U.S. EPA, 2009).

Figure 9-3 Heat map of associations observed between $PM_{2.5}$ and $PM_{2.5}$ components and birth outcomes and effects on pregnancy.

Additional studies have examined the relationship between PM component exposure and fetal growth (Fleisch et al., 2015; Brauer et al., 2008), and preterm birth (Darrow et al., 2009; Brauer et al., 2008). These studies generally report null associations for the components and fetal growth effects.

Among studies of pregnancy, a positive association between gestational diabetes and NO_3 was reported in a large U.S. cohort (Robledo et al., 2015). EC, organic carbon, and ammonium were not associated with gestational diabetes (Robledo et al., 2015; Fleisch et al., 2014).

In summary, there is no evidence than any component(s) is more strongly associated with any reproductive effects than $PM_{2.5}$.

9.1.5 Summary and Causality Determination

Overall, the evidence is suggestive of, but not sufficient to infer, a causal relationship between exposure to $PM_{2.5}$ and (1) male and female fertility and reproduction and (2) pregnancy and birth outcomes. Separate conclusions are made for these groups of reproductive and developmental effects because they are likely to have different etiologies and critical exposure windows over different lifestages. All available evidence examining the relationship between exposure to $PM_{2.5}$ and reproductive and developmental effects was evaluated using the framework described in the Preamble to the ISAs (U.S. EPA, 2015, HEROID). At the time of the 2009 PM ISA (U.S. EPA, 2009), evidence from the epidemiologic and toxicological studies had assessed the broader relationship between $PM_{2.5}$ exposure and reproductive and developmental effects. The 2009 ISA (U.S. EPA, 2009) concluded that the evidence was suggestive for a causal association between PM exposure and reproductive and developmental outcomes. The strongest evidence supporting the causality determination from the 2009 PM ISA (U.S. EPA, 2009) came from studies on low birth weight and developmental outcomes including infant mortality, especially due to respiratory causes during the post-neonatal period. This ISA continues to see strong supporting evidence from low birth weight. There is limited new evidence to inform the relationship between $PM_{2.5}$ and infant mortality from respiratory causes during the post-natal period; developmental outcomes are discussed in more detail in their specific organ system chapter. The developmental animal toxicological evidence has expanded greatly and is characterized elsewhere (respiratory, nervous system). The key evidence, as it relates to the causal framework, is summarized in Table 9-8. **Overall, the evidence is suggestive of, but not sufficient to infer, a causal relationship between $PM_{2.5}$ exposure and (1) Male and Female Reproduction and Fertility, (2) Pregnancy and Birth Outcomes.**

9.1.5.1 Male and Female Fertility and Reproduction

Overall the evidence is suggestive of, but not sufficient to infer a causal relationship between exposure to $PM_{2.5}$ and male and female fertility and reproduction. This is consistent with the 2009 PM ISA, which also concluded the evidence was suggestive of a causal relationship with reproductive and developmental effects. The key evidence supporting the causality determination is detailed below using the framework described in Table I of the Preamble to the ISAs (U.S. EPA, 2015, HERO ID) and is presented in Table 9-8. All available evidence examining the relationship between exposure to $PM_{2.5}$ and pregnancy and birth outcomes was thoroughly evaluated.

The relationship between $PM_{2.5}$ exposure and outcomes related to male and female fertility and reproduction are continuing to be evaluated in the literature, and thus, the number of studies for any one endpoint continues to grow. But questions remain surrounding uncertainties from lack of evaluation of copollutant confounding or multiple potential sensitive windows of exposure. Effects of $PM_{2.5}$ exposure on male reproduction have been studied in both the animal toxicology and the epidemiologic literature.

The strongest effects with $PM_{2.5}$ exposure come from studies on sperm motility (epidemiologic literature) and spermiation (animal toxicology literature). Other studies on sperm including the epidemiologic literature on sperm morphology have inconsistent results. Studies of female reproduction in association with $PM_{2.5}$ exposure also have mixed results. In rodents, ovulation and estrus are affected by PM exposure. In the epidemiologic literature, results on human fertility and fecundity in association with $PM_{2.5}$ exposure is limited, with evidence from IVF showing a modest association of $PM_{2.5}$ concentrations with decreased odds of becoming pregnant. Animal toxicological studies show inconsistent results from $PM_{2.5}$ exposure and its effects on reproduction. Biological plausibility for outcomes on Male and Female Fertility and Reproduction come from laboratory animal studies shown genetic and epigenetic changes to germ cells with $PM_{2.5}$ exposure (Section 9.1.1.1). **Collectively, the evidence is suggestive of, but not sufficient to infer, a causal relationship between $PM_{2.5}$ exposure and male and female reproduction and fertility.**

Table 9-8 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between $PM_{2.5}$ exposure and male and female reproduction and fertility.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Limited evidence from multiple epidemiologic studies on sperm quality, fertility and is generally supportive but not entirely consistent	Limited evidence for decreases in sperm motility	Section 9.1.1.2 Hammoud et al. (2009) Radwan et al. (2015)	~15 µg/m^3 34.5 µg/m^3
	Limited evidence for decreased IVF success	Section 9.1.1.3 Legro et al. (2010)	14.08 µg/m^3
	Limited evidence of decreases in fecundability	Section 9.1.1.3 Slama et al. (2013)	34.0 µg/m^3
Limited number of supportive toxicological evidence for effects on male and female fertility and reproduction	Limited evidence for effects on spermatogenesis and spermiation with prenatal or early postnatal exposure	Pires et al. (2011)	16.61 µg/m^3
	Limited evidence of effects on estrous cycle (prolonged cycle), and number of ova (decreased number of antral follicles)	Veras et al. (2009)	27.5 µg/m^3
	Inconsistent evidence of decreased litter size	Veras et al. (2009) (Klocke et al., 2017)	27.5 µg/m^3 92.7 µg/m^3

Table 9-8 (Continued): Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between $PM_{2.5}$ exposure and male and female reproduction and fertility.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Uncertainty regarding epidemiologic evidence from copollutant models to support an independent $PM_{2.5}$ association	$PM_{2.5}$ effect estimates robust in limited analyses of copollutant models, but generally evaluation of potential copollutant confounding is limited	Radwan et al. (2015)	
Uncertainty due to limited biological plausibility from studies of pregnancy and birth outcomes	Some evidence for initial events that could lead to subsequent effects on sperm, ovulation and the estrous cycle	Section 9.1.1.1 Figure 9-1 Table 9-1	

$PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm and greater than a nominal diameter of 2.5 μm.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the $PM_{10-2.5}$ concentrations with which the evidence is substantiated.

9.1.5.2 Pregnancy and Birth Outcomes

Overall the evidence is suggestive of, but not sufficient to infer a causal relationship between exposure to $PM_{2.5}$ and pregnancy and birth outcomes. This is consistent with the 2009 PM ISA, which also concluded the evidence was suggestive of a causal relationship with reproductive and developmental effects. All available evidence examining the relationship between exposure to $PM_{2.5}$ and pregnancy and birth outcomes was evaluated using the framework described in the Preamble to the ISAs (U.S. EPA, 2015b). The key evidence as it relates to the causal framework is summarized in Table 9-9. There are several well-designed, well-conducted studies that indicate an association between $PM_{2.5}$ and poorer birth outcomes, particularly low birth weight and preterm birth. Albeit, the collective evidence for many of the pregnancy and birth outcomes studies examined is not entirely consistent. There is also evidence for congenital heart defects of different types, as well as biological plausibility to support this outcome from the animal toxicology literature. For preterm birth, the timing of exposure was highly variable from study to study and limited assessment of potential copollutant confounding. The epidemiologic and toxicological literature generally show positive associations of $PM_{2.5}$ exposure with reduced fetal growth and reduced birth weight. Most of the epidemiologic studies do not control for copollutant confounding and do not have a specific sensitive window of exposure, but there is biological plausibility from the

animal toxicological literature in support of these outcomes as well as support for multiple sensitive windows for $PM_{2.5}$ exposure associated outcomes. Various pregnancy related pathologies including gestational hypertension, pre-eclampsia and gestational diabetes show inconsistent results in association with $PM_{2.5}$ exposure. Looking at gestational exposure during the second trimester for gestational diabetes, there are generally positive associations with $PM_{2.5}$ exposure.

There is some information on potential biological plausibility for effects of $PM_{2.5}$ on pregnancy and birth outcomes at relevant exposure levels for this ISA. $PM_{2.5}$ exposure in laboratory rodents induced impaired implantation, induced vascular endothelial dysfunction, and in humans was associated with epigenetic changes to the placenta, and impaired fetal thyroid function (Section 9.1.2.1). All of these pathways have the potential to contribute to the biological plausibility of $PM_{2.5}$ affecting pregnancy and birth outcomes. **In summary, the evidence is suggestive of, but not sufficient to infer, a causal relationship between exposure to $PM_{2.5}$ and pregnancy and birth outcomes.**

Table 9-9 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between $PM_{2.5}$ exposure and pregnancy and birth outcomes.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Evidence from multiple epidemiologic studies of fetal growth and birth weight is generally consistent, but uncertainties remain	Positive associations from many studies, but variability in timing of exposure and limited assessment of copollutant confounding	Section 9.1.2 Table 9-6 Table 9-4	Mean concentrations across studies: 4.0−17.5 μg/m^3
Limited toxicological evidence for an effect of $PM_{2.5}$ on fetal growth and birth weight	Limited evidence that $PM_{2.5}$ exposure results in decreased birth weight of pups or decreased body length at birth	Section 9.1.2.3 Table 9-7	
Evidence from multiple epidemiologic studies of preterm birth is generally consistent, but uncertainties remain	Positive associations from many studies, but variability in timing of exposure and limited copollutant models to evaluate potential copollutant confounding	Section 9.1.2.4 Table 9-8 Table 9-4	Mean concentrations across studies: 1.8−22.1 μg/m^3

Table 9-9 (Continued): Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between $PM_{2.5}$ exposure and maternal health during pregnancy and birth outcomes.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Limited toxicological evidence for an effect of $PM_{2.5}$ on preterm birth	Limited evidence that $PM_{2.5}$ exposure results in preterm birth in mouse pups	Section 9.1.2.4 Blum et al. (2017)	
Limited and inconsistent epidemiologic evidence for other pregnancy and birth outcomes	Some studies observe positive associations between $PM_{2.5}$ and pregnancy, birth defects, and fetal and infant mortality, while other studies observe no consistent pattern of association	Section 9.1.2.2 Section 9.1.2.3 Section 9.1.2.5	
Consistent positive epidemiologic evidence for associations between $PM_{2.5}$ exposure and fetal growth, birth weight and preterm birth across exposure measurement metrics	Positive associations consistently observed across studies that used ground-based (i.e., monitors), model (e.g., CMAQ, dispersion models) and remote sensing (e.g., AOD measurements from satellites) methods, including hybrid methods that combine two or more of these methods.	Table 9-6 Table 9-8	
Uncertainty regarding epidemiologic evidence from copollutant models to support and independent $PM_{2.5}$ association	$PM_{2.5}$ effect estimates robust in limited copollutant models with ozone, but generally evaluation of potential copollutant confounding is limited	Ha et al. (2014)	
Uncertainty due to limited biological plausibility from studies of pregnancy and birth outcomes	Some evidence for initial events that could lead to subsequent altered growth and development or preterm birth	Section 9.1.2.1 Figure 9-2 Table 9-4	

$PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the preamble.

[b]Describes the key evidence and references contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

9.1.5.3 Developmental Outcomes

Developmental outcomes with exposure to $PM_{2.5}$ are summarized in this chapter. Developmental evidence from the 2009 PM ISA (U.S. EPA, 2009) reported $PM_{2.5}$ associated with infant postnatal mortality, with effects stronger in those with respiratory illness. There is recent evidence from both epidemiologic and toxicological studies supporting a relationship between prenatal and childhood $PM_{2.5}$ exposure and effects on postnatal development, including effects on the respiratory, nervous, and cardiovascular systems (Table 9-7). These outcomes, while relevant to the broader reproductive and developmental category, are included in more depth in the specific organ systems of interest where causality determinations are made.

9.2 $PM_{10-2.5}$ Exposure and Reproductive and Developmental Effects

The evidence for effects of $PM_{10-2.5}$ on reproductive and developmental outcomes is characterized below. Infant respiratory mortality and decreased birth weight have the strongest evidence, reporting positive associations. Increased infant respiratory mortality was reported with increasing $PM_{10-2.5}$ exposure. Birth weight is associated with $PM_{10-2.5}$ exposure with reports of decreased birth weight with $PM_{10-2.5}$ exposure and increased odds of having a low birth weight baby with $PM_{10-2.5}$ exposure. Pre-term birth is associated with increasing $PM_{10-2.5}$ exposure as is infertility. Inconsistent evidence is seen with studies of birth defects and studies of pre-term birth with the literature being comprised of studies with positive associations as well as studies with null findings. Male and female reproduction and fertility studies show increased infertility and lower birth rates in epidemiologic studies of $PM_{10-2.5}$. No new studies on effects of $PM_{10-2.5}$ exposure on male and female reproduction and fertility have been reported in the animal toxicology literature. The 2009 PM ISA (U.S. EPA, 2009) contained studies of toxicological effects of $PM_{10-2.5}$ exposure with reproductive effects, but are not within the scope for this ISA. More detailed information on these studies is included in the sections that follow.

9.2.1 Male and Female Reproduction and Fertility

9.2.1.1 Biological Plausibility

There is a paucity of evidence for biological plausibility of health effects following exposure to $PM_{10-2.5}$ due to a dearth of information published in the literature. Thus, a biological plausibility figure

was not constructed for this size fraction. There have been a limited number of studies of reproductive health outcomes focused on $PM_{10-2.5}$ exposure; of these, few examine the same outcome. The studies are reported below as outcomes related to male and female reproduction and fertility.

9.2.1.2 Male and Female Reproduction and Fertility

$PM_{10-2.5}$ exposure has been studied in association with male and female reproduction and fertility in epidemiologic studies and details are reported herein. In examinations of the Nurses' Health Study, authors observed increased incident infertility and reduced endometriosis associated with increased $PM_{10-2.5}$ concentrations from a spatio-temporal model (Mahalingaiah et al., 2016; Mahalingaiah et al., 2014). In a cross-sectional study in Barcelona, Spain Nieuwenhuijsen et al. (2014) reported lower birth rates with increases in $PM_{10-2.5}$ from a land-use regression model.

No new studies on effects of $PM_{10-2.5}$ exposure on male and female reproductive effects and fertility have been reported in the literature. The 2009 PM ISA (U.S. EPA, 2009) contained studies of toxicological effects of $PM_{10-2.5}$ exposure with reproductive effects, but are not within the scope for this ISA.

In conclusion, increased infertility and lower birth rates were reported in epidemiologic studies of $PM_{10-2.5}$. No recent studies of laboratory animals studies on $PM_{10-2.5}$ are reported in this ISA. Overall, there are a limited number of studies which provide inconsistent evidence for an association between $PM_{10-2.5}$ exposure and a variety of reproductive effects. The results of these studies are summarized in Table 9-10.

9.2.2 Pregnancy and Birth Outcomes

9.2.2.1 Biological Plausibility

There is a paucity of evidence for biological plausibility of health effects following exposure to $PM_{10-2.5}$ due to a dearth of information published in the literature. Thus, a biological plausibility figure was not constructed for this size fraction. There have been a limited number of studies of pregnancy and birth outcomes focused on $PM_{10-2.5}$ exposure; of these, few examine the same outcome. The studies are reported below.

9.2.2.2 Pregnancy and Birth Outcomes

Pregnancy and birth outcomes from the epidemiologic literature have been reported in association with $PM_{10-2.5}$exposure and a summary of these studies follows. A Barcelona cohort found positive associations with preeclampsia (Dadvand et al., 2013a). In studies of preterm birth, time-series studies have reported null associations (Darrow et al., 2009) or elevated odds ratios (Salihu et al., 2012). Null effects were observed for PTB in pooled cohort study (ESCAPE) (Giorgis-Allemand et al., 2017). Salihu et al. (2012) observed elevated ORs for low birth weight, and Ebisu et al. (2016) observed small decreases in birth weight with increases in $PM_{10-2.5}$, including with adjustment for $PM_{2.5}$. A study of birth defects found both positive and negative associations with coarse PM exposure (Schembari et al., 2014).

In conclusion, a Barcelona cohort reported positive associations with pre-eclampsia rates, null effects were reported for preterm birth, elevated OR were reported for low birth weight and small decreases in birth weight were all reported in association with increasing $PM_{10-2.5}$. No recent studies of laboratory animals studies on pregnancy and birth outcomes with $PM_{10-2.5}$ exposure are reported in this ISA. Overall, there are a limited number of studies which provide inconsistent evidence for an association between $PM_{10-2.5}$ exposure and a variety of reproductive effects. The results of these studies are summarized in Table 9-10.

Table 9-10 Epidemiologic studies of exposure to $PM_{10-2.5}$ and reproductive effects.

Study	Endpoint Cohort/Location	Mean $PM_{10-2.5}$ $\mu g/m^3$	Exposure Assessment	Single Pollutant Odds Ratio[a] 95% CI	Copollutant Examination
†Mahalingaiah et al. (2014)	Endometriosis (Nurses98 Health Study/14 U.S. States)	10.9	Spatio-temporal models Subtraction method	0.96 (0.91, 1.01)	Correlation (r): NA Copollutant models with: NA
†Mahalingaiah et al. (2016)	Infertility (Nurses' Health Study/14 U.S. States)	11.4	Spatio-temporal models Subtraction method	1.05 (0.99, 1.10)	Correlation (r): NA Copollutant models with: NA
†Dadvand et al. (2013a)	Preeclampsia (Barcelona, Spain)	21.7	LUR model with input from $PM_{10-2.5}$ monitoring campaign	Entire pregnancy: 1.12 (0.84, 1.50) T1: 1.10 (0.79, 1.53) T2: 0.98 (0.74, 1.30) T3: 1.31 (0.96, 1.79)	Correlation (r): NA Copollutant models with: NA

Table 9-10 (Continued): Epidemiologic studies of exposure to $PM_{10-2.5}$ and reproductive effects.

Study	Endpoint Cohort/Location	Mean $PM_{10-2.5}$ $\mu g/m^3$	Exposure Assessment	Single Pollutant Odds Ratio[a] 95% CI	Copollutant Examination
†Darrow et al. (2009)	Preterm birth (Atlanta, GA)	9.1	Single, centrally-located dichot monitor	M1: 1.00 (0.95, 1.04) 1 week before birth: 0.98 (0.95, 1.02) 6 weeks before birth: 1.02 (0.96, 1.08)	Correlation (r): NA Copollutant models with: NA
†Salihu et al. (2012)	Birth weight, fetal growth, preterm birth (Hillsborough County, FL)	13.1	Centroid of ZIP code (n = 97) of residence linked to nearest centroid of ZIP code (n = 14) that included monitors Subtraction method	ORs for exposure >median vs. <median LBW: 1.09 (1.03, 1.15) Very LBW: 1.22 (1.07, 1.39) PTB: 1.05 (1.01, 1.09) Very PTB: 1.13 (1.01, 1.27) SGA: 1.07 (1.02, 1.12)	Correlation (r): NA Copollutant models with: NA
†Giorgis-Allemand et al. (2017)	Preterm birth (13 Cohorts from 11 European countries—ESCAPE cohort)	NR	LUR model with input from $PM_{10-2.5}$ monitoring campaign	Entire pregnancy: 1.00 (0.92, 1.08) T1: 0.99 (0.91, 1.07) T2: 1.00 (0.92, 1.08) Last week: 0.99 (0.94, 1.04) Last month: 0.98 (0.92, 1.02)	Correlation (r): NO_2: 0.71, $PM_{2.5}$: 0.63 Copollutant models with: NA
†Ebisu et al. (2016)	Birth weight (U.S.)	13.7	County-level average from co-located monitors Subtraction method	Change in birth weight (g) Entire pregnancy −4.2 (−4.6, −3.8) T1: −1.3 (−1.7, -0.8) T2: −1.3 (−1.8, −0.9) T3: −1.7 (−2.1, −1.3)	Correlation (r): NA Copollutant models with: $PM_{2.5}$ Entire pregnancy −3.5 (−3.9, −3.0) T1: −1.0 (−1.4, −0.5) T2: −1.2 (−1.6, −0.7) T3: −1.3 (−1.8, −1.0)
†Schembari et al. (2014)	Birth defects (Barcelona, Spain)	21.1	LUR model with input from $PM_{10-2.5}$ monitoring campaign	All cases: 1.01 (0.90, 1.14)	Correlation (r): PM_{10}: 0.89, $PM_{2.5}$: 0.86 Copollutant models with: NA

Table 9-10 (Continued): Epidemiologic studies of exposure to $PM_{10-2.5}$ and reproductive effects.

Study	Endpoint Cohort/Location	Mean $PM_{10-2.5}$ $\mu g/m^3$	Exposure Assessment	Single Pollutant Odds Ratio[a] 95% CI	Copollutant Examination
†Son et al. (2011a)	Infant mortality (Seoul, Korea)	30.6	City-wide average from co-located monitors Subtraction method	All-cause mortality: Entire pregnancy: 1.26 (0.78, 2.04) T1: 0.92 (0.79, 1.07) T2: 0.99 (0.85, 1.15) T3: 1.07 (0.93, 1.22) First year of life: 0.81 (0.67, 0.98) Respiratory mortality: Entire pregnancy: 4.12 (0.69, 24.86) T1: 1.65 (0.99, 2.79) T2: 0.92 (0.54, 1.51) T3: 0.91 (0.57, 1.45) First year of life: 0.41 (0.16, 1.03)	Correlation (r): NA Copollutant models with: NA
†Yorifuji et al. (2016)	Infant mortality (Tokyo, Japan)	$PM_{7-2.5}$: 5.0	Single, centrally-located monitoring station Subtraction method ($PM_{2.5}$ subtracted from suspended particulate matter [SPM; surrogate for PM_{10}])	Infant mortality (all): 0.99 (0.93, 1.05) Infant mortality (CVD): 1.00 (0.79, 1.29) Infant mortality (Resp): 1.24 (0.94, 1.63) Neonatal mortality: 0.88 (0.81, 0.96) Post-neonatal mortality: 1.10 (1.01, 1.19)	Correlation (r): NA Copollutant models with $PM_{2.5}$: Infant mortality (all): 0.97 (0.91, 1.03) Neonatal mortality: 0.87 (0.80, 0.95) Post-neonatal mortality: 1.07 (0.98, 1.17)
†Peel et al. (2011)	Postnatal apnea and bradycardia (Atlanta, GA)	9.6	Single, centrally-located dichot monitor	Apnea: 1.01 (0.99, 1.04) Bradycardia: 1.01 (0.99, 1.02)	Correlation (r): O_3 = 0.40; NO_2 = 0.39; CO = 0.36; SO_2 = 0.19; PM_{10} = 0.76; $PM_{2.5}$ = 0.47 Copollutant models with: NA

[a]Odds Ratio per 5 $\mu g/m^3$ change in $PM_{10-2.5}$ unless otherwise noted.

†Studies published since the 2009 PM ISA (U.S. EPA, 2009).

9.2.3 Developmental Outcomes

Studies of developmental outcomes have been reported from the epidemiologic literature in association with $PM_{10–2.5}$ exposure. Both a study in Seoul, South Korea and a study in Tokyo, Japan found increased infant mortality due to respiratory causes using coarse PM exposure from monitors (Son et al., 2011b) (Yorifuji et al., 2016). For exposures during the postnatal period, Peel et al. (2011) observed no associations between coarse PM and infant apnea and bradycardia.

9.2.4 Summary and Causality Determination

9.2.4.1 Male and Female Fertility and Pregnancy

Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between $PM_{10–2.5}$ exposure and male and female fertility and reproduction. Developmental outcomes are briefly summarized here with causality determination made in the outcome specific chapter (respiratory effects). Separate conclusions are made for the two groups of reproductive and developmental effects because they are likely to have different etiologies and critical exposure patterns over different lifestages. At the time of the 2009 PM ISA (U.S. EPA, 2009), evidence from the epidemiologic and toxicological studies had assessed the broader relationship between PM exposure and reproductive and developmental outcomes. The paucity of evidence for $PM_{10–2.5}$ in the 2009 PM ISA (U.S. EPA, 2009) remains. While there are more recent studies in this ISA, there continue to be fewer studies contributing to this size fraction than to other size groups. Developmental outcomes for the literature are discussed in more detail in the respiratory section of the ISA with infant respiratory mortality having the strongest evidence, reporting positive associations from multiple studies. In the developmental literature increased infant respiratory mortality was reported with increasing $PM_{10–2.5}$ exposure.

Evidence for male and female reproduction and fertility includes work from the Nurses' Health Study which observed increased incident infertility and reduced endometriosis associated with increased $PM_{10–2.5}$ concentrations and cross-sectional work from a Spanish cohort reporting lower birth rates with increases in $PM_{10–2.5}$. There is a dearth of evidence detailing biological plausibility between $PM_{10–2.5}$ and Male and Female Reproduction and Fertility. **Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between $PM_{10–2.5}$ exposure and male and female reproduction and fertility (Table 9-11).**

Table 9-11 Summary of evidence that it is inadequate to infer the presence or absence of a causal relationship between $PM_{10-2.5}$ exposure and male and female reproduction and fertility.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Limited and inconsistent epidemiologic evidence from on fertility and reproduction	Limited and inconsistent evidence for effects on incident infertility and decreased birth rates	Mahalingaiah et al. (2016) Nieuwenhuijsen et al. (2014)	9.9 µg/m^3 21.6 µg/m^3
Uncertainty regarding exposure measurement error in epidemiologic studies	Across studies, $PM_{10-2.5}$ concentrations are measured using a number of approaches (i.e., directly measured from dichotomous sampler, difference between PM_{10} and $PM_{2.5}$ concentrations measured at collocated monitors, and difference of area-wide concentrations of PM_{10} and $PM_{2.5}$), which have not been compared in terms of whether they have similar spatial and temporal correlations	Section 3.3.1.1	
Uncertainty regarding epidemiologic evidence from copollutant models to support and independent $PM_{10-2.5}$ association	$PM_{10-2.5}$ effect estimate robust to adjustment for $PM_{2.5}$ in a single study. No studies evaluated potential copollutant confounding for gaseous pollutants	Ebisu et al. (2016)	13.7 µg/m^3
Uncertainty due to limited biological plausibility from studies of pregnancy and birth outcomes	Some evidence for initial events that could lead to subsequent effects on sperm, ovulation and the estrous cycle	Section 9.2.1.1 Figure 9-3 Table 9-10	

$PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than a nominal diameter of 2.5 µm.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the $PM_{10-2.5}$ concentrations with which the evidence is substantiated.

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9.2.4.2 Pregnancy and Birth Outcomes

Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between $PM_{10-2.5}$ exposure and pregnancy and birth outcomes. At the time of the 2009 PM ISA (U.S. EPA, 2009), evidence from the epidemiologic and toxicological studies had assessed the broader relationship between PM exposure and reproductive and developmental outcomes. The paucity of evidence for $PM_{10-2.5}$ in the 2009 PM ISA (U.S. EPA, 2009) remains.

Evidence for pregnancy and birth outcomes in association with $PM_{10-2.5}$ follows. Decreased birth weight is associated with $PM_{10-2.5}$ exposure including increased odds of having a low birth weight baby with $PM_{10-2.5}$ exposure. Preterm birth is associated with increasing $PM_{10-2.5}$ exposure. Inconsistent evidence is seen with studies of birth defects and studies of preterm birth with the literature being comprised of studies with positive associations as well as studies with null findings. A paucity of information exists in support of potential biological plausibility for $PM_{10-2.5}$ exposure and Pregnancy and Birth Outcomes. **Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between $PM_{10-2.5}$ exposure and pregnancy and birth outcomes (Table 9-12).**

Table 9-12 Summary of evidence that it is inadequate to infer the presence or absence of a causal relationship between $PM_{10-2.5}$ exposure and pregnancy and birth outcomes.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Limited and inconsistent epidemiologic evidence for associations with pregnancy and birth outcomes	Limited and inconsistent evidence for effects on pre-eclampsia, preterm birth, birth weight, birth defects, and infant mortality	Section 9.2.2.1	
Uncertainty regarding exposure measurement error in epidemiologic studies	Across studies, $PM_{10-2.5}$ concentrations are measured using a number of approaches (i.e., directly measured from dichotomous sampler, difference between PM_{10} and $PM_{2.5}$ concentrations measured at collocated monitors, and difference of area-wide concentrations of PM_{10} and $PM_{2.5}$), which have not been compared in terms of whether they have similar spatial and temporal correlations		

Table 9-12 (Continued): Summary of evidence that it is inadequate to infer the presence or absence of a causal relationship between $PM_{10-2.5}$ exposure and pregnancy and birth outcomes.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Uncertainty regarding epidemiologic evidence from copollutant models to support and independent $PM_{10-2.5}$ association	$PM_{10-2.5}$ effect estimate robust to adjustment for $PM_{2.5}$ in a single study. No studies evaluated potential copollutant confounding for gaseous pollutants	Ebisu et al. (2016)	13.7 μg/m^3
Uncertainty due to limited biological plausibility from studies of pregnancy and birth outcomes	Some evidence for initial events that could lead to subsequent effects on pregnancy and birth outcomes.	Section 9.2.2.2	

$PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm and greater than a nominal diameter of 2.5 μm.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the $PM_{10-2.5}$ concentrations with which the evidence is substantiated.

9.3 UFP Exposure and Reproductive and Developmental Effects

The evidence for effects of UFP on reproductive and developmental outcomes is characterized below. Toxicological studies of male reproductive function show increased testosterone, increased testicular cholesterol, and increased activation of biomarkers on testicular cholesterol biosynthesis pathway with UFP exposure in male rodents. The epidemiologic literature for pregnancy and birth outcomes shows positive associations of UFP with preterm birth and low birth weight. In the UFP toxicological literature, neurodevelopmental outcomes are well studied and report neurological associations from multiple studies evaluating outcomes including increased impulsivity, ventriculomegaly, glial activation, and neurotransmitter changes with UFP exposure. More detailed information on these studies is included in the sections that follow.

9.3.1 Male and Female Reproduction and Fertility

9.3.1.1 Biological Plausibility

This section describes biological pathways that potentially underlie reproductive and developmental health effects of male and female reproduction and fertility, and pregnancy, birth weight and birth outcomes resulting from exposure to UFP PM. Figure 9-4 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" exposure to UFP may lead to reproductive and developmental health effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 9.3.

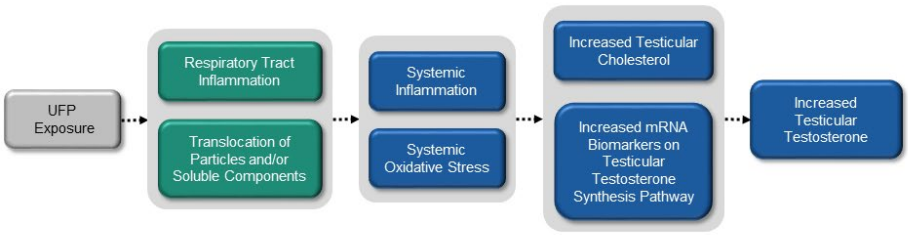

Figure 9-4 Potential biological pathways for male and female reproduction and fertility effects following UFP exposure.

[a] Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

The evidence that exists in support of biological plausibility of UFP inhalation for effect on male and female reproduction and fertility and pregnancy, birth weight and birth outcomes follows in Figure 9-4. Initial events begin when particles are translocated/solubilized to the lung or the olfactory bulb with the potential for inflammation and oxidative stress. UFP and its soluble components may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments. A fraction of UFP may deposit on the olfactory epithelium. UFP and its soluble components may be transported via the olfactory nerve to the olfactory bulb of the brain. The extent to which translocation into the systemic circulation or transport to the olfactory bulb occurs is currently uncertain. For further discussion of translocation and olfactory transport, see Chapter 4. UFP inhalation by adult male laboratory animals manifests with increased testicular testosterone and its precursor testicular cholesterol (Li et al., 2012). Prenatal exposure of laboratory animals to UFP CAPS results in offspring with decreased kidney weight (Li et al., 2009). The epidemiologic evidence for biological plausibility shows that UFP exposure is associated with low birth weight (Laurent et al., 2014) and preterm birth (Laurent et al., 2016). The biological plausibility for reproductive and developmental outcomes including effects on reproduction and fertility; and pregnancy, birth weight and birth outcomes is emerging. As future studies evaluate the effects of UFP inhalation, more data may become available to elucidate biological plausibility of reproductive and developmental effects.

Inhalation of UFP could lead to effects on male and female reproduction and developmental health effects as well as pregnancy, birth outcomes and birth weight following multiple pathways that are currently sparsely populated. Potential pathways involve, particle translocation/solubility, inflammation and oxidative stress, that may lead to changes in the offspring inducing, altered male reproductive hormone levels, decreased growth and development (e.g., low birth weight), or preterm birth. Evidence from laboratory animals and from epidemiologic studies show that there is potential for growth in the understanding of how the biological plausibility of inhaled UFP affect reproductive and developmental apical events. These limited data provide biological plausibility for epidemiologic results of reproductive and developmental health effects and will be used to inform a causality determination, which is discussed later in the chapter (Section 9.3.4).

9.3.1.2 Male Reproductive Function

The 2009 PM ISA (U.S. EPA, 2009) did not contain studies of UFP in association with male reproductive function. In more recent studies (Table 9-13), UFP exposure has been examined for its effects on male reproductive hormones and sperm production. In these studies, UFP size ranged from 1−100 nm with peak size concentration occurring at 20−30 nm (Li et al., 2009). A couple of studies of DE with adult or prenatal exposures have explored these effects in rodents (Li et al., 2012; Li et al., 2009). Adult male mice were exposed to low dose-DE (LD-DE), high dose-DE (HD-DE), filtered-DE (F-DE) or control clean air for 8 weeks (Li et al., 2012). The HD-DE male mice had significantly higher serum testosterone ($p < 0.05$) than the control or the F-DE; LD-DE showed a nonsignificant trend of

increased testosterone production. Most hormones were refractory to DE exposure (FSH, LH, and progesterone) with 8 weeks of exposure (Li et al., 2012). Epididymal sperm count and morphology were refractory to PM exposure (Li et al., 2012). Cholesterol is an essential substrate for testosterone production; testicular cholesterol biosynthesis pathways (HMG-CoA reductase, HMG-CoA synthase, LDLR) were significantly upregulated ($p < 0.05$) with HD-DE exposure compared to F-DE and control (Li et al., 2012). Other endpoints essential to testosterone biosynthesis were also significantly upregulated with HD-DE exposure v. control or F-DE exposure (SR-B1, PBR, StAR, P450scc, 3B-HSD, P45017a, 17B-HSD, $p < 0.05$) (Li et al., 2012). In a separate study, the same laboratory also explored prenatal effects of DE on young male offspring, exploring many of the same hormone pathways and looking at male reproductive tract histology (Li et al., 2009). Pregnant dams were exposed to DE, F-DE or control clean air over GD1−19. Immature male offspring were evaluated on PND28. Message levels (mRNA) of FSH receptor and serum concentrations of corticosterone were significantly increased with DE exposure compared to F-DE and control ($p < 0.01$). In these younger mice, other hormone and histology endpoints changed with DE exposure, but they also changed with F-DE exposure compared to control (Li et al., 2009), indicating a gaseous contribution to the DE effect not a PM-specific effect. There were sensitive windows of exposure to UFP PM; exposure of adult males to UFP PM from DE was associated with significantly elevated testosterone but prenatal exposure was not sufficient to induce similar changes in younger male animals. In summary, UFP exposure did not affect rodent sperm count or morphology. Inhalation of UFP in adult animals was associated with changes in concentrations of contributors to the testicular cholesterol biosynthesis pathways including testicular cholesterol, SR-B1, PBR, StAR, P450scc, 3B-HSD, P45017a, and 17B-HSD that likely contributed to the UFP dependent elevated serum testosterone.

9.3.1.3 Female Reproduction and Fertility

No studies on female reproduction and fertility were in the 2009 PM ISA (U.S. EPA, 2009) and no recent studies exist for these health outcomes.

Table 9-13 Key animal toxicological studies UFP and male and female reproduction.

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Li et al., 2009)	Pregnant and lactating F344 rats and their offspring	Pregnant F344 rats were exposed to DEP (148.86 g/m^3, 1.83 × 106 particles/cm^3, 3.40 ppm CO, 1.46 ppm NO_X), filtered-DE (F-DE; 3.10 g/m^3, 2.66 particles/cm^3, 3.30 ppm CO, 1.41 ppm NO_X), or clean air (as a control) from gestation days 1 to 19. UFP size ranged from 1−100 nm with peak size concentration occurring at 20−30 nm.	Male offspring were examined on postnatal Day 28 for endpoints including reproductive organ weight, and hormone concentrations (testosterone, LH, FSH, STAR protein, and 17B-OH dehydrogenase).
(Li et al., 2012)	Adult male C57BL/Jcl mice	Male C57BL/Jcl mice were exposed to clean air, low-dose NR-DE (Low NR-DE), high-dose NR-DE (High NR-DE), or filtered diesel exhaust (F-DE) for 8 weeks at respective PM concentrations of 0.78±0.25, 41.73±0.58, 152.01±1.18, or 0.69±0.36 µg/m^3. UFP size ranged from 1−100 nm with most particles of 20−30 nm in size.	After 8 weeks exposure to DE, F-DE or clean air, isolated testicular interstitial cells from exposed animals were challenged with HCG to understand testicular testosterone production and the role of its precursors (cholesterol, HMG-COA, LDL-R, SR-B1, 17BHSD)

9.3.2 Pregnancy and Birth Outcomes

9.3.2.1 Biological Plausibility

There is a paucity of evidence for biological plausibility of health effects following exposure to UFP due to a dearth of information published in the literature. Thus, a biological plausibility figure was not constructed for this UFP pregnancy and birth outcomes. There have been a limited number of studies of pregnancy and birth outcomes focused on UFP exposure; of these, few examine the same outcome. The studies are reported below.

9.3.2.2 Pregnancy and Birth Outcomes

Limited epidemiologic evidence exists for UFP exposure and pregnancy and birth outcomes. Evidence for effects on birth outcomes includes the results of two, California-based studies using the University of California Davis/CIT_Primary (UCD_*P*) chemical transport model to estimate concentrations. The first, a cohort study of births in Los Angeles county, found increased odds of low birth weight with IQR increases in $PM_{0.1}$ (Laurent et al., 2014). The second, a case-control study of births across the state, found increased odds of preterm birth with increases in $PM_{0.1}$ (Laurent et al., 2016).

Animal toxicology studies routinely measure birth outcomes including birth weight and crown to rump length, measures which have the potential to be affected by UFP PM exposure (Table 9-15). Dams were exposed to control clean air, UFP diesel exhaust (UFP DE), sized 100 nm or less with the majority of the particles of 20−30 nm in size, or F-DE during pregnancy (GD1−19, 5 hours/day) and litter parameters were reported at birth (Li et al., 2013). No markers of maternal endocrine function (dam body weight gain, liver weight, serum maternal LH and corticosterone, corpus luteum 450SSC, 3β-hydroxysteroid dehydrogenase, 17B-estradiol and LH receptor mRNA) were altered with F-DE or DE exposure in pregnant female rats. Both DE and F-DE pups had significantly increased birth weights and significantly decreased crown to rump length at birth versus clean air, indicating that the PM portion of exposure is likely not contributing to the deficit. Also, sex ratio or the ratio of males to females per litter was not altered between treatment groups and neither was anogenital distance, a marker of androgenization. In summary, from this study the UFP PM portion of DE was not responsible for changes in birth weight, crown to rump length, sex ratio, or anogenital distance with prenatal PM exposure.

Table 9-14 Animal toxicological study of pregnancy and birth outcomes.

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Li et al., 2013)	Pregnant female Fischer rats (F344/DuCrlCrli)	Pregnant rats were exposed to DE, F-DE or clean air for the entire pregnancy. Particle size: the average diameter of UFP ranged from 22 to 27 nm. Concentration: DE (148.86 μg/m^3, 1.83 × 106 particles/cm^3), F-DE (3.10 μg/m^3, 2.66 particles/cm^3). Inhalation for 5 h/day GD 1 to GD19. UFP size ranged from 1−100 nm with peak size concentration occurring at 20−30 nm.	At birth, maternal outcomes (liver weight, spleen weight, hormone concentrations) were assessed and birth outcomes (birth weight, crown to rump length) were followed in pups.

9.3.3 Developmental Effects

Prenatal or early neonatal exposures have the potential to affect developing organs. Multiple studies characterized in the neurodevelopment section and briefly below show the effects of UFP PM on the nervous system after early life exposure of laboratory rodents to UFP PM, the section that provides the bulk of the new research in the UFP PM Developmental Effects section. These studies find that early life UFP PM exposure to laboratory rodents induces neurobehavioral changes like inattention and depression. Also, brain structures are changed in ways that are similar to the diseases autism or schizophrenia with ventricular enlargement or ventriculomegaly. Also, stress axes like the sympathetic nervous system were differentially activated with UFP PM exposure. These neurological outcomes differ by the sex of the animal tested and by the developmental exposure window (prenatal versus neonatal). Also noted, prenatal UFP PM exposure is associated with decreased kidney size in young male animals; the kidneys of the young male offspring (PND28) prenatally exposed to UFP (DE) were significantly smaller than control clean air exposed animals or F-DE exposed animals ($p < 0.01$) (Li et al., 2009). Dams were exposed to UFP PM DE, F-DE or control clean air 5 hours/day GD1−19. The neuro-developmental studies are characterized below in Section 9.3.3.1 and in Table 9-16.

9.3.3.1 Neurodevelopmental Outcomes

9.3.3.1.1 Neurobehavioral Outcomes, Animal Toxicology

A series of studies evaluated behavioral and neurotoxicological endpoints in adult mice previously exposed to Rochester, NY concentrated ambient ultrafine particles (CAPs) (<100 nm) during the first two weeks of life (Allen et al., 2014b; Allen et al., 2014c; Allen et al., 2014a; Allen et al., 2013). These studies are covered in greater detail in the nervous system section of the ISA (Chapter 8) with brief summaries here. Allen et al. (2013) showed early postnatal CAPs exposure produced mice with preference for immediate with serum corticosterone and some brain region-specific neurotransmitters correlated with measures of impulsivity-linked behavior in male mice. In a second study with similar study design using early life (postnatal) CAPs exposure, Allen et al. (2014c) showed indices of learning/memory were affected by PM. Davis et al. (2013) saw that PM exposure affected internalizing behavior in offspring of dams that were exposed to UFP (prior to conception, mated with unexposed males and then exposed to UFP during gestation). In summary, learning and memory were significantly impaired with UFP exposure, with novel object recognition affected in males (postnatal UFP exposure) and changes in time to approach novel objects affected in females (postnatal UFP exposure). UFP exposure both prenatally and postnatally induced depression like behavior; prenatal exposure's effects were limited to male offspring. UFP exposure did not contribute to anxiety.

9.3.3.1.2 Changes in Brain Structure, Animal Toxicology

Allen et al. (2014a) and Allen et al. (2015) examined changes in the brains of weanling mouse pups exposed postnatally to UFP. Ventriculomegaly was seen in young and adult male, but not female mice. Ventriculomegaly can be associated with increased risk of adverse neurodevelopmental outcomes including schizophrenia ADHD or autism spectrum disorders, some of which tend to have a higher incidence in males. In addition, there was a UFP-dependent decrease in size (PND14, both sexes) and myelination (PND14, males only) of the corpus callosum. Findings of ventriculomegaly, reductions in corpus callosum size, and hypomyelination, especially in males, are consistent with morphologic changes associated with neurodevelopmental disorders such as autism spectrum disorder in humans. There were also sex-specific and region specific alterations in neurotransmitters and hormones (concentration of glutamate, dopamine, norepinephrine, GABA, HVA and corticosterone as well as dopamine turnover (Allen et al., 2014c). Multiday exposure of weaning mice to UFP induced early (astrocyte and microglial) and persistent (microglial) activation, especially in males (Allen et al., 2014a) (Allen et al., 2015).

Table 9-15 Summary of UFP: Developmental outcomes.

Developmental Effects	Summary of Evidence	Cross-link to Study Details	Causality Determination
Neurodevelopment	Toxicological evidence: Early postnatal UFP exposure, Behavioral testing for impulsivity; Early postnatal and adult UFP exposure, measurements of potential brain ventriculomegaly, neurochemical disruption, and glial activation. Sex-dependent measurements; Susceptibility to induction of the Parkinson's disease phenotype (PDP) in adulthood following neonatal CAPS exposure, locomotion activity, and striatal GABA inhibitory function; Measurement of meso-corticolimbic monoamines/glutamate, brain glial activation, and brain histopathology; cerebral cortex primary neuronal cultures; locomotor activity and anxiety-related parameters by open field and elevated plus-maze; depression-like responses by tail-suspension tests.	Section 8.6.6	A Causal relationship is likely to exist for long-term exposure to UFP and nervous system effects
Renal	Toxicological evidence: Kidney development in male offspring, kidney weight. is impacted by $PM_{2.5}$ exposure.	Section 9.3.3	

9.3.4 Summary and Causality Determination

Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between UFP exposure and male and female reproduction and fertility. Causality determinations are made for developmental outcomes in the specific chapters associated with the developmental outcome (i.e., nervous system). This causality determination is consistent with the 2009 PM ISA, which also reported limited evidence for reproductive and developmental effects in association with UFP exposure. The key evidence supporting the causality determination is detailed below using the framework described in Table I of the Preamble to the ISAs (U.S. EPA, 2015)and is presented in Table 9-16. All available evidence examining the relationship between exposure to UFP male and female reproduction and fertility as well as pregnancy and birth outcomes was thoroughly evaluated.

9.3.4.1 Male and Female Reproduction and Fertility

At the time of the 2009 PM ISA (U.S. EPA, 2009), there were not a lot of studies on UFP. The paucity of evidence for UFP in the 2009 PM ISA (U.S. EPA, 2009) remains, however there has been an expansion of studies in neurodevelopment in the laboratory animal toxicology literature. Limited evidence for effects on male reproductive function is provided by the animal toxicology literature which shows increased testosterone, increased testicular cholesterol, and increased activation of biomarkers related to testicular cholesterol biosynthesis with UFP exposure. The evidence for these determinations is contained below in Table 9-16.

Overall, many uncertainties remain when evaluating the evidence for these health endpoints; therefore, **the evidence is inadequate to infer the presence or absence of a causal relationship between UFP exposure and male and female reproduction and fertility.**

Table 9-16 Summary of evidence that is inadequate to infer the presence or absence of a causal relationship between UFP exposure and male and female reproduction and fertility.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	UFP Concentrations Associated with Effects[c]
Reproduction and Fertility: Limited and supportive toxicological evidence of effects on male reproductive endpoints	Adult UFP exposure induced increased testosterone and increased testicular cholesterol, increased activation of biomarkers on testicular cholesterol biosynthesis pathway	(Li et al., 2012)	149 μg/m^3

Table 9-16 (Continued): Summary of evidence that is inadequate to infer the presence or absence of a causal relationship between UFP exposure and male and female reproduction and fertility.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	UFP Concentrations Associated with Effects[c]
Limited evidence for biological plausibility.	Adult UFP impaired testicular T synthesis and biomarkers along the pathway.	(Li et al., 2012)	
Uncertainty regarding exposure measurement error	Chemical transport model to predict UFP concentrations with a 4-km spatial resolution		
Uncertainty regarding epidemiologic evidence from copollutant models to support and independent UFP association	No studies examine potential confounding of UFP associations by copollutants	Section 9.3.1.1	
Uncertainty due to limited biological plausibility from studies of male and female reproduction and fertility; pregnancy and birth outcomes	Dearth of evidence for biological plausibility related to (1) male and female reproduction and fertility.	Sections 9.3.1.1	

$PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm and greater than a nominal diameter of 2.5 μm.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the $PM_{10-2.5}$ concentrations with which the evidence is substantiated.

9.3.4.2 Pregnancy and Birth Outcomes

Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between UFP exposure and pregnancy and birth outcomes. This causality determination is consistent with the 2009 PM ISA, which also reported limited evidence for reproductive and developmental effects in association with UFP exposure. The key evidence supporting the causality determination is detailed below using the framework described in Table I of the Preamble to the ISAs (U.S. EPA, 2015, HERO ID) and is presented in Table 9-17. All available evidence examining the relationship between exposure to UFP and pregnancy and birth outcomes was thoroughly evaluated.

At the time of the 2009 PM ISA (U.S. EPA, 2009), there were not a lot of studies on UFP. The paucity of evidence for UFP in the 2009 PM ISA (U.S. EPA, 2009) remains. Pregnancy and birth

outcomes show positive associations of UFP with preterm birth and low birth weight. There is limited evidence for biological plausibility in support of the reproductive and developmental outcomes. The evidence for these determinations is contained below in Table 9-17.

Overall, many uncertainties remain when evaluating the evidence for these health endpoints; therefore, **the evidence is inadequate to infer the presence or absence of a causal relationship between UFP exposure and pregnancy and birth outcomes.**

Table 9-17 Summary of evidence that is inadequate to infer the presence or absence of a causal relationship between UFP exposure and pregnancy and birth outcomes.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	UFP Concentrations Associated with Effects[c]
Pregnancy and birth outcomes: Limited epidemiologic evidence for associations with pregnancy and birth outcomes	Two studies utilize exposure model for $PM_{0.1}$ to examine associations with birth weight and preterm birth	Section 9.3.2.2 Laurent et al. (2014) Laurent et al. (2016)	1.13 µg/m^3
Uncertainty regarding exposure measurement error	Chemical transport model to predict UFP concentrations with a 4-km spatial resolution		
Uncertainty regarding epidemiologic evidence from copollutant models to support and independent UFP association	No studies examine potential confounding of UFP associations by copollutants	Section 9.3.2	
Uncertainty due to limited biological plausibility from studies pregnancy and birth outcomes	Dearth of evidence for biological plausibility related to pregnancy and birth outcomes.	Section 9.3.2.1	

$PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than a nominal diameter of 2.5 µm.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the $PM_{10-2.5}$ concentrations with which the evidence is substantiated.

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CHAPTER 10 CANCER

Summary of Causality Determinations for Long-Term Particulate Matter (PM) Exposure and Cancer

This chapter characterizes the scientific evidence that supports causality determinations for long-term PM exposure and cancer. The types of studies evaluated within this chapter are consistent with the overall scope of the ISA as detailed in the Preface (Section P.3.1). In assessing the overall evidence, strengths and limitations of individual studies were evaluated based on scientific considerations detailed in the Appendix. More details on the causal framework used to reach these conclusions are included in the Preamble to the ISA (U.S. EPA, 2015).

Size Fraction	Causality Determination
$PM_{2.5}$	Likely to be Causal
$PM_{10-2.5}$	Suggestive of, but not sufficient to infer
UFP	Inadequate

10.1 Introduction

10.1.1 Evaluation of the Relationship Between Long-term PM Exposure and Cancer

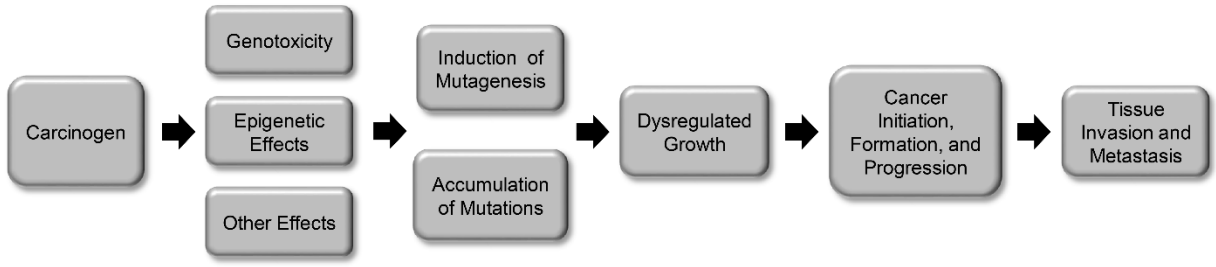
The 2009 Particulate Matter Integrated Science Assessment (2009 PM ISA) evaluated the relationship between long-term PM exposure and cancer, with an emphasis on specific PM size fractions ($PM_{2.5}$, $PM_{10-2.5}$, and UFPs) (U.S. EPA, 2009), with most studies focused on $PM_{2.5}$ exposure. This body of evidence was supported by decades of research on whole PM exposures (i.e., no defined size fraction), including diesel exhaust, gasoline exhaust, and wood smoke.

Since completion of the 2009 PM ISA, the International Agency for Research on Cancer (IARC) classified outdoor air pollution, including PM, as a Group 1 carcinogen (carcinogenic to humans) (IARC, 2016). IARC conducted a weight-of-evidence assessment for hazard identification that involved evaluating epidemiologic, animal toxicological, and mechanistic studies associated with outdoor air pollution. Studies evaluated in the IARC assessment consisted of those that examined inhalation as well as other routes of exposure, PM concentrations higher than 1−2 orders of magnitude above ambient, and individual PM components and specific PM size fractions. The conclusion of the IARC assessment was based primarily on epidemiology studies of ambient $PM_{2.5}$ exposures and lung cancer incidence and

mortality, on inhalation studies of promotion-initiation in mice exposed to ambient air PM_{10}, and on evidence from mechanistic studies using PM of various size fractions. In contrast, this ISA is tasked with evaluating only inhalation exposures of specific PM size fractions at relevant ambient concentrations (i.e., up to one to two orders of magnitude above ambient). The evaluation of the relationship between long-term exposure to $PM_{2.5}$, as well as other PM size fractions, and cancer is guided by the overall scope of the ISA as detailed in the Particulate Matter Integrated Review Plan (U.S. EPA, 2016) and summarized briefly in the Preface (Section P.3.1).

10.1.2 Carcinogens and the Development of Cancer

Development of cancer is a complex, multistep disease process (Figure 10-1). Evidence collected over decades of scientific research suggests that dysregulation of cellular pathways controlling cell growth, survival, and genetic stability results in aberrant, unregulated cell division and is central to disease initiation and progression. The most widely accepted pathway to unregulated growth is accumulation of mutations in critical genes. However, more recently, epigenetic mechanisms, such as gene silencing through promotor methylation, or receptor-mediated cell proliferation have been proposed to be important to disease development (Smith et al., 2016).



Note: This scheme depicts important steps in the development of cancer and is adapted from Goodson et al. (2015) and Smart et al. (2008).

Figure 10-1 Key steps in the development of cancer.

Hanahan and Weinberg (2000) and Hanahan and Weinberg (2011) have proposed several hallmarks of cancer that describe the phenotype of cancer cells and developed tumors. These hallmarks organize the dysregulated pathways identified in cancer cells in terms of biological properties that are acquired during tumor development in humans (Hanahan and Weinberg, 2011). They include sustained proliferative signaling, evasion of growth suppressors, resistance of cell death, enabling of replicative immortality, induction of angiogenesis, activation of invasion and metastasis, reprogramming of energy

metabolism, and evasion of immune destruction. Few studies of exposure to PM size fractions have specifically examined dysregulated pathways associated with cancer cells and developed tumors. However, as described below, some studies of exposure to PM size fractions demonstrate perturbation of pathways related to the hallmarks of cancer, such as methylation of a tumor suppressor gene, which is relevant to evasion of growth suppressors.

Smith et al. (2016) has proposed ten characteristics of carcinogens as important to the etiology and progression of cancer. These characteristics are related to the mechanisms through which it is currently thought carcinogenic agents act. These characteristics include the ability to (1) be electrophilic either directly or after metabolic activation, (2) be genotoxic, (3) alter DNA repair or cause genomic instability, (4) induce epigenetic alterations, (5) induce oxidative stress, (6) induce chronic inflammation, (7) be immunosuppressive, (8) modulate receptor-mediated effects, (9) cause immortalization, and (10) alter cell proliferation, cell death, or nutrient supply. Numerous studies published prior to the 2009 PM ISA showed that PM of various size fractions exhibit many of these characteristics, especially the first six (IARC, 2016). Studies published since the 2009 PM ISA provide evidence that the PM size fractions of interest in this ISA, (i.e., $PM_{2.5}$, $PM_{10–2.5}$, and UFP) exhibit several of the key characteristics of carcinogens. New findings describe the capability of these PM size fractions to induce oxidative stress and to damage DNA, which can be processed by the cell into gene and chromosomal mutations. Furthermore, studies link PM size fractions to the expression of genes that are relevant to metabolic activation or biotransformation and to epigenetic alterations.

In addition to consideration of the hallmarks of cancer (Hanahan and Weinberg, 2000); (Hanahan and Weinberg, 2011) and the characteristics of carcinogens (Smith et al., 2016), studies examining the effects of exposure to PM size fractions provide information on other cancer-related biomarkers. Some studies detail the presence of mutagenic compounds in PM size fractions collected from ambient air, while others measure the formation of DNA adducts and carcinogenic potential.

10.2 $PM_{2.5}$ Exposure and Cancer

The 2009 PM ISA concluded that the overall body of evidence was "suggestive of a causal relationship between relevant $PM_{2.5}$ exposures and cancer" (U.S. EPA, 2009).[76] This conclusion was based primarily on positive associations observed in epidemiologic studies of lung cancer mortality. Epidemiologic studies evaluating $PM_{2.5}$ and lung cancer incidence or cancers of other organs and systems generally did not show evidence of an association. Toxicological studies did not focus on exposures to specific PM size fractions, but rather investigated the effects of exposures to total ambient PM, or other source-based PM such as wood smoke. Collectively, results of in vitro studies were consistent with the

[76] As detailed in the Preface, risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations unless otherwise noted.

larger body of evidence demonstrating that ambient PM and PM from specific combustion sources are mutagenic and genotoxic. However, animal inhalation studies found no evidence of tumor formation in response to chronic exposures, except for one study demonstrating enhanced formation of urethane-induced tumors. In addition, a small number of studies provided preliminary evidence that PM exposure can lead to changes in methylation of DNA, which may also contribute to biological events related to cancer.

Recent studies expand upon the evidence for long-term $PM_{2.5}$ exposure and cancer detailed in the 2009 PM ISA. Although previous studies tended to focus more broadly on PM exposures, recent studies address a number of uncertainties and limitations with respect to the role of $PM_{2.5}$ exposure in the development of cancer. Evidence from experimental and epidemiologic studies demonstrate that $PM_{2.5}$ exposure can lead to a range of effects indicative of mutagenicity, genotoxicity, and carcinogenicity, as well as epigenetic effects. These cellular and molecular changes are supported by epidemiologic evidence demonstrating consistent positive associations between long-term $PM_{2.5}$ exposure and lung cancer mortality and incidence.

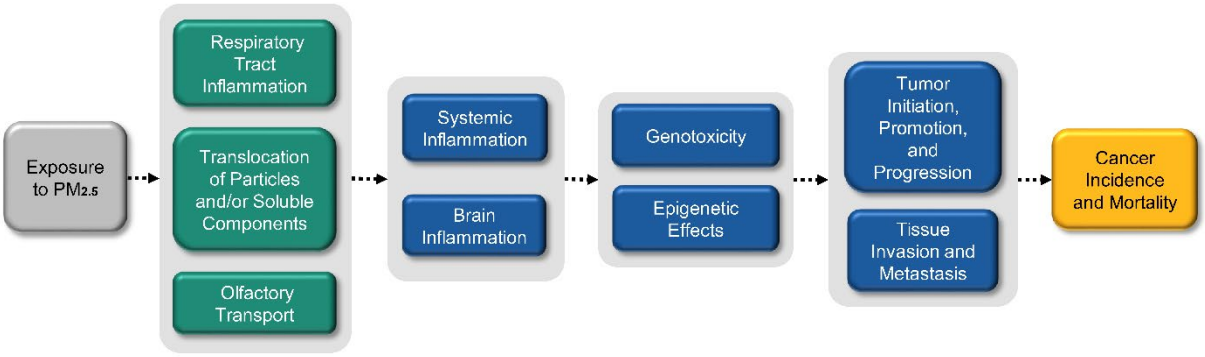
The following sections evaluate studies published since completion of the 2009 PM ISA. Although the ISA is tasked with reviewing new evidence describing the mutagenicity, genotoxicity, and carcinogenicity for each PM size fraction, it is recognized that there exists a large body of historical evidence demonstrating these effects resulting from exposure to total PM. Throughout this section recent studies are evaluated in the context of this larger collective body of evidence.

10.2.1 Biological Plausibility

This section describes biological pathways that potentially underlie the development of cancer resulting from exposure to $PM_{2.5}$. Figure 10-2 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" exposure to $PM_{2.5}$ may lead to the development of cancer contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 10.2.

Once $PM_{2.5}$ deposits in the respiratory tract, it may be retained, cleared, or solubilized (see Chapter 4). $PM_{2.5}$ and its soluble components may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate reactive oxygen species (ROS) and this capacity is termed "oxidative potential". Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see CHAPTER 4). Immune system responses due to the presence of particles in the interstitial space may contribute to chronic health effects. Inflammatory

mediators may diffuse from the respiratory tract into the systemic circulation and lead to inflammation in extrapulmonary compartments (see Chapter 6). Soluble components of $PM_{2.5}$ and poorly soluble particles that are part of the $PM_{2.5}$ fraction and smaller than approximately 200 nm may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments. A fraction of $PM_{2.5}$ may deposit on the olfactory epithelium. Soluble components of $PM_{2.5}$ and poorly soluble particles that are part of the $PM_{2.5}$ fraction and smaller than approximately 200 nm may be transported via the olfactory nerve to the olfactory bulb of the brain. The extent to which translocation into the systemic circulation or transport to the olfactory bulb occurs is currently uncertain. For further discussion of translocation and olfactory transport, see Chapter 4. The potential contribution of olfactory transport to brain inflammation or to upregulation of gene expression in the brain is discussed in Chapter 8.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 10-2 Potential biological pathways for the development of cancer following exposure to $PM_{2.5}$.

Evidence is accumulating that exposure to $PM_{2.5}$ may lead to carcinogenesis by two pathways. The first pathway involves genotoxicity, where electrophilic compounds induce DNA damage, such as DNA strand breaks or DNA adducts (where a compound is bound covalently to DNA), and such damage is then processed by the cell to result in a change in DNA sequence—i.e., a mutation. The second pathway involves epigenetic effects that alter gene expression, further altering cell growth, regulation, and other processes. Carcinogenesis is essentially dysregulated growth; one or the other or a combination of both pathways above can lead to cancer. A general scheme for cancer induction involves initiation, promotion, and progression, leading eventually to tissue invasion and metastasis. Although most of

epidemiologic evidence links $PM_{2.5}$ exposure to lung cancer, a plausible link to other kinds of cancer may exist. Evidence for these pathways and cancer-related biomarkers is described below. A discussion of the hallmarks of cancer (Hanahan and Weinberg, 2000); (Hanahan and Weinberg, 2011) and the characteristics of carcinogens (Smith et al., 2016), as they relate to $PM_{2.5}$, follows.

Genotoxicity

Genotoxicity is a term that refers to DNA damage, mutations, or both (Shaughnessy and DeMarini, 2009). DNA damage consists of alterations to DNA such as a DNA strand break (breakage of the phosphodiester bonds) or a DNA adduct (the covalent binding of a chemical to DNA). The DNA damage itself generally does not alter the sequence or number of the four bases/nucleotides in DNA, whose order form the basis of the genetic code. DNA damage can be caused by spontaneous errors of nucleic acid metabolism or by endogenous or exogenous mutagens. In contrast, mutations are changes in DNA sequence (i.e., in the order or number of the bases/nucleotides), and they occur when the cell processes DNA damage incorrectly, such as by failing to repair the damage or by trying to perform DNA replication past the unrepaired damage. Thus, mutagenesis is a cellular process, usually involving DNA replication and DNA repair. There are three classes of mutations: gene, chromosomal, and genomic. Mutations within a single gene are called gene or point mutations, such as base substitutions. Mutations involving more than one gene are called chromosomal mutations, such as chromosomal aberrations involving multigenetic deletions, inversions, duplications, or translocations. The gain or loss of a whole chromosome (aneuploidy) is an example of genomic mutation. As detailed below, $PM_{2.5}$ exposure is associated with mutagenicity, DNA adducts and other DNA damage, oxidative stress, biotransformation, and chromosomal (or cytogenetic) effects.

Mutations are considered biomarkers of early biological effect (Demetriou et al., 2012). The Ames *Salmonella*/mammalian-microsome mutagenicity assay is a bacterial assay and the most widely used assay of any kind for detecting the mutagenic activity of an agent (Claxton et al., 2010). In the absence of metabolic activation, it detects agents that are called direct-acting mutagens; in the presence of metabolic activation, it detects agents that are indirect-acting mutagens, i.e., those requiring metabolism to electrophilic forms. The somatic mutation theory of cancer is the most widely accepted theory of cancer etiology, and it postulates that cancer occurs at a minimum from the accumulation of mutations in critical genes. The presence of mutagens within PM and the mutagenicity of organic extracts of PM provide biological plausibility for observations made in epidemiologic studies of cancer incidence. Although the Ames assay has several technical limitations and is criticized due to its use of bacteria as a model species, more than four decades of published results evaluating 10,000 compounds have clearly demonstrated the validity of this assay for evaluating the mutagenicity of PM collected from ambient air (Claxton et al., 2010; U.S. EPA, 2009). New studies published since the 2009 PM ISA provide evidence to support mutagenicity resulting from $PM_{2.5}$ exposure (Section 10.2.2.1).

DNA adducts are a type of DNA damage and serve as a biological marker of exposure (Demetriou et al., 2012). They form via a covalent bond between DNA and a carcinogen or a metabolite of a carcinogen. Repair proteins may remove DNA adducts. However, persistent adducts may result in mutations when the DNA polymerase tries to replicate past the adduct, resulting in nucleotide (base) substitutions, deletions, duplications, and chromosome rearrangements. An in vitro toxicological study described in the 2009 PM ISA provides evidence for the formation of DNA adducts following exposure to $PM_{2.5}$ (De Kok et al., 2005). In this study, rat liver S9 metabolism was found to increase DNA reactivity (i.e., the induction of DNA adducts). Supporting evidence is provided by recent epidemiologic studies showing benzo[a]pyrene (B[a]P) -like DNA adducts in association with $PM_{2.5}$ exposure (Li et al., 2014; Rossner et al., 2013b). Other types of DNA damage involve the formation of oxidized bases or nucleotides, as well as the induction of single- or double-strand breaks, all of which can be determined by the comet assay (Demarini, 2013). Evidence for such DNA damage following $PM_{2.5}$ exposure is provided by several in vitro studies using the comet assay and by a study measuring phosphorylated H2AX, which measures double-strand breaks (Section 10.2.2.2). A single epidemiologic study provides supportive evidence for DNA damage, as assessed by the comet assay, in association with $PM_{2.5}$ concentrations (Chu et al., 2015).

Some of the studies examining DNA damage identified oxidized bases, suggesting a role for oxidative stress in the development of the DNA lesions (Section 10.2.2.2). These oxidized DNA nucleobases are considered a biomarker of exposure (Demetriou et al., 2012). Exposure to PM can result in oxidative stress either through the direct generation of ROS, or indirectly through the induction of inflammation. Treatment with an antioxidant blocked strand breaks due to $PM_{2.5}$ exposure (Oh et al., 2011). Other in vitro studies showed that exposure to $PM_{2.5}$ increased the production of reactive oxygen species (ROS) in vitro. The in vitro results are supported by both animal toxicological and controlled human exposure studies. An inhalation study involving $PM_{2.5}$ in male mice found oxidized DNA bases in lung tissue (Soberanes et al., 2012). A study in human subjects found increased lipid peroxidation products in urine (Liu et al., 2015). The presence of oxidative stress-mediated DNA lesions, including adducts, can lead to the introduction of fixed mutations into the genome after incorrect repair of the damaged base or replication past the base by low fidelity DNA polymerases. The potential for oxidative stress to result in mutagenesis is underscored by the DNA repair mechanisms that have evolved to protect the genome from mutagenesis caused by these lesions.

Some components of PM, especially organic compounds, may undergo metabolism in a variety of cell types, resulting in electrophilic compounds that may bind to DNA, RNA, or proteins. Evidence that genes participating in polycyclic aromatic hydrocarbon (PAH) biotransformation are upregulated as a result of $PM_{2.5}$ exposure is provided by in vitro studies Borgie et al. (2015b) and Gualtieri et al. (2011). Biotransformation via Cyp1A1 may result in the production of PAH metabolites capable of reacting with DNA to form bulky DNA adducts. As in the case of oxidative-stress mediated DNA adducts, when DNA repair of bulky adducts is absent or ineffective, mutational events may occur.

Cytogenetic effects, such as micronuclei formation and chromosomal aberrations, are also biomarkers of genotoxicity (Demarini, 2013). Micronuclei are small nuclei formed either by chromosomal breakage or aneuploidy, which is the addition or deletion of a whole chromosome (Demetriou et al., 2012). $PM_{2.5}$ exposure increased micronuclei formation in vitro (Lemos et al., 2016; Oh et al., 2011). This effect was blocked by an antioxidant, suggesting that oxidative stress may play a role (Oh et al., 2011). The formation of micronuclei correlated with the amount of DNA damage detected by the comet assay in the same study. Epidemiologic studies provide supporting evidence of chromosomal aberrations in association with $PM_{2.5}$ exposure (Rossner et al., 2013a; Rossner et al., 2011).

Epigenetic Effects

Epigenetic mechanisms regulate the transcription of genes without altering the nucleotide sequence of DNA. Three sets of epigenetic effects were examined in studies of $PM_{2.5}$: methylation of tumor suppressor genes, global DNA methylation, and alteration in noncoding miRNA. Changes in DNA methylation patterns can affect gene expression and genomic instability (Demetriou et al., 2012). They are considered a biomarker of early exposure. In general, transcription repression is associated with DNA methylation in promoter regions of genes. Inhalation exposure to $PM_{2.5}$ increased methylation of the p16 promotor in the lung (Soberanes et al., 2012). The p16 protein is a tumor suppressor, suggesting an epigenetic mechanism for dysregulated growth. Methylation of repetitive elements, a surrogate of global DNA methylation, was correlated with $PM_{2.5}$ concentrations in blood and lung tissue of Wistar rats (Ding et al., 2016). Global DNA methylation is a measure of genomic instability which can contribute to the accumulation of mutations in critical genes involved in the development of cancer. In general, hypomethylation is associated with genomic instability. In an in vitro study, methylation of repetitive elements and methyltransferase gene expression were decreased due to $PM_{2.5}$ exposure (Miousse et al., 2015). Support for a relationship between $PM_{2.5}$ exposure and global DNA methylation is provided by several epidemiologic studies (Section 10.2.3). Alteration in a third type of epigenetic effect, specific noncoding miRNA, was also found as a result of $PM_{2.5}$ exposure (Borgie et al., 2015b). These effects may contribute to the accumulation of mutations or dysregulated growth.

Carcinogenic Potential

None of the toxicological studies involving $PM_{2.5}$ exposure provides direct evidence of carcinogenesis. However, an animal inhalation study found that $PM_{2.5}$ exposure led to tumor promotion in a model of urethane-induced tumor initiation (Cangerana Pereira et al., 2011). Furthermore, exposure to $PM_{2.5}$ in vitro increased cell invasion, a measure of metastatic potential, which correlated with PAH content (Yue et al., 2015). This effect was blocked by treatment with an antioxidant, suggesting a role for oxidative stress. Epidemiologic studies provide initial evidence that exposure to long-term $PM_{2.5}$ concentrations may contribute to reduced cancer survival (Section 10.2.5.3). This could involve an enhancement of tumor progression or metastasis/tissue invasion or some other mechanism.

Characteristics of Carcinogens and Hallmarks of Cancer

$PM_{2.5}$, as described in the studies evaluated in this chapter, exhibits several characteristics of carcinogens (Smith et al., 2016). Exposure to $PM_{2.5}$ results in genotoxic effects, epigenetic alterations, and oxidative stress. In addition, exposure to $PM_{2.5}$ induces expression of genes involved in PAH biotransformation, indicating that $PM_{2.5}$ contains electrophilic species. Additional studies provide evidence that $PM_{2.5}$ exposure may lead to perturbations of pathways related to the hallmarks of cancer (Hanahan and Weinberg, 2000); (Hanahan and Weinberg, 2011). Findings of enhanced tumor formation may indicate the sustaining of proliferative signaling; increased cell invasion may indicate the activating of invasion and metastasis; methylation of a tumor suppression gene may indicate the evading of growth suppressors; and increased telomerase activity may indicate the enabling of replicative immortality.

Summary of Biological Plausibility

As described here, there are two proposed pathways by which exposure to $PM_{2.5}$ could lead to the development of cancer. The first pathway involves genotoxicity, including DNA damage that could lead to mutational events, such as gene mutation and cytogenetic effects. The second pathway involves epigenetic effects, including methylation of a tumor suppressor gene. Although experimental studies in animals and humans contribute most of the evidence of upstream events, epidemiologic studies report associations between exposure to $PM_{2.5}$ and DNA damage (including DNA adducts), chromosomal mutation (chromosomal aberrations), and epigenetic changes (altered global DNA methylation). Evidence of tumor promotion, a measure of carcinogenic potential, was found in an animal toxicological study. Together, these proposed pathways provide biological plausibility for the epidemiologic results of lung cancer incidence and mortality and will be used to inform a causality determination, which is discussed later in the chapter (Section 10.2.5).

10.2.2 Genotoxicity

In the 2009 PM ISA, there were many toxicological studies that examined mutagenicity, DNA damage, and other endpoints related to genotoxicity. The presence of mutagens in PM extracts collected from ambient air was first demonstrated by Pitts et al. (1975). In agreement with that work and many similar subsequent findings published over the past 40 years, results from studies evaluated in the 2009 PM ISA confirmed that PM and/or PM extracts collected from both ambient air and multiple combustion sources can induce DNA mutations in various strains of *Salmonella* developed by Bruce Ames and others. PM exposure in other in vitro assay systems resulted in changes in molecular and cellular markers that have been associated with genotoxicity. In addition, an in vivo study by Sato et al. (2003) reported increased DNA adducts in lung, liver, and nasal mucosal tissues after inhalation exposure to urban roadside air. Because this study evaluated effects of exposure to a mixture of PM and gases, it does not inform the current ISA, which identifies the hazard for effects after exposures to only the PM component

of complex mixtures. Furthermore, a small number of epidemiologic studies evaluated in the 2009 PM ISA examined molecular and cellular markers that have often been linked with genotoxicity. Many of these studies focused only on PM_{10} exposures or individual components of PM. As a result, these epidemiologic studies did not thoroughly examine the relationship between $PM_{2.5}$ exposure and genotoxicity.

As noted in the 2009 PM ISA, there was a paucity of available studies that investigated the effects of exposures to specific PM size fractions. There were no new studies that evaluated in vivo effects of exposures to $PM_{2.5}$ present in ambient air. Although new in vitro studies were reviewed that confirmed previous reports demonstrating induction of mutagenesis, DNA strand breaks, micronuclei, and oxidative stress after $PM_{2.5}$ and/or $PM_{2.5}$ extract exposures, the relationships between observations from in vitro assays and in vivo endpoints and complex biological disease processes such as carcinogenesis remained uncertain. Moreover, the diversity of in vitro assay protocols and measured endpoints limited the ability to draw more than general conclusions regarding the carcinogenic potential of $PM_{2.5}$.

Since the 2009 PM ISA, new studies continue to investigate mutagenicity, genotoxicity, and carcinogenicity of PM, including many studies that, as in the past, evaluate the effects of total particulate matter (TPM), PM_{10}, and total PM collected from specific combustion sources including diesel and gasoline exhaust and woodsmoke. In addition, recent studies also investigate cancer-related effects following inhalation of $PM_{2.5}$ CAPs, ambient air, and emissions from specific combustion sources. The findings from these studies are supportive of findings from previous studies. However, as discussed in the Preface, the focus of the PM ISA is on the evaluation of the health effects due to exposures to specific PM size fractions (i.e., $PM_{2.5}$, $PM_{10–2.5}$, and UFPs). As a result, in the evaluation of long-term $PM_{2.5}$ exposure and cancer, in the assessment of the experimental evidence for mutagenicity, genotoxicity, and other endpoints associated with carcinogenesis and cancer, the focus is on exposures to $PM_{2.5}$.

10.2.2.1 Mutagenicity

Evidence for mutagenicity is provided by toxicological studies. The Ames *Salmonella*/mammalian-microsome mutagenicity assay has been used for more than 40 years to identify the presence of chemical mutagens (Claxton et al., 2010; Ames, 1971). Developed to screen single chemicals for their potential to induce mutagenesis, the assay was first extended to investigate the mutagenicity of extracted organic material (EOM) from PM collected from air in Los Angeles (Pitts et al., 1975). The *Salmonella* test provided a simple, fast, and inexpensive method for detecting the presence of mutagens within the complex mixture of chemical species that can be present in ambient air.

Assay results over the past 40 years have provided meaningful information regarding the mutagenicity of airborne compounds. The *Salmonella* test, however, is not without technical limitations. For example, it is difficult to draw detailed conclusions based upon direct comparisons between study results because of assay sensitivity to differences in methods. Many studies examine only the organic

matter adsorbed onto collected particles and extraction protocols including solvent and extraction method selection have been shown to affect the amount and class of compounds recovered (Claxton et al., 2004). In addition, several strains of *Salmonella* and variations in assay protocols have been developed. One advantage of the assay is that various strains selectively respond to specific chemical classes, such as nitroarenes, PAHs, or aromatic amines, providing the ability to infer some of the chemical classes responsible for the mutagenicity. However, differences in strains and protocols can modify the reproducibility of results and/or the sensitivity of the assay to certain classes of mutagens (Claxton et al., 2004; Gatehouse et al., 1994). Moreover, studies have revealed that mutagenicity fluctuates seasonally (Claxton et al., 2004). Together, these factors can affect the number of revertant colonies observed and thus limit direct comparisons between disparate studies.

Analyses using various data bases have been performed to see how well the *Salmonella* mutagenicity assay predicts rodent carcinogenicity. The values that have been calculated for both the sensitivity (the percentage of known carcinogens to elicit a positive response in *Salmonella*) and specificity (the percentage of known noncarcinogens to elicit a negative response in *Salmonella*) are 45−80 and 67−100% for sensitivity and specificity, respectively (Kirkland et al., 2005; Zeiger, 1998; Zeiger et al., 1990; Tennant et al., 1987; Kier et al., 1986). Thus, agents that are not carcinogenic in rodents can also be mutagenic in the assay, and some chemical classes of rodent carcinogens are not mutagenic in the *Salmonella* assay (Zeiger et al., 1990). Considering also that PM is a heterogeneous and dynamic mixture with many unknown chemical species, *Salmonella* assay results are accordingly accompanied by uncertainty.

As discussed above, most studies of PM with the *Salmonella* mutagenicity assay evaluated only the EOM adsorbed onto particles. Because extraction results in an enriched preparation of organic compounds, the concentration applied in the assay may not reflect the administered dose delivered to the lung via inhalation of ambient air, nor accurately represent the mixture present on PM as species such as metals and volatile organic compounds (VOCs) will not be responsive to organic extraction. Further, the bioavailability of extracted compounds may not be comparable to the bioavailability of those adsorbed onto particles.

As with many bioassay, the *Salmonella* strains used in the Ames assay have been engineered to improve their ability to detect mutagens. Thus, there is a mutation in a gene coding for a component of the cell wall that makes the cells more permeable to large molecules. This permits PM components such as PAHs to enter the cell and get to the DNA. Likewise, there are various DNA repair deficiencies, such as the elimination of nucleotide excision repair or the addition of error-prone DNA repair, that also enhance the sensitivity of the strains to mutagens. Several different mutations in the histidine genes are present in the strains, permitting the detection of all six types of base substitutions, a 2-base frameshift mutation, as well as some small deletions. One of the most important developments that has made the strains especially useful for complex mixtures is the development of strains with various metabolic capabilities, permitting the inference of specific chemical classes in a complex mixture as being

responsible for some of the mutagenicity of that mixture. Thus, some strains express excess nitroreductase, which activates nitroarenes, and others express acetyltransferase, which can help activate aromatic amines.

Although many new studies using the *Salmonella*/mammalian-microsome assays have been published, only a fraction evaluated the mutagenic activity of $PM_{2.5}$. Of these, all were conducted outside of the U.S. in Brazil, Japan, India, and Italy. In general, the findings support previously published results that organic extracts from collected PM (various size fractions) contain compounds capable of inducing mutagenesis in the *Salmonella* assay. Specifically, results from these studies demonstrate that organic extracts of $PM_{2.5}$ collected from diverse sampling locations exhibit mutagenic activity. The induction of mutations in both the absence and presence of mammalian S9 fractions indicate the presence of compounds that are capable of interacting with DNA without biotransformation as well as those that require metabolic activation to generate ultimate carcinogens (Lemos et al., 2016; Traversi et al., 2014; de Rainho et al., 2013; Rainho et al., 2013; Lemos et al., 2012; Singla et al., 2012; Traversi et al., 2011; Kawanaka et al., 2008; Traversi et al., 2008). In addition to these general findings, several studies also identified the presence of certain compound classes, seasonal variation in mutagenic activity, and the tendency for $PM_{2.5}$ to elicit a greater increase in mutagenicity compared to PM_{10} (Lemos et al., 2016; Traversi et al., 2014; de Rainho et al., 2013; Rainho et al., 2013; Lemos et al., 2012; Singla et al., 2012; Traversi et al., 2011; Kawanaka et al., 2008; Traversi et al., 2008).

As has been documented by past studies, use of plasmid-modified strains sensitive to nitro-PAH species in new studies confirmed the presence of those compounds in airborne particulate matter from sites in Brazil and Italy. Sites included low traffic areas identified as urban background or residential locations (Lemos et al., 2016; de Rainho et al., 2013; Rainho et al., 2013; Lemos et al., 2012; Traversi et al., 2011). For example, Traversi et al. (2011) used three isogenic strains with varying nitroreductase activity to qualitatively demonstrate the contribution of nitroaromatic compounds to the overall mutagenicity observed. $PM_{2.5}$ was most mutagenic in strains with elevated nitroreductase activity, suggesting the presence of nitroaromatic compounds in the extracts evaluated. The knowledge that these compounds are present in PM emissions and that they can induce mutagenesis in the *Salmonella* assay is well established (NTP, 2014; Claxton et al., 2004; Purohit and Basu, 2000; Rosenkranz and Mermelstein, 1983).

Kawanaka et al. (2008) investigated the mutagenicity of EOM from $PM_{2.5}$ collected roadside in Saitama City, Japan. Using a cascade impactor, 12 fractions of varying aerodynamic diameters were collected including fine fractions (<0.12, 0.12−0.20, 0.20−0.30, 0.30−0.50, 0.70−1.2, 1.2−2.1, 2.1−3.5, 3.5−5.2, 5.2−7.8, 7.8−11, >11 μm). The authors used the *Salmonella* assay to determine the mutagenic potency of each fraction and GC/NCI/MS/MS to determine the mass contribution of select nitroaromatic compounds to the total PM mass collected. They used known quantities of those compounds to estimate the contribution of those species to total mutagenicity. Using this approach, the authors reported that the quantity of nitro-PAHs per unit mass in the ultrafine fraction (<0.12) was greater than in that of $PM_{2.5}$ or

$PM_{10-2.5}$. In addition, the authors determined that mutagenicity per unit mass of $PM_{2.5}$ was less than that of UFP in both strains. Moreover, of the six nitroaromatic compounds evaluated, the contribution to mutagenic activity calculated was greatest for 1,8-dinitropyrene in all three fractions of PM extracts evaluated. Due to biological variability of the *Salmonella* assay as well as incomplete details regarding the statistical analysis of the data collected, it is difficult to calculate definitive values for these contributions.

Several studies evaluated seasonal variation in mutagenesis using the *Salmonella* assay (Lemos et al., 2016; Traversi et al., 2011; Traversi et al., 2008). Each observed greater mutagenic activity in extracts from PM collected during the autumn and winter seasons compared to that from PM collected during the spring and summer seasons. These findings agree with previous studies that have also demonstrated the inverse correlation between temperature and mutagenic activity (IARC, 2016; Claxton et al., 2004). Singla et al. (2012) also compared seasonal variation in mutagenic activity. Although the authors did not provide a statistical analysis of the variation in values, they did report a consistent trend in which the mutagenicity of extracts from PM collected during the winter season was greater than the mutagenicity of those from PM collected during the monsoon season. In this study, they suggested that this divergence may be due not only to the increase in temperature, but also to the increase in rainfall.

Singla et al. (2012) and Traversi et al. (2011) analyzed the mutagenic activity of $PM_{2.5}$ and PM_{10} collected during the same timeframes. In experiments using the frameshift strain TA98 without the addition of S9, which especially detects nitroarenes (Singla et al., 2012), the authors reported that the organic extracts collected from $PM_{2.5}$ had higher mutagenic potencies that those from PM_{10}. However, this same effect was not observed in experiments using TA100, which detects primarily PAHs. Likewise in the study by Traversi et al. (2011), the mutagenic potency of the organics extracted from $PM_{2.5}$ was 6.5-fold greater than that from PM_{10} in strain TA98. Further, the authors reported greater mutagenicity for the organic extracts from $PM_{2.5}$ collected in the winter season compared to that from PM_{10} when using the nitro-PAH sensitive YG1021 strain (5.75-fold increase). A third study carried out a similar analysis. Lemos et al. (2012) compared the mutagenic activity of organic extracts from $PM_{2.5}$ and total suspended particles (TSP). The authors reported that the mutagenic potencies of the organic extracts from $PM_{2.5}$ were generally greater than those from TSP; however, a statistical analysis was not provided. Lemos et al. (2012) showed that an aqueous extract generated sequentially after the organic extraction was not mutagenic, showing that all the measured mutagenic activity was in the organic extract.

In summary, while the Ames *Salmonella*/mammalian-microsome mutagenicity assay has several technical limitations and is criticized due to its use of bacteria as a model species, four decades of published results from this assay have clearly demonstrated the presence of mutagenic agents in PM of various size fractions collected from ambient air (IARC, 2016; U.S. EPA, 2009). New studies involving $PM_{2.5}$ exposure published since the 2009 PM ISA also provide evidence of the presence of mutagenic agents (Lemos et al., 2016; Traversi et al., 2014; de Rainho et al., 2013; Rainho et al., 2013; Lemos et al., 2012; Singla et al., 2012; Traversi et al., 2011; Kawanaka et al., 2008; Traversi et al., 2008).

10.2.2.2 DNA Damage

10.2.2.2.1 Toxicological Evidence

In addition to *Salmonella* studies that evaluated mutagenicity, new reports that measured other effects relevant to genotoxicity and carcinogenicity as a result of $PM_{2.5}$ exposures have been published. Many of these studies used a variety of in vitro assays including cell-free and cell culture systems that are designed to identify specific cellular endpoints. For example, the comet assay measures DNA single- and double-strand breaks and can be adapted to identify the presence of apurinic and apyrimidinic (together noted as AP) sites by the introduction of alkaline conditions, and certain types of damaged bases, including oxidized bases, through the additional use of lesion-specific endonucleases (Collins et al., 2008). Several other assays to identify the presence of oxidative stress after $PM_{2.5}$ exposures have also been used in new studies. The relevance of data generated in the comet assay is supported by the fact that oxidative stress is one of the key characteristics of carcinogens (Smith et al., 2016).

The presence of reactive oxygen species (ROS) in a cell is a consequence of normal physiological processes, however oxidative stress, which is the imbalance between the generation of ROS and the protective mechanisms by which ROS are detoxified or ROS-induced damage is repaired, has been associated with the development of several health effects including cancer. ROS and ROS-induced lipid peroxidation products interact with DNA to form DNA lesions such as 7,8-dihydro-8-oxoguanine (8-oxoG), thymine glycol, 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FaPy), etheno-DNA adducts, and malondialdehyde DNA adducts (Smart et al., 2008). The presence of these lesions can lead to the introduction of fixed mutations into the genome after incorrect repair of the damaged base or replication past the base by low fidelity DNA polymerases. The potential for oxidative stress to result in mutagenesis is underscored by the DNA repair mechanisms that have evolved to protect the genome from mutagenesis caused by these lesions. Increased 8-oxoG levels, one of the most widely studied lesions, has been demonstrated to result in spontaneous tumorigenesis in MTH1-deficient mice (Tsuzuki et al., 2001).

Since the 2009 PM ISA, several new studies have been published to identify the potential for oxidative stress resulting from exposure to $PM_{2.5}$. They have focused primarily on evaluating the oxidative potential of PM in acellular in vitro assays, as well as the capability of PM to induce oxidative stress in cultured cells. Because an important source of oxidative stress is inflammation, one new study measured in vitro inflammatory responses to $PM_{2.5}$ exposure. Evidence for inflammation at the organ and system level resulting from $PM_{2.5}$ exposure is described in Chapters 4 and 5.

Collectively, results from the in vitro studies demonstrate that damage to DNA bases and DNA strands can occur due to exposure to $PM_{2.5}$ in these systems and that production of ROS may contribute to that damage. As with *Salmonella* assay results, the findings are limited by the well understood caveats that apply to many in vitro model systems, including uncertainty regarding the relationship between measures of molecular markers and in vivo outcomes. As with the *Salmonella* assay, PM processing after

collection and use of extracted material in many studies may result in PM that is not representative of that in ambient air and/or alter its toxicity. For example, Turner et al. (2015) investigated how the use of EOM from collected particles may affect results for a suite of in vitro toxicity tests. The authors reported that the use of EOM from diesel exhaust particles (DEP) induced greater biological responses than intact DEP in suspension. They also evaluated the effect of cell type and observed that, in general, human premacrophage monocyte (GDM-1) cells were more sensitive than A549 cells.

Several studies measured DNA damage after exposure to ambient $PM_{2.5}$ (Lemos et al., 2016; Danielsen et al., 2011; Oh et al., 2011; Bonetta et al., 2009) and DEP (Dumax-Vorzet et al., 2015; Jalava et al., 2015; Gualtieri et al., 2011) using the comet assay. Although the variety of PM preparation and comet assay methods make direct comparisons difficult, the results suggest that exposure of cultured cells in vitro to $PM_{2.5}$ extracted material and/or suspensions can result in DNA damage. Oh et al. (2011) collected $PM_{2.5}$ from a traffic area in Suwon City, South Korea that was located approximately 20 miles south of Seoul and exposed human bronchial epithelial (BEAS-2B) cells to the organic crude extracted (CE) fraction as well as fractions of the CE that were separated by acid-base partitioning. Using the alkaline comet assay, the authors identified increased damage compared to control in the CE as well as the aliphatic, aromatic, and slightly polar fractions ($p < 0.01$). Repetition of the same assay with the addition of several different oxidant modulators rescued the damage to some extent in all cases, suggesting that the observed damage was, in part, the result of oxidative stress. Further, the authors also assessed the presence of specific lesions through the addition of formamidopyrimidine DNA glycosylase (FPG) and endonuclease III which can detect the presence of oxidized bases and some alkylation damage. For these experiments, increased damage was observed compared with controls in the CE as well as the fractions noted above ($p < 0.01$), providing support for the hypothesis that $PM_{2.5}$-induced oxidative stress can result in DNA damage.

These findings are supported by others (Danielsen et al., 2011; Gualtieri et al., 2011). Danielsen et al. (2011) detected DNA damage in A549 and human monocyte (THP-1) cells after exposure to PM (collection efficiency of 60−80% between 0.2 and 0.8 μm; upper cut point of 2.3 μm) suspension collected from two sites near Slagslunde, North Zealand, Denmark and confirmed the capability of the collected PM to generate ROS in other acellular and cell culture-based assays. Throughout their results, however, statistically significant increases ($p < 0.05$) were frequently observed only after exposure to suspension concentrations of greatest magnitude. In the study by Gualtieri et al. (2011), exposure to $PM_{2.5}$ suspension from PM collected near Milan, Italy resulted in an increase in DNA damage ($p < 0.05$) in BEAS-2B cells compared to controls.

In contrast to the findings by Danielsen et al. (2011) and Gualtieri et al. (2011), Jalava et al. (2015) did not observe DNA damage after exposure to fine PM suspensions. In this study, the authors exposed mouse macrophages (RAW 264.7) to $PM_{10–2.5}$, $PM_{2.5–1}$, $PM_{1–0.2}$, and $PM_{0.2}$ suspensions collected at Nanjing University in China and measured DNA damage using the alkaline comet assay. Although the

authors noted an increase in damage following some exposures to PM of other size fractions, there was no change in the damage measured in suspensions of $PM_{2.5–1}$ or $PM_{1–0.2}$ compared to controls.

Bonetta et al. (2009) also demonstrated the capability of PM extract exposure to result in DNA damage in the comet assay and observed that the amount of damage measured can vary with sampling location, which is consistent with similar findings in *Salmonella* assay studies. Using aqueous and organic extracts from $PM_{2.5}$ collected at urban, highway, and industrial sites near Alessandria, Italy, DNA damage was measured in human lung epithelial (A549) cells with the comet assay. The authors reported that exposure to organic extracts from $PM_{2.5}$ collected from all three sites resulted in an increase in damage using the alkaline comet assay compared to controls ($p < 0.001$). The increase was greatest for exposure to the highway site $PM_{2.5}$ organic extracts (p-value not provided). Exposure to aqueous extracts resulted in an increase in damage compared to control ($p < 0.001$) using the FPG-modified alkaline comet assay for $PM_{2.5}$ collected from the industrial site only.

Wessels et al. (2010) demonstrated that DNA damage after exposure to subfractions of $PM_{2.5}$ can vary with sampling location. To represent and compare diverse PM mixture profiles, the authors collected PM from four locations including a rural location at a beach on the west coast of Ireland and three urban locations in Birmingham, U.K. that varied in the extent to which vehicle traffic would contribute to the PM mixture sampled. Five size fractions were collected. $PM_{2.5}$ was collected in four fractions of particles with aerodynamic diameters of <0.5, 0.5−0.95, 0.95−1.5, and 1.5−3 µm. The fifth fraction comprised particles with diameters in the range of 3−7 µm. To evaluate the genotoxicity of aqueous PM suspensions, cultured A549 cells were used in the FPG-modified comet assay. The authors generally observed greater amounts of DNA damage after exposure to urban roadside PM suspensions compared to exposure to PM of equal mass collected from the rural site ($p < 0.1$) for size fractions with aerodynamic diameters of <0.5, 0.95−1.5, and 1.5−3 µm. This contrasts with the 3−7 µm fraction for which there was not a significant difference in the amount of damage induced after exposure to PM collected from any of the urban locations compared to that collected from the rural location. The variation in damage between size fractions was also examined. After adjusting for sampling site, the amount of DNA damage induced by extracts of PM from different particle size fractions was similar.

Borgie et al. (2015b) compared the effects of exposure to intact ambient $PM_{2.5}$ with aerodynamic diameters between 0.3 and 2.5 µm (described as $PM_{2.5–0.3}$) collected from an urban site in Beirut, Lebanon to that collected from a rural site in Byblos, Lebanon which is located 35 km from Beirut. The authors measured phosphorylated H2AX (γ-H2AX), a marker of DNA double strand breaks (DSB), in cultured BEAS-2B cells. Exposure to$PM_{2.5}$ collected from the urban location increased double-strand breaks at both low and high concentrations (3 and 12 µg/cm^2). In contrast, exposure to $PM_{2.5}$ collected from the rural location induced breaks only at the high concentration (12 µg/cm^2) only ($p < 0.05$), indicating that the $PM_{2.5}$ collected from the urban location had greater DNA damaging potency than that collected from the rural location.

The induction of oxidative stress after exposure to ambient $PM_{2.5}$ and DEP extracts and suspensions in cell culture demonstrated by comet assay results has been supported by studies that have used other in vitro methods to measure oxidative stress (Dumax-Vorzet et al., 2015; Miousse et al., 2015; Mirowsky et al., 2015; Gordon et al., 2013). Mirowsky et al. (2015) collected $PM_{2.5}$ as well as $PM_{10–2.5}$ from two rural and three urban sites in California and generated aqueous suspensions of both soluble and insoluble material. Using cultured human pulmonary microvasculature endothelial (HPMEC-ST11.6R) cells, they measured ROS with 2′,7′-dichlorofluorescein diacetate (DCFH-DA). DCFH-DA, after removal of the acetate groups by cellular esterases, can be oxidized to highly fluorescent DCF that can then be used to quantify the amount of intracellular ROS. The results identified two variables. That is, both the size fraction and location at which the PM was collected can affect the amount of intracellular ROS generated after exposure to aqueous PM suspension. Suspensions of $PM_{2.5}$ collected at urban sites were characterized by less ROS activity than those of $PM_{10–2.5}$ ($p < 0.001$). The same outcome was not observed, however, after exposure to $PM_{2.5}$ and $PM_{10–2.5}$ suspensions from the rural sites because the ROS activity generated by both was similar. When comparing the same size fractions between urban and rural sites, no differences were reported between sites for the $PM_{2.5}$ suspensions, whereas greater ROS activity was observed in experiments with $PM_{10–2.5}$ from the urban sites than $PM_{10–2.5}$ collected at the rural sites (*p*-value not provided).

Additional studies were identified that also used the DCFA-FA assay to assess intracellular ROS after exposure to PM (Dumax-Vorzet et al., 2015; Gordon et al., 2013). Gordon et al. (2013) exposed BEAS-2B and HBEpC cells to suspensions of size-fractionated PM from ambient air collected from five diverse sampling locations across the U.S. The PM size fractions collected were described as $PM_{2.5–0.2}$, $PM_{10–2.5}$, and $PM_{0.2}$. Like several other findings already highlighted, the authors reported variation in ROS production because of sampling site, season, and particle size. The report also noted that exposure to the $PM_{2.5}$ resulted in ROS production that was less than that of either $PM_{10–2.5}$ or UFP on an equal mass exposure when sampling locations were combined. Dumax-Vorzet et al. (2015) used cultured mouse embryonic fibroblasts (MEFs) in the DCFA-DA assay in addition to an acellular plasmid scission assay to estimate ROS after exposure to DEP suspension. The authors noted a dose-dependent increase in ROS (*p*-value not provided) using both methods.

Studies that used in vitro methods other than DCFA-FA to evaluate ROS or measured other endpoints that are relevant to oxidative stress have also been published. A change in superoxide was not detected in a study by Miousse et al. (2015) using dihydroethidium oxidation after exposure to aqueous extracts from $PM_{2.5}$ collected at an underground parking deck, but an increase in catalase expression ($p < 0.01$) was noted by the authors. Mirowsky et al. (2015) evaluated infiltrating polymorphonuclear cells (PMNs) as inflammation and ROS generated by PMNs in response to PM exposure has also been proposed as a pathway that may result in genotoxicity. The authors compared the effect of exposure on the percent of PMNs in lavage fluid for the various sampling locations and PM size fractions using oropharyngeal aspiration of aqueous PM suspension exposure in mice (FVB/N). Except for one rural location, the increase in percentage of PMNs after exposure to $PM_{2.5}$ suspensions were less than that after

exposure to $PM_{10–2.5}$ ($p < 0.001$). Upregulation of genes involved in antioxidant defense, i.e., the Phase 2 enzymes, were also observed in different in in vitro systems after $PM_{2.5}$ exposure. Borgie et al. (2015b), as described above, found increased gene expression of NQO1 in BEAS-2B cells.

In addition to in vitro studies, one in vivo study examined DNA damage. Exposure of male C57BL/6 mice to concentrated ambient $PM_{2.5}$ ($PM_{2.5}$ CAPs) in Chicago, IL resulted in an increase in 8-oxoG positive nuclei in lung tissue ($p < 0.01$) (Soberanes et al., 2012). This finding provides evidence of oxidative DNA damage in lungs following $PM_{2.5}$ exposure.

In summary, numerous in vitro studies conducted in cultured cells provide evidence of DNA damage, measured as single- and double-strand breaks, following exposure to suspended $PM_{2.5}$ or $PM_{2.5}$ extracts. Increased ROS production was also found in cellular assays. These results indicate that exposure to $PM_{2.5}$ induces oxidative stress, one of the identified characteristics of a carcinogen (Smith et al., 2016). Additionally, there is evidence of a direct relationship between oxidative stress and DNA damage. In an in vivo study, $PM_{2.5}$ CAPs inhalation resulted in oxidative DNA damage in lungs.

10.2.2.2.2 Evidence from Controlled Human Exposure Studies

Controlled human exposure studies have evaluated various markers relevant to DNA damage. Hemmingsen et al. (2015) reported mostly negative findings for DNA damage and oxidative stress from a controlled, cross-over, repeated measures human exposure study carried out in central Copenhagen, Denmark. In this study, overweight, older adults were exposed for 5 hours in chambers with and without high efficiency particulate adsorption filters. Peripheral blood mononuclear cells collected immediately before and after the exposure were negative for change from controls for several endpoints evaluated. These include ROS production, DNA strand breaks, oxidized DNA bases, and mRNA expression of CCL2, IL8, TNF, HMOX1, and OGG1. The only positive association identified was between FPG sensitive sites and exposure to urban air although it failed to reach statistical significance.

Another controlled human exposure study by Liu et al. (2015) measured malondialdehyde (MDA) in blood and urine and 8-oxo-dG in urine. The former is a lipid peroxidation product capable of reacting with DNA bases, whereas the latter is excreted after oxidized dGTP molecules in cellular dNTP pools used for nuclear and mitochondrial DNA replication throughout the cell are acted upon by MTH1 followed by 8-oxo-dGMPase in the process of dNTP pool sanitization. In this single-blind randomized crossover study, nonsmoking adults were exposed for 130 minutes to $PM_{10–2.5}$, $PM_{2.5}$, and UFP CAPs drawn from a downtown street in Toronto, Canada. Participant blood and urine were collected before exposure and after exposure at two-time points (1-hour, 21 hours). Positive associations between urinary MDA concentrations and $PM_{2.5}$ CAPs were reported for both time points (1-hour post-exposure: $p < 0.05$; 21 hours post-exposure $p < 0.1$). Urinary creatinine was used to normalize biomarker concentrations. No association was observed between blood MDA concentration and concentration of $PM_{2.5}$.

10.2.2.2.3 Epidemiologic Evidence

Several recent studies have examined a variety of molecular and cellular markers often associated with DNA damage. Study characteristics including $PM_{2.5}$ concentrations, study population, and exposure assignment approach for the studies that examined long-term $PM_{2.5}$ exposure and DNA damage are detailed in Table 10-1.

Table 10-1 Study specific details and $PM_{2.5}$ concentrations from recent studies that examined DNA damage.

Study Years	Location Population	Endpoints	Mean Concentration µg/m^3	Exposure Assessment
†Rossner et al. (2013b) (Winter and Summer 2009; Winter 2010)	Prague and Ostrava, Czech Republic (Prague: 61−65, nonsmoking policemen; Ostrava: 98−149; policemen, office workers, and volunteers)	B[a]P-like DNA adducts	Winter 2009: Prague: 13.8 Ostrava: 40.0 Summer 2009: Prague: 13.3 Ostrava: 12.0 Winter 2010: Prague: 42.6 Ostrava: 78.9	Personal monitoring for 48 h in each month, ambient concentrations measured up to 90 days before personal sampling
†Li et al. (2014) (2009−2010)	Shanghai, China (107 traffic policemen, 101 office workers)	BPDE-DNA adducts	Traffic policemen: 115.4 Office workers: 74.9	Personal 24-h concentrations
†Chu et al. (2015) (Not reported)	Zhuhai, Wuhan, and Tianjin China (307 subjects)	% tail DNA (comet assay)	Zhuhai: 68.4[a] Wuhan: 115.0[a] Tianjin: 146.6[a]	Personal 24-h concentrations
†Ma et al. (2015) (2013)	Shenyang, China (16 traffic policemen, 16 nonfield traffic policemen)	% tail DNA (comet assay)	Traffic policemen: 162.7 Nonfield traffic policemen: 51.5	2-week monitoring (April 8−19, 2013) campaign at traffic sites and indoor offices

B[a]P = benzo[a]pyrene; BPDE = (+) -enantiomer of antibenzo[a]pyrene 7,8-diol-9,10-epoxide; 8-OHdG = 8-hydroxy-2'-deoxyguanosine.

[a]Median concentration.

†Studies published since the 2009 PM ISA.

Rossner et al. (2013b) examined bulky B[a]P-like DNA adducts in study populations in two Czech Republic cities, Prague and a more polluted city (i.e., higher concentrations of not only PM but other pollutants as well), Ostrava. Whereas the study population in Prague consisted of only nonsmoking policeman, the study population in Ostrava was comprised of policeman, office workers, and volunteers.

This resulted in two different types of study populations where one consisted of individuals that may have smoked. Smoking status was not specifically adjusted for in the statistical models, but measures of cotinine in the blood, a proxy for tobacco smoke exposure was included as a covariate. This study found a higher number of B[a]P-like adducts in people that resided in Ostrava in association with $PM_{2.5}$ concentrations ($\beta = 0.002$ [95% CI: 0.002, 0.003]). These results are consistent with Li et al. (2014) in a study conducted in Shanghai, China that examined B[a]P-like adducts in a population of nonsmoking men that were traffic policemen or office workers. Using $PM_{2.5}$ concentrations collected through personal monitoring the 24-hours preceding biological sample collection, the authors observed an overall increase in BPDE-DNA adducts (0.8% [95% CI: 0.4, 1.2]), which was driven by the exposure group (1.2% [95% CI: 0.6, 1.5]) consisting of traffic policeman with limited evidence of an increase (0.1% [95% CI: 0.02, 0.23]) in the control group (i.e., office workers).

A study conducted in a cohort from three Chinese cities (Zhuhai, Wuhan, and Tianjin) broadly examined $PM_{2.5}$-modulated DNA damage by focusing on tail DNA and whether specific genetic polymorphisms modify the effect (Chu et al., 2015). Using $PM_{2.5}$ data from a personal monitoring campaign, Chu et al. (2015) reported evidence of a weak positive association between $PM_{2.5}$ concentrations and percentage of tail DNA from peripheral blood samples ($\beta = 0.001$ [95% CI: 0.000, 0.002]). These results are consistent with some of the results from Ma et al. (2015) in a study of DNA damage conducted in Shenyang consisting of traffic and nonfield traffic policemen. The authors graded the extent of DNA damage on a scale of 1 to 3, where 1 and 2 represented DNA damage <40% and 3 >40% damage. For DNA damage graded 1 and 2, Ma et al. (2015) did not observe a difference in the level of DNA damage between policemen exposed to high and low $PM_{2.5}$ concentrations. However, when examining Grade 3, there was a much larger percent of DNA damage in the traffic policemen compared to the nonfield policemen.

10.2.2.2.4 Summary

In summary, several lines of evidence provide support for a relationship between exposure to $PM_{2.5}$ and DNA damage. in vitro toxicological studies demonstrate that damage to DNA bases and DNA strands can occur after exposure to $PM_{2.5}$ in these systems and that production of ROS may contribute to that damage. An animal inhalation study (Soberanes et al., 2012) and a controlled human exposure study (Liu et al., 2015) also provide evidence of oxidative DNA damage. These findings are supported by epidemiologic studies that demonstrate DNA damage in association with $PM_{2.5}$ concentrations (Chu et al., 2015; Ma et al., 2015). In addition, epidemiologic studies indicated a larger percentage of B[a]P-like DNA adducts in people exposed to higher $PM_{2.5}$ concentrations (Li et al., 2014; Rossner et al., 2013b).

10.2.2.3 Cytogenetic Endpoints

10.2.2.3.1 Toxicological Evidence

New in vitro studies also demonstrated the presence of chromosomal abnormalities using the cytokinesis block micronucleus assay (CBMN) after exposure to $PM_{2.5}$ (Lemos et al., 2016; Oh et al., 2011). The CBMN assay detects acentric chromosome fragment loss and whole chromosome loss resulting from clastogenic and aneugenic agents, respectively (Kirsch-Volders et al., 2003). Lemos et al. (2016) exposed Chinese hamster lung fibroblasts (V79) to EOM material from $PM_{2.5}$ collected near a petrochemical complex in Triunfo, Brazil. In total, 23 results were reported comprising exposures to two concentrations of samples collected in two locations over several different seasons. Of those 23 results, increases over controls were noted for only three ($p < 0.05$). The remaining 20 results were negative for increases. Oh et al. (2011) also measured micronuclei and reported results consistent with comet assay results reported in the same study (see Section 10.2.2.2). That is, increases in micronuclei in the aliphatic, aromatic, and slightly polar fractions as well as the highest doses of CE compared to controls ($p < 0.01$) were observed in organic extracts from $PM_{2.5}$ collected near Seoul, Korea and this damage was prevented by the addition of ROS scavengers, as was the case for the comet assay results.

10.2.2.3.2 Epidemiologic Evidence

Recent studies have examined cytogenetic endpoints such as chromosomal aberrations and micronuclei. Study characteristics including $PM_{2.5}$ concentrations, study population, and approaches to exposure assignment are detailed in Table 10-2.

Table 10-2 Study specific details and $PM_{2.5}$ concentrations from recent studies that examined cytogenetic endpoints.

Study Years	Location Population	Endpoints	Mean Concentration µg/m^3	Exposure Assessment
†Rossner et al. (2011) (Feb−May 2007)	Prague, Czech Republic (59 city policemen)	FG/100; %AB.C; ace	Feb: 26.1 May: 28.4	Personal monitoring for 48 h in each month, ambient concentrations measured up to 90 days before personal sampling
†Rossner et al. (2013a) (Winter and Summer 2009; Winter 2010)	Prague and Ostrava, Czech Republic (Prague: 61−65, nonsmoking policemen; Ostrava: 98−149; policemen, office workers, and volunteers)	FG/100; %AB.C; ace; MN/1,000 BC	Winter 2009: Prague: 13.8 Ostrava: 40.0 Summer 2009: Prague: 13.3 Ostrava: 12.0 Winter 2010: Prague: 42.6 Ostrava: 78.9	Personal monitoring for 48 h in each month, ambient concentrations measured up to 90 days before personal sampling
†Ceretti et al. (2014) (Winter 2012 and 2013)	Brescia, Italy (RESPIRA, 181 children, 3−6 yr old)	% MN; % nuclear buds; % binucleated cells; % basal cells; % condensed chromatic cells; % karyorrhectic cells; % pyknotic cells; % karyolitic cells; % without nucleus cells	Same day[a]: 24−96 1 week: 32.8−93.1 2 weeks: 40.1−82.6 3 weeks: 41.7−70.1	Ambient concentrations obtained from Regional Agency for Environmental Protection database
†O'Callaghan-Gordo et al. (2015) (Feb 2009−2010)	Crete, Greece (136 mother-child pairs)	MN/1,000 BC	14.4[b]	2 week monitoring at 40 sites used as input to LUR model based on ESCAPE protocol as detailed in (Beelen et al., 2013); (Eeftens et al., 2012b) to maternal home address

FG/100 = genomic frequency of translocations; %AB.C = percentage of aberrant cells; ace = number of acentric fragments; MN/1,000 BC = frequency of micronuclei per 1,000 binucleated cells; % MN = percent of micronuclei; RESPIRA = Italian acronym for Rischio ESPosizione Inquinamento aRia Atmosferica study.

[a]Range of mean concentrations across days of biological sampling, same day and 1−3 weeks prior to biological sampling.

[b]Median concentration.

†Studies published since the 2009 PM ISA.

Recent studies conducted in the Czech Republic that examined the relationship between $PM_{2.5}$ exposure and cytogenetic effects did not report clear evidence of associations. Rossner et al. (2011), in a study of nonsmoking policemen working more than 8 hours outdoors per day in Prague, reported no association between $PM_{2.5}$ concentrations measured by ambient monitors in the 2-days prior to personal sampling and the genomic frequency of translocations, percentage of aberrant cells, or the number of acentric fragments. However, when examining different time windows by extending out to longer lags, there was evidence of a positive association between $PM_{2.5}$ concentrations in the 15−28 days prior to personal sampling and the number of acentric fragments (β = 0.64 [95% CI: 0.05, 1.24]). This initial study by Rossner et al. (2011) that focused on Prague was expanded upon to include participants that were defined as living in a more polluted city, Ostrava (Rossner et al., 2013a). As detailed in Section 10.2.2.2, the study populations between Prague and Ostrava differed in that individuals in Ostrava may have smoked. Similar to Rossner et al. (2013b), smoking status was not specifically adjusted for in Rossner et al. (2013a), but measures of cotinine in the blood, a proxy for tobacco smoke exposure was included as a covariate. Rossner et al. (2013a) examined the same markers of chromosomal aberration as Rossner et al. (2011), but also examined the number of micronuclei. When comparing the stable chromosomal aberrations (i.e., genomic frequency of translocations, percentage of aberrant cells, or the number of acentric fragments), the authors observed relatively similar results in both study locations in the 2-days prior to personal sampling even though the $PM_{2.5}$ concentrations were much higher in Ostrava. However, when examining longer lags of exposure (i.e., 1−14 days prior to sampling) there was evidence of a positive association between $PM_{2.5}$ concentrations and the percentage of aberrant cells in Prague (OR = 2.43 [95% CI: 1.26, 4.68], increment not specific). An examination of the frequency of micronuclei found a lower percentage in Ostrava (β = −0.032 [95% CI: −0.042, −0.022]) than Prague (β = −0.074 [95% CI: −0.114, −0.034]).

Additional studies conducted in Italy and Greece examined associations between $PM_{2.5}$ and cytogenetic endpoints with a focus on micronuclei frequency. Ceretti et al. (2014) as part of the RESPIRA study, examined cytogenetic endpoints in exfoliated buccal cells of children residing in Brescia, Italy. The study focused on air pollution concentrations during the winter months because that period of the year has higher concentrations of pollutants, including $PM_{2.5}$. The authors reported no evidence of a positive association between $PM_{2.5}$ concentrations assessed on the same day or during the 1, 2, or 3 weeks prior to biological sample collection and micronuclei frequency. However, there was some evidence of increases in the frequency of nuclear buds, binucleated cells, basal cells, and condensed chromatin cells with $PM_{2.5}$ concentrations in the 1 week prior to biological sample collection. O'Callaghan-Gordo et al. (2015) took a different approach to examining micronuclei frequency in children by focusing on whether a higher micronuclei frequency in pregnant women attributed to air pollution exposure led to higher micronuclei frequencies in children at the time of birth. As part of the Rhea mother-child cohort, O'Callaghan-Gordo et al. (2015) reported positive associations between $PM_{2.5}$ concentrations over the entire pregnancy and micronuclei frequency in maternal (RR = 1.5 [95% CI: 1.0, 2.3]), but not cord, blood (RR = 0.97 [95% CI: 0.63, 1.50]). However, when stratifying by smoking status, an association larger in magnitude was observed in smoking mothers (RR = 1.7 [95% CI: 0.95, 3.1]) compared to nonsmokers (RR = 1.4 [95%

CI: 0.80, 2.5]), but 95% confidence intervals crossed the null for both. Additionally, the association between $PM_{2.5}$ and micronuclei frequency was found to be increased among women with a lower intake of vitamin C during pregnancy (i.e., <85 ng/day).

10.2.2.3.3 Summary

In summary, there is some support for a relationship between exposure to $PM_{2.5}$ and cytogenetic effects. Toxicological studies demonstrate chromosomal abnormalities and micronuclei formation after exposure to $PM_{2.5}$ in in vitro systems and suggest that production of ROS may contribute to the damage (Oh et al., 2011). Epidemiologic studies provide weaker evidence of cytogenetic effects in association with exposure to $PM_{2.5}$; however, there is initial evidence that micronuclei frequency may be correlated with the intake of an antioxidant nutrient (O'Callaghan-Gordo et al., 2015).

10.2.2.4 Other Markers

10.2.2.4.1 Toxicological Evidence

Studies have also evaluated several other molecular and cellular endpoints that are relevant to carcinogenesis. Many of these studies describe events important to the DNA damage response and gene expression that may be relevant to cancer initiation and progression. Expression of genes that participate in PAH biotransformation have been commonly measured in new studies and include AhR, AhRR, ARNT, Cyp1A1 and Cyp1B1 (Yoshizaki et al., 2016; Borgie et al., 2015b; Gualtieri et al., 2011; Oh et al., 2011). Biotransformation may result in the production of PAH metabolites capable of reacting with DNA to form DNA adducts. When DNA repair is absent or ineffective, the formation of DNA adducts may be processed by the cell to mutations.

Borgie et al. (2015b) compared the effects of exposure to intact ambient $PM_{2.5}$ with aerodynamic diameters between 0.3 and 2.5 μm (described as $PM_{2.5–0.3}$) collected from an urban site in Beirut, Lebanon to that collected from a rural site in Byblos, Lebanon which is located 35 km from Beirut. The authors measured AhR, ARNT, AhRR, CYP1A1, and CYP1B1 gene expression in cultured BEAS-2B cells. A general pattern was observed for measurements of CYP1A1 and AhRR expression. That is, after exposure to $PM_{2.5}$ collected from the urban location, increases in expression were observed compared to controls after exposure to both low and high concentrations (3 and 12 $\mu g/cm^2$). In contrast, $PM_{2.5}$ collected from the rural location resulted in an increase compared to control for the high concentration exposure (12 $\mu g/cm^2$) only ($p < 0.05$), indicating that the $PM_{2.5}$ collected from the urban location may possess greater potency than that collected from the rural location. Some increases were also observed for CYP1B1 expression, whereas results were generally negative for AhR and ARNT expression. The finding of increased CYP1A1 expression was confirmed by Oh et al. (2011), discussed above. They estimated

CYP1A1 activity using the ethoxyresorufin-O-deethylase (EROD) assay and reported an increase compared with controls in the total extract as well as the aromatic fraction ($p < 0.01$). Gualtieri et al. (2011) also measured gene expression. They too noted an increase in Cyp1A1 ($p < 0.0001$), Cyp1B1 (p-value not provided) and AhRR (p-value not provided) expression, similar to both Borgie et al. (2015b) and Oh et al. (2011). AhR (p-value not provided) and ARNT (p-value not provided) expression decreased after exposure of BEAS-2B cells to $PM_{2.5}$. Dumax-Vorzet et al. (2015) also measured Cyp1A1 expression; however, the authors did not observe evidence of an increase in Cyp1A1 mRNA after exposure to DEP particle suspension. Because the authors did observe an increase in ROS in the same study, they concluded that Cyp1A1 activity was not the source of the increased ROS.

mRNA expression of some of the same genes detailed in the previous paragraph were measured in an animal study by Yoshizaki et al. (2016). In this study, mRNA from nasal epithelium was quantified for AhR, Cyp1A1, Cyp1A2, Cyp1B1, Erβ-1, and Erβ-2 in male and female BALB/c mice exposed to $PM_{2.5}$ CAPs in São Paulo, Brazil. After exposure, only two changes were reported. Cyp1B1 mRNA expression was increased in exposed female ($p = 0.01$), but not male mice compared with animals exposed to ambient air, and Erβ-2 mRNA expression was decreased in exposed female ($p = 0.007$), but not male mice compared with animals exposed to ambient air. There was not an increase in mRNA for the other four genes evaluated in male or female mice. The authors also measured AhR- and Erβ-positive nuclei in nasal epithelium cells. They observed an increase in the percent of AhR-positive nuclei in $PM_{2.5}$-exposed female ($p = 0.044$) but not male mice compared with controls, and a decrease in the percent of Erβ-positive nuclei in female, but not male mice compared with mice exposed to ambient air.

In addition, one study evaluated the effect of $PM_{2.5}$ exposure on telomerase. Telomerase is a protein that adds telomere repeat sequences to the ends of chromosomes. This is one way in which cells avoid senescence and arrested cell division. Telomerase can play a role in cancer development by conferring cellular immortality. Borgie et al. (2015b) reported increased telomerase activity in cultured BEAS-2B cells exposed to $PM_{2.5}$.

10.2.2.4.2 Evidence from Controlled Human Exposure Studies

Hemmingsen et al. (2015) reported negative findings for mRNA expression of CCL2, IL8, TNF, HMOX1, and OGG1 in a controlled, cross-over, repeated measures human exposure study carried out in central Copenhagen, Denmark. In this study, overweight, older adults were exposed in chambers with and without high efficiency particulate adsorption filters. Peripheral blood mononuclear cells collected immediately before and after the exposure were negative for change from controls for several endpoints evaluated.

10.2.2.4.3 Epidemiologic Evidence

In addition to examining specific changes in the genome that could lead to cancer, an additional study focused on whether $PM_{2.5}$ exposure resulted in differential expression of genes related to a specific health outcome, such as cancer (Chu et al., 2016). Within the TrIPS study, a panel of 63 nonsmoking white men were selected to examine the relationship between gene expression and long-term traffic-related pollution exposure (i.e., $PM_{2.5}$, EC, and OC). Long-term $PM_{2.5}$ exposure was defined as the exposure during the first and last work shift within a week. To focus the analysis on a collection of genes that may influence a health outcome, the authors applied Gene Set Enrichment Analysis (GSEA) to examine gene specific networks. The GSEA analysis identified 44 genes that were previously related to various cellular and biological processes. Chu et al. (2016) then used GeneMANIA network analysis to examine the inter-relationship among this core set of 44 genes. The authors found evidence that long-term exposure to traffic-related pollutants, including $PM_{2.5}$, increased the expression of five genes (ACP1, HSP90AA1, LEF1, MLH1, and RBM5) that are common in cancer pathogenesis.

10.2.2.4.4 Summary

Studies in cultured cells in vitro and in an animal model have demonstrated the upregulation of genes involved in PAH biotransformation following exposure to suspended $PM_{2.5}$ or $PM_{2.5}$ extracts. These results indicate that $PM_{2.5}$ contains electrophilic species, one of the identified characteristics of a carcinogen (Smith et al., 2016). $PM_{2.5}$ exposure also increased telomerase activity in vitro. This result indicates that $PM_{2.5}$ may promote cellular immortalization, another of the characteristics of a carcinogen. Epidemiologic studies link exposure to $PM_{2.5}$ with the upregulation of several genes that may be involved in cancer pathogenesis.

10.2.2.5 Summary of Genotoxicity

Studies published since the completion of the 2009 PM ISA (U.S. EPA, 2009) provide a broader evaluation of the relationship between $PM_{2.5}$ exposure and mutagenicity, DNA damage, cytogenetic effects, and other markers of genotoxicity. The importance of *Salmonella* assay results is that positive results demonstrate the presence of species capable of inducing mutations. It can identify the presence of species that can result in mutations as the result of direct interactions with DNA as well as those that require metabolic activation. Because the most widely accepted theory of cancer etiology is the accumulation of mutations in critical genes, the presence of mutagens within $PM_{2.5}$ and the mutagenicity of organic extracts of $PM_{2.5}$ provide biological plausibility for observations made in epidemiologic studies. Further, results can suggest the presence of certain species such as nitro-polycyclic aromatic compounds (nitro-PAHs). The *Salmonella* assay, however, does not capture the complex biological in vivo activity of human cells, tissues, and other processes or systems of increasing biological

organization. Therefore, although exposure to mutagens present in $PM_{2.5}$ clearly could result in the introduction of mutations that could lead to initiated cells in vivo, strictly interpreted, the results from *Salmonella* only provide evidence for the presence of species capable of inducing mutagenesis. Thus, it is also necessary to consider results from in vitro assays that use mammalian cell lines and in vivo animal studies to completely characterize the effects of PM exposure in humans.

Toxicological studies conducted in mammalian cell lines demonstrated damage to DNA bases, DNA strand breaks, oxidative stress, micronuclei formation, and chromosomal aberrations in response to $PM_{2.5}$ exposure. Upregulation of enzymes involved in antioxidant defense or biotransformation was also found. Dampening oxidative stress using inhibitors decreased DNA damage and micronuclei formation, supporting a role for oxidative stress in mediating genotoxicity (Oh et al., 2011). Although limited in number, some in vivo studies also examined DNA damage following $PM_{2.5}$ exposure. One study, using $PM_{2.5}$ CAPs collected in Chicago, found evidence of oxidative DNA damage in lung tissue (Soberanes et al., 2012). Controlled human exposure studies, including a study using $PM_{2.5}$ CAPs, also demonstrated oxidative DNA damage. A limitation of the collective body of in vitro evidence is that $PM_{2.5}$ was mainly collected overseas in locations with high pollution levels. A limitation of the in vivo evidence is that there are only a few studies. However, one of these found both evidence of oxidative DNA damage and methylation of the promotor region of a tumor suppressor gene in the lung (see also Section 10.2.3.1).

Epidemiologic studies examined a variety of biomarkers and collectively did not provide clear evidence of a relationship between any specific marker and $PM_{2.5}$ exposure. Although there was some evidence indicating a larger percentage of B[a]P-like DNA adducts in people exposed to higher $PM_{2.5}$ concentrations (Li et al., 2014; Rossner et al., 2013b), clear associations between $PM_{2.5}$ and various cytogenetic parameters were not observed in recent studies in the Czech Republic (Rossner et al., 2013b; Rossner et al., 2011). Only one study examined the association between $PM_{2.5}$ and micronuclei frequency in maternal blood and reported evidence of increased micronuclei frequency, specifically in women with low intake of vitamin C during pregnancy (O'Callaghan-Gordo et al., 2015). Those studies that examined DNA damage, by focusing on tail DNA, reported weak positive associations between personal $PM_{2.5}$ concentrations and percentage of tail DNA (Chu et al., 2015; Ma et al., 2015). Additionally, there is preliminary evidence that long-term $PM_{2.5}$ exposure may result in the differential expression of genes linked with cancer pathogenesis.

10.2.3 Epigenetic Effects

Epigenetic mechanisms regulate the transcription of genes without altering the nucleotide sequence of DNA. These mechanisms generally involve DNA methylation, histone modifications, chromatin remodeling, and changes in noncoding mRNA and nuclear organization and lead to alterations that may have long-term consequences or are heritable (Keverne and Curley, 2008; Jones and Baylin, 2007). DNA methylation and histone modifications, which include methylation, acetylation,

phosphorylation, ubiquitylation, and sumoylation, are known to be linked (Hitchler and Domann, 2007; Jones and Baylin, 2007). Numerous studies have identified epigenetic processes in the control of cancer (Foley et al., 2009; Gopalakrishnan et al., 2008; Jones and Baylin, 2007; Valinluck et al., 2004), embryonic development (Foley et al., 2009; Gopalakrishnan et al., 2008; Keverne and Curley, 2008), and inflammation and other immune system functions (Adcock et al., 2007).

Epigenetic modifications resulting in decreased expression of tumor suppressor genes and increased expression of transforming genes have been observed in human tumors (Valinluck et al., 2004). In general, transcription repression is associated with DNA methylation in promoter regions of genes. Cytosine methylation in CpG dinucleotides has emerged as an important, heritable epigenetic modification that can result in chromatin remodeling and decreased gene expression. Global changes in DNA methylation are also seen in cancer and hypomethylation is associated with genomic instability (Gopalakrishnan et al., 2008).

Growing evidence demonstrates the epigenetic effects of PM exposure, which is associated primarily with alterations in DNA methylation. In the 2009 PM ISA, there were a small number of epidemiologic studies that examined epigenetic effects, specifically methylation. DNA methylation is an epigenetic mechanism that regulates the proper expression of genetic information in a tissue-, cell-, and sex-dependent manner and controls the expression of tumor promotor and suppressor genes and of repetitive elements. Repetitive elements comprise up to ⅔ of mammalian genomes and are heavily methylated to prevent their aberrant transcription. Thus, repetitive element methylation levels have been used as surrogate biomarkers of global DNA methylation, which is linked to genomic instability and thus may contribute to the accumulation of mutations. A large subset of studies has evaluated the effect of PM exposure on this marker. In particular, research has focused on retrotransposons LINE-1 and Alu (SINE in mouse) and satellite DNA. Studies evaluated in the 2009 PM ISA found inconsistent evidence of an association between PM exposure and methylation of Alu and long interspersed nuclear element-1 (LINE-1) sequences, two sequences linked previously with global genomic DNA methylation. Recent epidemiologic studies further evaluated DNA methylation, and provide evidence for both hyper- and hypomethylation in response to $PM_{2.5}$ exposure. Both DNA hyper- and hypomethylation have been observed in malignant cells. Recent animal toxicological studies investigated epigenetic effects resulting from $PM_{2.5}$ exposure and provide evidence for methylation of a tumor promotor gene and alteration in noncoding mRNA.

10.2.3.1 Methylation of Tumor Suppressor Genes

Evidence that exposure to $PM_{2.5}$ results in the methylation of tumor promoter genes is provided by animal toxicological studies. Soberanes et al. (2012) measured molecular markers that have been associated with an increased risk of cancer in a high-risk smoking cohort. Using male C57BL/6 mice, the authors reported increased promotor methylation of p16 (CDNK2A), a tumor suppressor, and of matrix

metalloproteinase-2 (MMP-2) compared to controls ($p < .001$) in whole lung genomic DNA following inhalational exposure to $PM_{2.5}$ CAPs in Chicago, IL. The authors also reported an increase in DNA methyltransferase 1 (DNMT1) mRNA and protein ($p < 0.01$), but not DNMT3a or DNMT3b expression. Finally, they also noted an increase in 8-oxoG positive nuclei in lung tissue ($p < 0.01$), supporting the presence of ROS following $PM_{2.5}$ exposure. Alveolar epithelial cells exposed to the same $PM_{2.5}$ CAPs exhibited increased DNMT1 transcription and methylation of the p16 promotor; these effects were inhibited by treatment with an antioxidant targeted to mitochondria and by an inhibitor of JNK.

Another study using Wistar rats measured changes in p16CDNK2A (CDNK2A) and APC promoter methylation following $PM_{2.5}$ exposures of 4 hours to 28 days (Ding et al., 2016). Animals were exposed to ambient air at three sites in Zhejiang, China. Exposed rats were housed in cages roadside of a traffic tunnel and busy intersection; control rats were housed in cages at a university greenspace 0.5 mile from the nearest road. Although the authors made separate measurements for spring and autumn seasons, the DNA methylation was not different between the seasons, so seasonal data were analyzed together. The authors reported β-values and 95% confidence intervals for methylation of p16CDNK2A and APC promoters in peripheral blood and lung tissue after exposures of 4 hours and 7 days. The authors did not observe an association between $PM_{2.5}$ mass over exposures of these durations and p16CDNK2A promoter methylation in blood or lung tissue. An association was calculated for APC promoter methylation for only the 7-day exposure in lung tissue (0.009 [0.001, 0.019], $p = 0.046$). The study also reported associations after 14−28 days of exposure and note a positive exposure between $PM_{2.5}$ mass and p16CDNK2A promoter methylation in blood (0.037 [0.017, 0.057], $p = 0.001$) and lung tissue (0.011 [0.003, 0.019], $p = 0.011$), as well as APC promoter methylation in lung tissue (0.008 [0.002, 0.015], $p = 0.046$). The authors noted that methylation changes generally returned to levels comparable to controls after the longer 28-day exposures. The appreciable difference in environment between the exposure sites and plausible introduction of other stressors into the environment of the experimental animals elevates the uncertainty in the reported results.

10.2.3.2 Methylation of Repetitive Line Elements

10.2.3.2.1 Toxicological Evidence

In the experimental animal study discussed above using Wistar rats, Ding et al. (2016) also characterized global epigenetic changes represented by LINE-1 and Alu methylation after exposure to $PM_{2.5}$. Animals were exposed to low, medium, and high levels of traffic-related air pollution in Zhejiang, China. The authors reported β-values and 95% confidence intervals for methylation of LINE-1 in peripheral blood and lung tissue. They observed associations with 4-hour $PM_{2.5}$ exposure and decreased LINE-1 methylation in blood (−0.027 [−0.041, −0.013], $p = 0.003$) and lung (−0.041 [−0.049, −0.032], $p < 0.001$) tissues as well as with exposure for 7 days (blood: −0.064 [−0.104, −0.023], $p = 0.003$; lung:

−0.033 [−0.058, −0.008], $p = 0.012$). After 14 and 28 days, decreased LINE−1 methylation was associated with $PM_{2.5}$ exposure in the lung (−0.015 [−0.028, −0.002], $p = 0.024$). No associations were observed with Alu methylation. The authors do note that methylation changes generally returned to levels comparable to controls after the longer 28-day exposures.

Montrose et al. (2015) also investigated global DNA methylation in peripheral blood in a study of sled dogs residing in kennels in and near Fairbanks, AK. During Alaskan winters, severe temperature inversions result in elevated $PM_{2.5}$ concentrations in Fairbanks. Sled dogs housed at three kennels were recruited to participate. Average $PM_{2.5}$ mass was 90 μg/m^3 at Kennel A, 48 μg/m^3 at Kennel B, and 16 μg/m^3 at Kennel C. The authors did not identify any differences in the levels of global DNA methylation or percentage of methylated cytosine bases between the dogs from three kennels, and thus did not find an association between $PM_{2.5}$ mass and global DNA methylation.

Epigenetic effects following PM exposure have also been investigated using in vitro methods. Miousse et al. (2015) measured epigenetic changes at repetitive sequences and changes in methyltransferase gene expression in cultured murine macrophages (RAW264.7) after exposure to aqueous extracts of PM (number median aerodynamic diameter of 0.42 μm) collected from the lowest level of a multilevel underground parking deck at the University of Arkansas in Little Rock. Measurements of DNMT1 and DNMT3b mRNA transcripts following PM extract (50 μg/mL) exposure revealed a decrease after 24 hours compared to control ($p < 0.05$ and $p < 0.001$, respectively). No change was observed in the amount of DNMT3a mRNA measured at 24 hours, however, an increase was noted at 72 hours ($p < 0.001$). When the authors measured methyltransferase enzymatic activity, however, no change was observed after exposure to PM extracts. Several repetitive elements were studied to identify their methylation status and expression level after PM extract exposure. Weak hypomethylation of SINE B1/B2 was observed at the 24-hour time point control ($p < 0.01$ and $p < 0.05$, respectively). After 72 hours, methylation levels of SINE B1 returned to levels similar to that of the control; however, SINE B2 remained weakly hypomethylated ($p < 0.05$). Analysis of SINE B1/B2 expression did not reveal any differences between exposed and control cells at either time point. No change in methylation or expression of the other transposable element evaluated, L1, was observed.

In the same report, Miousse et al. (2015) also measured the change in methylation of major and minor satellites after 24 and 72 hours of exposure to aqueous extracts of PM. Only one change from the controls was observed. After 72 hours of exposure to 50 μg/mL PM extract, hypomethylation of the major satellites was reported. The authors again also measured the corresponding mRNA levels. No change in expression of either the major or minor satellites at either time point was observed.

10.2.3.2.2 Epidemiologic Evidence

Recent epidemiologic studies have expanded upon the examination of the relationship between $PM_{2.5}$ exposure and DNA methylation. These studies encompass both the examination of the methylation

of specific parts of the genome that may play an important role in carcinogenesis as well as an overall assessment of DNA methylation. Study characteristics, including $PM_{2.5}$ concentrations, study population, and approach to assigning $PM_{2.5}$ exposure, are detailed in Table 10-3.

Table 10-3 Study specific details and $PM_{2.5}$ concentrations from recent studies that examined DNA methylation.

Study Years	Location Population	Endpoints	Mean Concentration µg/m^3	Exposure assessment
†De Prins et al. (2013) (2010)	Flanders, Belgium (48 nonsmoking adults)	%5mdC	All-year: 17.1 Winter: 26.9 Summer: 15.2	Ambient concentration interpolated to 4 km grid cell by RIO as detailed in Janssen et al. (2008) and assigned to residential address
†Madrigano et al. (2011) (1999−2007)	Boston, MA (706 men, NAS)	%5mC of LINE-1 and Alu	28-day: 10.3 45-day: 10.3 60-day: 10.3 90-day: 10.4 180-day: 10.5	Ambient concentrations from one monitor
†Panni et al. (2016) (KORA F3: 2004−2005; KORA F4: 2006−2008; NAS: 1999−2007)	Germany (KORA F3: 500; KORA F4: 1,799; NAS: 657 white men)	% methylation for every CpG site	KORA F3: 20.0 KORA F4: 14.2 NAS: 10.6	Ambient concentrations from one monitor for each cohort
†Guo et al. (2014) (Jun−July 2008)	Beijing, China (Beijing Truck Driver Air Pollution Study, 60 truck drivers, 60 office workers)	%5mC of SATα, NBL2, and D4Z4	Truck drivers: 126.8 Office workers: 94.6	Average personal $PM_{2.5}$ on examination days using gravimetric samplers during 8 h of work
†Sanchez-Guerra et al. (2015) (Jun−July 2008)	Beijing, China (Beijing Truck Driver Air Pollution Study, 60 truck drivers, 60 office workers)	%5mC; %5hmC	Truck drivers: 126.8 Office workers: 94.6	Average personal $PM_{2.5}$ on examination days using gravimetric samplers during 8 h of work

Table 10-3 (Continued): Study specific details and $PM_{2.5}$ concentrations from recent studies that examined DNA methylation.

Study Years	Location Population	Endpoints	Mean Concentration µg/m^3	Exposure assessment
†Janssen et al. (2013) (2009−2012)	Limburg Province, Belgium (ENVIRONAGE; 240 mother-child pairs)	%5mdC	1−5 days: 16.9 6−12 days: 16.9 6−21 days: 16.7 22−28 days: 17.3 1st trimester: 16.7 2nd trimester: 17.4 3rd trimester: 18.2 Entire pregnancy: 17.4	Combination of kriging using land cover data from satellites and monitoring data at 4 km grid cells to estimate $PM_{2.5}$ at residential address as detailed in Janssen et al. (2008); temporal $R^2 > 0.80$, spatial $R^2 > 0.80$

%5mdC = percent 5-methyl-2'-deoxycytidine; %5mC = percentage of sum of methylated and unmethylated cytosine; %5hMC = percentage change in 5-hydroxymethylcytosine; Alu = short interspersed nucleotide element Alu; CpG = cytosine-guanine dinucleotide; ENVIRONAGE = environmental influence on early ageing; LINE-1 = long interspersed nucleotide element-1; NAS = Normative Aging Study.

†Studies published since the 2009 PM ISA.

Those studies that examined overall global methylation provide an assessment as to whether exposure to $PM_{2.5}$ can result in either hyper- or hypomethylation of DNA. De Prins et al. (2013) in a study conducted in Flanders, Belgium examined global DNA methylation (percentage 5-methyl-2′-deoxycytidine, %5 mdC) in 48 nonsmoking adults. The authors examined methylation at two-time periods, once in the summer and once in the winter, and whether any changes in methylation were associated with cumulative $PM_{2.5}$ exposures that were either short or long in duration (i.e., <1 week or up to a few months). In analyses combining the two sampling periods, De Prins et al. (2013) reported evidence indicating a reduction in overall DNA methylation across the lags examined with the magnitude of the reduction increasing over time, with the most pronounced reductions occurring at a 30-day lag (−0.14 [95% CI: −0.28, 0.00] for an IQR increase in $PM_{2.5}$ concentrations of 14.2 µg/m^3) and 60-day lag (−0.18 [95% CI: −0.37, 0.01] for an IQR increase in $PM_{2.5}$ concentrations of 11.4 µg/m^3). In seasonal analyses, there was also evidence of a reduction in methylation, but mostly in the summer and at shorter lags (i.e., 2-day and 3-day). In a subsequent genome-wide meta-analysis of DNA methylation in the Normative Aging Study (NAS) as well as the German KORA F3 and F4 studies, associations between $PM_{2.5}$ (trailing 2-day average), $PM_{2.5}$ (trailing 7-day average), and $PM_{2.5}$ (trailing 28-day average) was found to result in 1, 1, and 10 CpG sites that had changes in methylation, respectively (Panni et al., 2016). At the 10 CpG sites identified using 28-day average $PM_{2.5}$ exposure, 7 sites had higher methylation and 3 lower methylation. In a sensitivity analysis, the authors reported associations with $PM_{2.5}$ (trailing 28-day average) that were generally similar after adjustment for annual average $PM_{2.5}$ (trailing 1-year average). Although De Prins et al. (2013) and Panni et al. (2016) examined global DNA methylation across the entire genome, Madrigano et al. (2011) examined global methylation by focusing on specific portions of the genome, i.e., the LINE-1 and Alu repetitive elements. Within the NAS cohort, the authors examined multiple exposure time windows, 28, 45, 60, 90, and 180 days prior to biological sampling. For analyses

focusing on $PM_{2.5}$ exposure, Madrigano et al. (2011) reported some evidence of a small decrease in methylation at 45- and 60-days for only LINE-1, but 95% confidence intervals were large.

Additional studies that examined DNA methylation at specific sites of the genome relied on an assessment of $PM_{2.5}$ exposure using personal monitors. Guo et al. (2014) examined associations between personal $PM_{2.5}$ concentrations and blood DNA methylation (percentage 5 methylcytosine, %5 mC) of the tandem repeats SATα, NBL2, and D4Z4 in 60 office workers and 60 truck drivers within the Beijing Truck Driver Air Pollution Study. Biological samples from participants were provided twice, 1−2 weeks apart. The authors reported an inverse association between $PM_{2.5}$ concentrations and SATα methylation ($\beta = -1.35$, SE = 0.54) in office workers and truck drivers combined, with the association stronger in truck drivers ($\beta = -2.34$, SE = 0.94). There was also evidence of an inverse association between $PM_{2.5}$ concentrations and NBL2 methylation, but only in truck drivers ($\beta = -0.88$, SE = 0.84). These results indicate that higher exposures to $PM_{2.5}$ may result in the differential methylation of some parts of the genome. Sanchez-Guerra et al. (2015) also examined the Beijing Truck Driver Air Pollution Study cohort to examine methylation of both 5mC and 5-hydroxymethylcytosine (5hmC). Most DNA methylation studies focus on 5mC because it is often considered a marker of suppressed gene expression; however, 5mC is oxidized to 5hmC which is a potential marker of gene expression (Sanchez-Guerra et al., 2015). The authors examined whether PM exposure increases the oxidation of 5mC to 5hmC and subsequently increases blood levels of 5hmC. Using the same personal $PM_{2.5}$ measurements as the Beijing Truck Driver Air Pollution studies described previously, the authors did not report any evidence of an increase in 5hmC in response to $PM_{2.5}$ exposure.

Although the previous studies evaluated focused on DNA methylation in adults, a study conducted in Belgium examined the relationship between maternal $PM_{2.5}$ exposure and placental DNA methylation. Janssen et al. (2013) within the ENVIRONAGE cohort, examined the association between global DNA methylation and $PM_{2.5}$ exposure during each trimester of gestation and the entire pregnancy. The authors reported evidence of an overall reduction in placental DNA methylation by 2.2% (95% CI: −3.7, −0.73) when examining $PM_{2.5}$ exposures over the entire pregnancy. Analyses of individual trimesters as well as a model that simultaneously included each trimester provide evidence of the greatest reduction in methylation occurring in the 1st trimester, −2.4 and −2.1%, respectively.

10.2.3.3 Noncoding mRNAs

In addition to DNA methylation, interest in how environmental exposures affect miRNA expression has also increased since the 2009 PM ISA. miRNAs are small, evolutionary conserved, noncoding RNAs involved in the regulation of gene expression. Recently, animal toxicological studies have reported that exposure to various environmental stressors, including PM, can lead to alterations in miRNA expression and subsequent alterations in the expression of genetic information.

Borgie et al. (2015b) compared the effects of exposure to intact ambient $PM_{2.5}$ with aerodynamic diameters between 0.3 and 2.5 μm (described as $PM_{2.5–0.3}$) collected from an urban site in Beirut, Lebanon to that collected from a rural site in Byblos, Lebanon, which is located 35 km from Beirut. The authors measured miR-21, miR-26b, and miR-27a expression in cultured BEAS-2B cells. After exposure to PM collected from the urban location, miR-21 expression was increased compared to controls after exposure to both low and high concentrations (3 and 12 $\mu g/cm^2$). In contrast, PM collected from the rural location resulted in an increase compared to control for the high concentration exposure (12 $\mu g/cm^2$) only ($p < 0.05$), indicating that the $PM_{2.5}$ collected from the urban location may possess greater potency than that collected from the rural location.

10.2.3.4 Summary of Epigenetic Effects

Studies published since the completion of the 2009 PM ISA provide a broader evaluation of the relationship between $PM_{2.5}$ exposure and epigenetic effects. An animal toxicological study involving inhalation of $PM_{2.5}$ CAPs (Chicago) found methylation of the tumor suppressor gene p16 and upregulation of methylation enzymes in lung tissue (Soberanes et al., 2012). An in vitro experiment found similar results in the same study, as well as evidence for oxidative stress contributing to the effects. Other evidence from animal toxicological studies includes methylation of p16 and the repetitive line element LINE-1 in blood and lung tissue in association with $PM_{2.5}$ concentrations in a field study conducted in China (Ding et al., 2016) and upregulation of noncoding mRNA in an in vitro study involving $PM_{2.5}$ collected in Lebanon (Borgie et al., 2015b).

Recent epidemiologic studies of ambient and personal $PM_{2.5}$ concentrations generally reported some evidence of a change in DNA methylation. In studies examining both global methylation as well as methylation of specific genomic sites (i.e., CpG sites, LINE-1, Alu, SATα, and NBL2), there was evidence indicating hypomethylation in response to $PM_{2.5}$ exposure (Panni et al., 2016); Guo et al. (2014); (De Prins et al., 2013; Madrigano et al., 2011). However, there was also evidence of hypermethylation in some instances (Panni et al., 2016). A recent study in a cohort of mother-child pairs in Belgium also noted associations with $PM_{2.5}$ concentrations and changes in global DNA methylation (Janssen et al., 2013). Collectively, studies of $PM_{2.5}$ exposure and DNA methylation provide some evidence of epigenetic effects, but the broad number of biomarkers and measures of DNA methylation examined complicate the overall interpretation of results across studies.

10.2.4 Carcinogenic Potential

In the 2009 PM ISA (U.S. EPA, 2009), there were a small number of in vivo toxicological studies that examined carcinogenic potential. No evidence of increased tumor formation was found after chronic inhalation of diesel exhaust (Reed et al., 2004) or hardwood smoke (Reed et al., 2006) in a cancer-prone

mouse model. However, urban air in Brazil enhanced the formation of tumors in mice that were pretreated with urethane to initiate tumor formation (i.e., a model of tumor promotion) (Cury et al., 2000; Reymao et al., 1997). Because these in vivo studies evaluated effects of exposure to mixtures of PM and gases, they do not directly inform the current ISA, which identifies the hazard for effects after exposures to only the PM component of complex mixtures. Studies published since the 2009 PM ISA include an in vivo study of tumor promotion and an in vitro study of cell invasion, which is an indicator of metastasis.

Cangerana Pereira et al. (2011) exposed female Swiss mice to ambient $PM_{2.5}$ in downtown São Paulo, Brazil, 20 m from the roadside. Some animals were pretreated with the tumor initiator urethane, while others received saline. Exposed animals were housed in exposure chambers fitted with a filter designed to trap large particles but not $PM_{2.5}$. Control group animals were housed in exposure chambers fitted with a series of three filters designed to trap all ambient particles. After 60 days of exposure to 4.54 $\mu g/m^3$ and 17.66 $\mu g/m^3$ $PM_{2.5}$ in the filtered and nonfiltered chambers respectively, the authors counted the number of urethane-induced nodules (classified as adenomas) present at the pleural surface. The number of nodules observed in urethane-pretreated mice exposed to $PM_{2.5}$ was 4.0 ± 3.0; the number of nodules observed in the urethane-pretreated control group was 2.0 ± 2.0 ($p = 0.02$). Of animals treated with saline rather than urethane, neither those exposed to $PM_{2.5}$ nor those exposed to filtered air developed tumors. The results of this study, together with previously published observations that investigated the effect of air pollution on urethane-exposed mice (Cury et al., 2000; Reymao et al., 1997), demonstrate that ambient PM may have a promoting effect in lung carcinogenesis. The mechanism by which exposure to $PM_{2.5}$ enhanced tumorigenesis in this study was not explored; however, activation of inflammatory pathways, suppression of DNA repair, and an enhancement of DNA replication errors are all possibilities.

Yue et al. (2015) collected $PM_{2.5}$ over spring, summer, autumn, and winter from a peri-urban residential area of Taiyuan, China. Using A549 cells and $PM_{2.5}$ suspensions in a cell invasion assay, the authors report that cell invasion was greatest after exposure to $PM_{2.5}$ collected in the winter (p values not provided). The concentrations of 18 PM-bound PAHs were also measured. The authors reported that the amounts of PAHs measured for each season roughly corresponded to the extent to which cell invasion was observed for the same season, i.e., the amount of PM-bound PAH was greatest for that collected in the winter season, and the number of invading cells was greatest after exposure to PM collected during the winter season as well. When the authors repeated the experiment with a range of winter $PM_{2.5}$ suspension concentrations, the increase in invasive cells compared to controls was observed at the greatest doses only (3 µg/mL: $p < 0.05$; 10 µg/mL: $p < 0.01$). The authors also measured changes in mRNA of proteins important to the suppression and promotion of cell migration and invasion and noted a decrease in E-cad and TIMP-2 and an increase in Fib and MMP-2. Lastly, the authors also demonstrated the generation of ROS after exposure to the winter $PM_{2.5}$ with the DCFH-DA assay and demonstrated attenuation of cell migration in the presence of the antioxidant N-acetyl-L-cysteine, providing support for the contribution of ROS to additional events relevant to carcinogenesis.

In summary, although neither of the toxicological studies involving $PM_{2.5}$ exposure provides direct evidence of carcinogenesis, both demonstrated increased carcinogenic potential. Chronic inhalation of $PM_{2.5}$ CAPs collected in Brazil resulted in tumor promotion in an animal model. Furthermore, exposure to $PM_{2.5}$ in vitro increased cell invasion, a measure of metastatic potential, which correlated with PAH content. This effect was blocked by treatment with an antioxidant, suggesting a role for oxidative stress in mediating cell invasion. Epidemiologic studies provide initial evidence that exposure to long-term $PM_{2.5}$ concentrations may contribute to reduced cancer survival (see Section 10.2.5.3). This could involve an enhancement of tumor progression or metastasis/tissue invasion or some other mechanism.

10.2.5 Cancer Incidence, Mortality, and Survival

At the completion of the 2009 PM ISA, epidemiologic studies that examined the association between long-term $PM_{2.5}$ exposure and cancer primarily focused on lung cancer mortality, with a more limited number of studies examining lung cancer incidence and other types of cancers. Although these studies tended to support a relationship between long-term $PM_{2.5}$ exposure and lung cancer mortality, the overall body of evidence was rather small and mostly limited to analyses and reanalyses of a few cohorts (i.e., American Cancer Society [ACS], Harvard Six Cities [HSC], Netherlands Cohort Study on Diet and Cancer [NLCS-Air], and Adventist Health and Smog Study [AHSMOG]). Since then, several new cohort studies and meta-analyses, as well as extensions and reanalyses of older cohorts, have examined $PM_{2.5}$ and both lung cancer incidence and mortality along with the potential relationship between long-term $PM_{2.5}$ exposure and cancers in other organs. Additionally, epidemiologic studies have examined the potential impact of $PM_{2.5}$ exposure on the survival of cancer patients. Overall, when evaluating recent epidemiologic studies, the strongest evidence demonstrating an association between long-term $PM_{2.5}$ exposure and cancer comes from studies that examine lung cancer incidence and mortality. This evidence is further supported by studies that examined associations in never smokers.

10.2.5.1 Lung Cancer

Epidemiologic studies that examine the relationship between long-term $PM_{2.5}$ exposure and lung cancer often focus on lung cancer mortality, which could be a reflection of the high case-fatality rate of lung cancer, resulting in measures of lung cancer mortality and incidence being comparable (Hamra et al., 2014). Recent studies of $PM_{2.5}$ and lung cancer have expanded upon the body of evidence for both lung cancer mortality and incidence. The following section focuses on those recent studies that adequately examine the relationship between long-term $PM_{2.5}$ exposure and lung cancer mortality and incidence using either modeled or monitored $PM_{2.5}$ concentrations. Many of the studies that examine lung cancer mortality are also evaluated in the long-term $PM_{2.5}$ exposure and mortality section (see Section 11.1.2). As a result, the focus of this section is specifically on issues inherent to the evaluation of the relationship between long-term $PM_{2.5}$ exposure and lung cancer mortality or incidence. Other studies with identified

limitations including, but not limited to, ecological study design, estimation of $PM_{2.5}$ concentrations for entire study duration from concentrations of other pollutants using conversion factors, and inadequate control for potential confounders are not the focus of this section. These studies are available at: https://hero.epa.gov/hero/particulate-matter.

Study characteristics including $PM_{2.5}$ concentrations, study population including number of deaths or cases, and exposure assignment approach for the large cohort studies that focused on national or regional analyses evaluated in the 2009 PM ISA, along with recent cohort studies that examine lung cancer mortality and incidence are detailed in Table 10-4. The results from these studies are highlighted in Figure 10-3, and provide evidence of generally consistent, positive associations across different exposure assignment approaches and study locations. Within the cohorts summarized in Table 10-4 and Figure 10-3, additional analyses were conducted to further examine the associations observed in the main analysis, which comprise the focus of the following sections.

Table 10-4 Study specific details and $PM_{2.5}$ concentrations from recent studies and studies evaluated in the 2009 PM ISA that examined lung cancer mortality and incidence.

Study	Cohort Location	Years Air Quality/Follow-up	Events/ Population	Mean Concentration µg/m^3	Exposure Assessment
Lung cancer mortality					
North America					
McDonnell et al. (2000)[a]	AHSMOG (California)	$PM_{2.5}$: 1973−1977 Follow-up: 1977−1992	Deaths: 13[e] Pop: 1,228[e]	31.9	Monthly average concentration for Airshed where participant resided
Laden et al. (2006)[b,c]	HSC Extension (Six U.S. cities)	$PM_{2.5}$: 1979−1987; 1985−1998[f] Follow-up: 1974−1998	Deaths: 226 Pop: 8,096	Across sites: 10.2−29.0 Overall mean: 16.4	One centrally located monitoring site in each city
Krewski et al. (2009)[b,d]	ACS-CPS II (1979−1983: 58 U.S. MSAs; 1999−2000: 116 U.S. MSAs)	$PM_{2.5}$: 1979−1983/ 1999−2000 Follow-up: 1982−2000	Deaths: NA Pop: 351,338 (1979−1983) 499,968 (1999−2000)	1979−1983: 21.2 1999−2000: 14.0	Average of all monitoring sites in each MSA

Table 10-4 (Continued): Study specific details and $PM_{2.5}$ concentrations from recent studies and studies evaluated in the 2009 PM ISA that examined lung cancer mortality and incidence.

Study	Cohort Location	Years Air Quality/Follow-up	Events/ Population	Mean Concentration µg/m^3	Exposure Assessment
†Jerrett et al. (2013)	ACS-CPS II (California)	$PM_{2.5}$: 1998−2002 Follow-up: 1982−2000	Deaths: 1,481 Pop: 73,711	14.1	LUR at geocoded addresses as detailed in Beckerman et al. (2013a) and van Donkelaar et al. (2010)
†Thurston et al. (2013)	ACS-CPS II (100 U.S. MSAs)	$PM_{2.5}$: 2000−2005 Follow-up: 1982−2004	Deaths: NA Pop: 445,860	14.2	Average of all monitoring sites in each MSA
†Turner et al. (2016)	ACS-CPS II	$PM_{2.5}$: 1999−2004 Follow-up: 1982−2004	Deaths: 16,432 Pop: 669,046	12.6	National-level hybrid LUR and BME interpolation model at geocoded address as detailed in Beckerman et al. (2013b); R^2 = 0.79
†Turner et al. (2011)	ACS-CPS II (1979−1983: 61 U.S. MSAs; 1999−2000: 117 U.S. MSAs; 1979−1983/ 1999−2000: 53 U.S. MSAs)	$PM_{2.5}$: (1) 1979−1983; (2) 1999−2000; (3) 1979−1983/ 1999−2000 Follow-up: 1982−2008	(1) Deaths: 772 Pop: 131,864 (2) Deaths: 1,042 Pop: 177,752 (3) Deaths: 714 Pop: 120,917	1979−1983: 21.1 1999−2000: 14.0 1979−1983/ 1999−2000: 17.6	Average of all monitoring sites in each MSA
†Turner et al. (2014)	ACS-CPS II	$PM_{2.5}$: 1999−2004 Follow-up: 1982−1988	Deaths: 1,921 Pop: 429,406	12.6	National-level hybrid LUR and BME interpolation model at geocoded address as detailed in Beckerman et al. (2013b); R^2 = 0.79
†Lipsett et al. (2011)	CTS (California)	$PM_{2.5}$: 1999−2005 Follow-up: 2000−2005	Deaths: 234 Pop: 73,489	15.6	IDW interpolation; limited to residences within 20 km from neighborhood and urban/regional monitors

Table 10-4 (Continued): Study specific details and $PM_{2.5}$ concentrations from recent studies and studies evaluated in the 2009 PM ISA that examined lung cancer mortality and incidence.

Study	Cohort Location	Years Air Quality/Follow-up	Events/ Population	Mean Concentration µg/m^3	Exposure Assessment
†Hart et al. (2011)	TrIPS (U.S.)	$PM_{2.5}$: 2000 Follow-up: 1985−2000	Deaths: 800 Pop: 53,814	14.1	Annual average concentration in year 2000 from nearest monitoring location to last known residential address
†Crouse et al. (2015)	CanCHEC (Canada)	$PM_{2.5}$: 1998−2006 Follow-up: 1991−2006	Deaths: 30,545 Pop, 2,521,525	8.9	10 km grid cells from three satellite instruments to residential postal code as detailed in van Donkelaar et al. (2014)
†Weichenthal et al. (2016)	CanCHEC (Ontario, Canada)	$PM_{2.5}$: 1998−2009 Follow-up: 1991−2009	Deaths: 3,200 Pop: 193,300	9.8	Mean concentration across all years of $PM_{2.5}$ data from provincial monitoring site within 5 km from residential address
†Pinault et al. (2016)	CCHS (Canada)	$PM_{2.5}$: 1998−2012 Follow-up: 2000−2011	Deaths: 2,700 Pop: 299,500	6.3	1 km grid cells from satellite measurements in combination with GEOS-Chem using geographically weighted regression to residential address as detailed in van Donkelaar et al. (2015)
†Lepeule et al. (2012)	HSC (U.S.)	$PM_{2.5}$: 1979−2009[g] Follow-up: 1974−2009	Deaths: 350 Pop: 8,096	Across sites: 11.4−23.6	One centrally located monitoring site in each city (1979−1988), average of all U.S. EPA monitors in each city (1986−2009)

Table 10-4 (Continued): Study specific details and $PM_{2.5}$ concentrations from recent studies and studies evaluated in the 2009 PM ISA that examined lung cancer mortality and incidence.

Study	Cohort Location	Years Air Quality/Follow-up	Events/ Population	Mean Concentration µg/m^3	Exposure Assessment
†Villeneuve et al. (2015)	CNBSS (Canada)	$PM_{2.5}$: 1998−2006 Follow-up: 1980−2005	Deaths: 1,011 Pop: 89,248	9.1[h]	10 km grid cells from three satellite instruments adjusted using GEOS-Chem to residential postal code as detailed in van Donkelaar et al. (2010) and van Donkelaar et al. (2014)
Europe					
Naess et al. (2007)[b]	Oslo Cohort (Oslo, Norway)	$PM_{2.5}$: 1992−1995 Follow-up: 1992−1998	Deaths: 1,453 Pop: 143,842	15.0	AirQUIS dispersion model
Brunekreef et al. (2009)I originally detailed in Beelen et al. (2008b)	NLCS-Air (Netherlands)	$PM_{2.5}$: 1987−1996 Follow-up: 1987−1996	Full cohort Deaths: 1,670 Case-Cohort deaths: 1,059 Pop: 117,528	28.2	Combination of IDW interpolation and land-use regression as detailed in Beelen et al. (2007)
†Carey et al. (2013)	National English (U.K.)	$PM_{2.5}$: 2002 Follow-up: 2003−2007	Deaths: 5,273 Pop: 830,842	12.9	1 km grid cells from air dispersion model based on estimation of emissions by sector; 1 km grid centroid linked to nearest residential postcode centroid as detailed in Atkinson et al. (2013); R^2 = 0.23−0.71
†Cesaroni et al. (2013)	RoLS (Rome, Italy)	$PM_{2.5}$: 2005 Follow-up: 2001−2010	Deaths: 12,208 Pop: 1,256,058	23.0	1 km grid Eulerian dispersion model to each residential address as detailed in Gariazzo et al. (2007) and Gariazzo et al. (2011)

Table 10-4 (Continued): Study specific details and $PM_{2.5}$ concentrations from recent studies and studies evaluated in the 2009 PM ISA that examined lung cancer mortality and incidence.

Study	Cohort Location	Years Air Quality/Follow-up	Events/ Population	Mean Concentration µg/m^3	Exposure Assessment
Asia					
†Wong et al. (2016)	(Hong Kong)	$PM_{2.5}$: 1998−2011 Follow-up: 1998−2011	Deaths: 1,408 Pop: 66,820	33.7	Combination of monitoring data, geospatial height information, and satellite data to estimate concentrations at geocoded residential address as detailed in Li et al. (2005) and Lai et al. (2010)
Lung cancer incidence					
North America					
†Puett et al. (2014)	NHS (U.S.)	$PM_{2.5}$: 1988−2007 Follow-up: 1994−2010	Cases: 2,155 Pop: 103,650	13.1[i]	GIS-based spatiotemporal model to each residential address as detailed in Yanosky et al. (2008); R^2 = 0.76−0.77
†Gharibvand et al. (2016)	AHSMOG-2 (U.S.)	$PM_{2.5}$: 2000−2001 Follow-up: 2002−2011	Cases: 250 Pop: 80,285	12.9	IDW interpolation to geocoded residential address
†Hystad et al. (2013)	NECSS (Canada)	$PM_{2.5}$: 1975−1994 Follow-up: 1994−1997	Cases: 2,390 Controls: 3,507	11.9	Spatiotemporal model to geocoded postal code of residential address as detailed in Hystad et al. (2012)
†Tomczak et al. (2016)	CNBSS (Canada)	$PM_{2.5}$: 1998−2006 Follow-up: 1980−2004	Cases: 932 Pop: 89,234	9.1[i]	10 km grid cells from three satellite instruments adjusted using GEOS-Chem to residential postal code as detailed in van Donkelaar et al. (2010)

Table 10-4 (Continued): Study specific details and $PM_{2.5}$ concentrations from recent studies and studies evaluated in the 2009 PM ISA that examined lung cancer mortality and incidence.

Study	Cohort Location	Years Air Quality/Follow-up	Events/ Population	Mean Concentration µg/m^3	Exposure Assessment
Europe					
Brunekreef et al. (2009)[j] originally detailed in Beelen et al. (2008a)	NLCS-Air (Netherlands)	$PM_{2.5}$: 1987−1996 Follow-up: 1987−1996	Full cohort Cases: 1,940 Case-Cohort cases: 1,294 Pop: 111,816	28.3	Combination of IDW interpolation and land-use regression as detailed in Beelen et al. (2007)
†Raaschou-Nielsen et al. (2013)	ESCAPE (Europe)	$PM_{2.5}$: 2008−2011 Follow-up: 1990s[k]	Cases: 2,095 Pop: 312,944	Across sites: 6.6−31.0	LUR at geocoded addresses as detailed in Eeftens et al. (2012a)
†Raaschou-Nielsen et al. (2016)	TRANSPHORM (Europe)	$PM_{2.5}$: 2008−2011 Follow-up: 1990s[l]	Cases: 1,878 Pop: 245,782	Across sites: 6.6−31.0	LUR at geocoded addresses as detailed in Eeftens et al. (2012a)
†Hart et al. (2015)	NLCS-Air (Netherlands)	$PM_{2.5}$: 1987−1996 Follow-up: 1986−2003	Cases: 3,355 Pop: 120,852	28.3	Combination of IDW interpolation and land-use regression as detailed in Beelen et al. (2007) and Beelen et al. (2008a)

ACS-CPS = American Cancer Society-Cancer Prevention Study; AHSMOG = Adventist Health Study on Smog; BME = Bayesian maximum entropy; CanCHEC = Canadian Census Health and Environment Cohort; CCHS = Canadian Community Health Survey; CNBSS = Canadian National Breast Screening Study; CTS = California Teacher's Study; ESCAPE = European Study of Cohorts for Air Pollution Effects; GIS = Geographic Information System; HSC = Harvard six cities cohort; IDW = Inverse distance-weighted; NECSS = National Enhanced Cancer Surveillance System project; NHS = Nurses' Health Study; NCLS-Air = Netherlands Cohort Study on Diet and Cancer; RoLS = Rome Longitudinal Study; TrIPS = Trucking Industry Particle Study; TRANSPHORM = European Study of Transport-related Air Pollution and Health Impacts-Integrated Methodologies for Assessing Particulate Matter.

[a]Evaluated in 2004 PM AQCD.

[b]Evaluated in 2009 PM ISA.

[c]Builds off the studies conducted by Dockery et al. (1993) and Krewski et al. (2000).

[d]Builds off the studies conducted by Pope et al. (1995) and Pope et al. (2002).

[e]Males only.

[f]During this period $PM_{2.5}$ estimated using city-specific regression equations based on extinction coefficient.

[g]For a subset of years when $PM_{2.5}$ was not monitored 1986−1988 through 1998, $PM_{2.5}$ concentrations were estimated from PM_{10}.

[h]Median concentration.

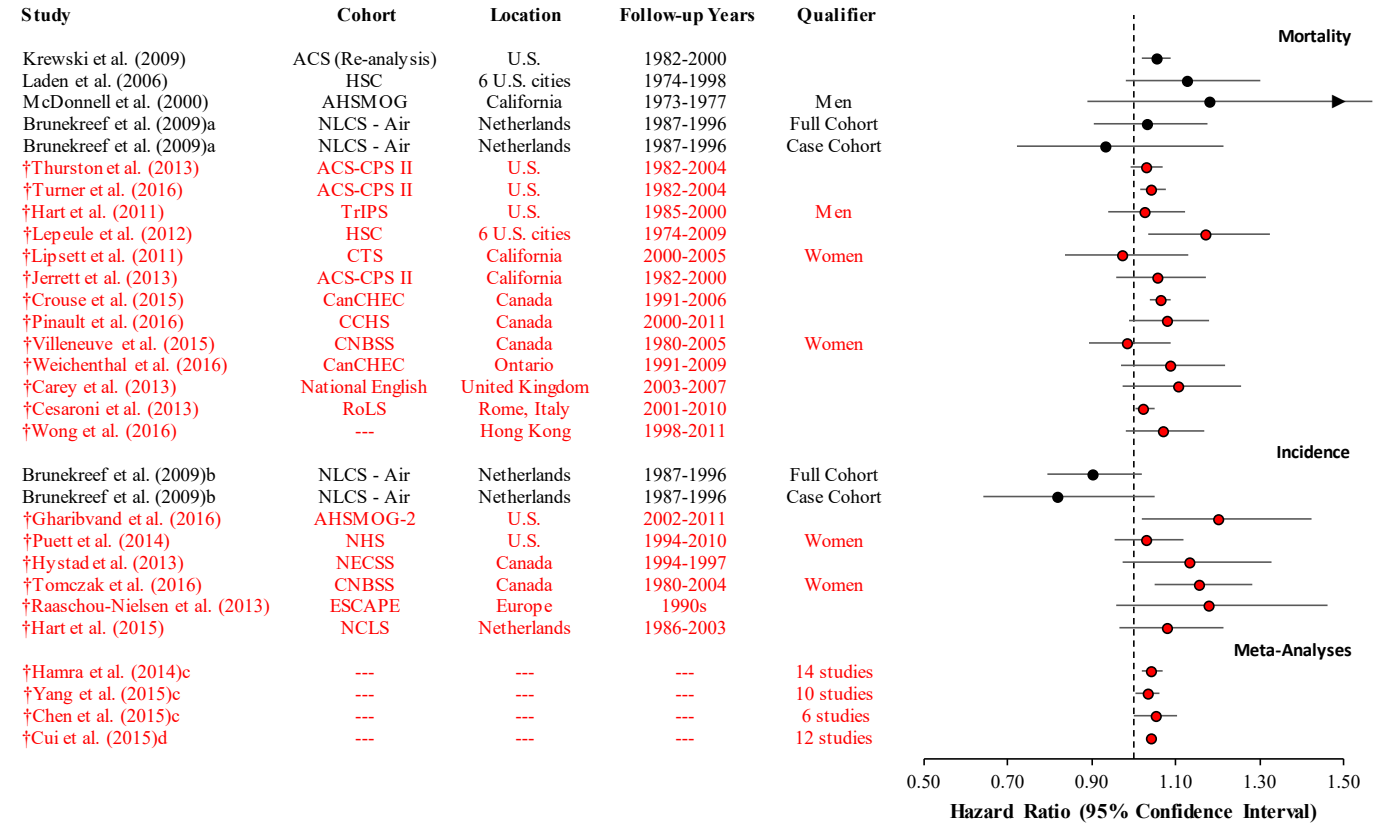
[i]Overall 72 mo cumulative average $PM_{2.5}$ concentration.

[j]$PM_{2.5}$ exposure assigned to residential address at 1986, study only reports population for all natural causes, not lung cancer, in Case-Cohort, and Beelen et al. (2008b) and Beelen et al. (2008a) presented the results of Brunekreef et al. (2009) prior to its publication.

[k]Only 14 or the 17 cohorts were examined for lung cancer, of the cohorts examined initial recruitment started generally in the 1990s with an average follow-up time of 12.8 years.

[l]TRANSPHORM used 14 of the 17 cohorts in the ESCAPE study where initial recruitment started generally in the 1990s with an average follow-up time of 13.1 years.

†Studies published since the 2009 PM ISA.



ACS-CPS = American Cancer Society-Cancer Prevention Study; AHSMOG = Adventist Health Study on Smog; CanCHEC = Canadian Census Health and Environment Cohort; CCHS = Canadian Community Health Survey; CNBSS = Canadian National Breast Screening Study; CTS = California Teacher's Study; ESCAPE = European Study of Cohorts for Air Pollution Effects; HSC = Harvard six cities cohort; NECSS = National Enhanced Cancer Surveillance System project; RoLS = Rome Longitudinal Study; TrIPS = Trucking Industry Particle Study. Hazard ratios are standardized to a 5 μg/m^3 increase in annual $PM_{2.5}$ concentrations.

[a]Lung cancer mortality results originally reported in Beelen et al. (2008b).

[b]Lung cancer incidence results originally reported in Beelen et al. (2008a).

[c]Risk estimate is a combination of lung cancer mortality and incidence estimates.

[d]Risk estimate is only for lung cancer mortality.

Corresponding quantitative results are reported in Supplemental Material. See U.S. EPA (2018).

Note: †Studies published since the 2009 PM ISA. Studies in black were included in the 2009 PM ISA.

Figure 10-3 Summary of associations reported in previous and recent cohort studies that examined long-term $PM_{2.5}$ exposure and lung cancer mortality and incidence.

10.2.5.1.1 Lung Cancer Mortality

Recent studies that examined the association between long-term $PM_{2.5}$ exposure and lung cancer mortality have attempted to account for the potential confounding effects of exposure to cigarette smoke

through detailed information on smoking status as well as exposure to second-hand smoke (SHS). These studies have assessed the role of smoking status on the relationship between long-term $PM_{2.5}$ exposure and lung cancer mortality through two approaches, either including smoking status as a covariate in the main statistical model or examining whether smoking status modifies the $PM_{2.5}$-lung cancer mortality association. The following section discusses both approaches, focusing first on those studies that had individual-level data on smoking status and then those studies that used proxy measures to account for smoking status within the study population.

Individual-Level Data on Smoking Status

The majority of studies that examined the $PM_{2.5}$-lung cancer mortality relationship focused on the ACS-CPS II cohort, building off the initial work presented in Pope et al. (1995) and then reanalyzed in subsequent studies (e.g., (Krewski et al., 2009)). These studies differed primarily in the years of $PM_{2.5}$ data examined, years of follow-up, exposure assignment approaches, and geographic extent of the cohort examined (i.e., national or specific location; Table 10-4). A summary of the results from studies that focused on the ACS-CPS II cohort that are evaluated in this section are detailed in Table 10-5.

Whereas the initial ACS-CPS II studies focused on assigning exposure using the average $PM_{2.5}$ concentrations across all monitors, Jerrett et al. (2013) conducted a more detailed exposure assessment using LUR in a subset of the full cohort limited to California. The authors reported a positive association with lung cancer mortality (HR = 1.06 [95% CI: 0.96, 1.17]). Although specific to California, the results of Jerrett et al. (2013) are consistent with those observed in the full cohort using cruder exposure assessment techniques, which includes Krewski et al. (2009) as well as a recent analysis by Thurston et al. (2013) that focused on mortality and long-term exposure to $PM_{2.5}$ components and sources. Using a similar exposure assignment approach as Krewski et al. (2009), Thurston et al. (2013) reported a HR = 1.03 (95% CI: 0.99, 1.08) for lung cancer mortality in a model adjusting for a range of individual- and ecological-level covariates including cigarette smoking history.

Table 10-5 Summary of results from studies that examined long-term $PM_{2.5}$ exposure and mortality in the American Cancer Society-Cancer Prevention Study II.

Study	ACS-CPS II Population	Location	Result[a]
Krewski et al. (2009)	Full cohort	National	1.05 (1.02, 1.09)
†Jerrett et al. (2013)	Full cohort	California	1.06 (0.96, 1.17)
†Thurston et al. (2013)	Full cohort	National	1.03 (0.99, 1.08)
†Turner et al. (2016)	Never smokers	National	1.04 (1.01, 1.08)
†Turner et al. (2011)	Full cohort	National	1979−1983: 1.07 (0.99, 1.16) 1999−2000: 1.13 (1.01, 1.25) 1979−1983; 1999−2000: 1.09 (0.98, 1.21)
†Turner et al. (2014)	Full cohort[b]	National	Never smoker (high vs. low): 1.26 (0.90, 1.77) Current smoker (high vs. low): 1.19 (1.03, 1.38)

[a]All results are for a 5 μg/m^3 increase in $PM_{2.5}$ concentrations except Turner et al. (2014) where results were based on comparing results between the 25th percentile (≤10.59 μg/m^3) and 75th percentile (>14.44 μg/m^3) of $PM_{2.5}$ concentrations.

[b]Study population that produced these results was smaller than the total population of the study detailed in Table 10-4, Never Smokers (Lung Cancer Deaths = 144, Population = 149,617); Current Smokers (Lung Cancer Deaths = 793, Population = 65,275).

†Studies published since the 2009 PM ISA.

Using a more refined exposure assignment approach in the full ACS-CPS II cohort, Turner et al. (2016) examined associations between both overall $PM_{2.5}$ concentrations using a national-level hybrid LUR Bayesian maximum entropy interpolation (LURBME) model as well as $PM_{2.5}$ concentrations decomposed into near-source (LUR) and regional (LURBME-LUR) components. The authors reported a positive association between overall $PM_{2.5}$ from the LURBME model and lung cancer mortality (HR = 1.04 [95% CI 1.01, 1.08]). Positive associations were also observed when examining both the near-source (HR = 1.08 [95% CI: 0.98, 1.18]) and regional (HR = 1.04 [95% CI: 1.00, 1.07]) components of ambient $PM_{2.5}$ concentrations. The results of Turner et al. (2016) provide evidence that within the ACS-CPS II, regardless of the exposure assignment approach used there is evidence of a consistent positive association between long-term $PM_{2.5}$ exposure and lung cancer mortality (see Figure 10-3).

As detailed above, traditionally ACS-CPS II studies have included covariates for smoking status or exposure to SHS in statistical models, but have not accounted for potential residual confounding by cigarette smoke. Often the examination of the association between long-term air pollution exposure, including $PM_{2.5}$, and lung cancer mortality in never smokers has been limited by the small number of lung cancer deaths (Turner et al., 2011). Within the ACS-CPS II cohort Turner et al. (2011) examined lung cancer mortality only in never smokers by using the three $PM_{2.5}$ exposure periods (i.e., 1979−1983,

1999−2000, and average of 1979−1983 and 1999−2000) initially detailed in Pope et al. (2002). Across the three different exposure periods and the three different statistical models examined, which varied by the degree of individual- and ecological covariates included, associations were consistently positive with HRs ranging from 1.07−1.14. In the fully adjusted model, which in addition to controlling for a number of individual-level covariates also controlled for county-level residential radon concentrations, Turner et al. (2011) found little evidence that radon confounded the $PM_{2.5}$-lung cancer mortality relationship, reporting a HR = 1.07 (95% CI: 0.99, 1.16) and HR = 1.13 (95% CI: 1.10, 1.25) for 1979−1983 and 1999−2000, respectively.

In Turner et al. (2011) the examination of the relationship between long-term $PM_{2.5}$ exposure and lung cancer mortality was on never smokers, while Turner et al. (2014) took this initial analysis one step further and focused on whether there is evidence of an interaction between long-term $PM_{2.5}$ exposure and smoking status. While the discussion of the interaction between smoking status and $PM_{2.5}$ is more informative in identifying populations potentially at increased risk of a PM-related health effect (see Chapter 12), analyses focusing solely on never smokers and current smokers in Turner et al. (2014) provide additional supporting evidence for a relationship between long-term $PM_{2.5}$ exposure and lung cancer mortality. In analyses comparing lung cancer mortality in never smokers exposed to low (≤25th percentile = 10.59 μg/m^3) and high (>75th percentile = 14.44 μg/m^3) $PM_{2.5}$ concentrations the authors reported a HR = 1.26 (95% CI: 0.90, 1.77) while for current smokers the authors reported a HR = 1.19 (95% CI: 1.03, 1.38). Although 95% confidence intervals are larger for the strata of never smokers due to the small number of cases, the results of Turner et al. (2014) support a relationship between long-term $PM_{2.5}$ exposure and lung cancer mortality, particularly in locations with higher $PM_{2.5}$ concentrations.

Similar to the ACS-CPS II cohort, the HSC cohort had detailed individual-level data on smoking status. Lepeule et al. (2012) extended the analysis of the original HSC cohort and reported a positive association between $PM_{2.5}$ concentrations in the 1−3 years prior to lung cancer death (or censoring; HR = 1.17 [95% CI: 1.03, 1.32]). This lag structure between $PM_{2.5}$ exposure and lung cancer mortality was also observed in the Canadian Community Health Survey (CCHS) cohort. In models controlling for smoking status using individual-level data, Pinault et al. (2016) reported a HR = 1.08 (95% CI: 0.99, 1.18) when examining $PM_{2.5}$ exposures over the 3 years prior to death.

In additional analyses stratifying by smoking status, Lepeule et al. (2012) reported that the association between $PM_{2.5}$ and lung cancer mortality persisted in never smokers, but the 95% confidence intervals were large (HR = 1.12 [95% CI: 0.73, 1.70]) due to only 26 out of the 350 lung cancer deaths occurring in never smokers. Overall, the association largest in magnitude for $PM_{2.5}$ and lung cancer mortality were observed for former smokers (HR = 1.40 [95% CI: 1.14, 1.73]). The results of Lepeule et al. (2012) indicating an association larger in magnitude for never smokers compared to the full cohort are consistent with the results of Carey et al. (2013) in a National English cohort. Carey et al. (2013) reported a HR = 1.22 (95% CI: 1.08, 1.41) in a model that included covariates for smoking and BMI. In models

including additional variables for education and income separately the lung cancer mortality association was attenuated, but remained positive (with income: HR = 1.05; with education HR = 1.11). When restricting the analysis to never smokers, the authors observed a rather large increase in the lung cancer mortality association (HR = 1.41 [95% CI: 1.22, 1.62]).

There was no evidence of an association between long-term $PM_{2.5}$ exposure and lung cancer mortality in two cohorts of women, the California Teachers Study (CTS) and the Canadian National Breast Screening Survey (CNBSS). In the CTS, 67% of participants were never smokers, and Lipsett et al. (2011) reported no evidence of an association between long-term $PM_{2.5}$ exposure and lung cancer mortality (HR = 0.97 [95% CI: 0.84, 1.13]). The results from the CTS cohort are consistent with the CNBSS cohort, which had a lower percentage of never smokers, 49.3% (HR = 0.98 [95% CI: 0.89, 1.09]) (Villeneuve et al., 2015). In the CTS cohort, the null $PM_{2.5}$-lung cancer mortality association persisted in several sensitivity analyses including, but not limited to, only post-menopausal women as well as women who did not relocate during follow-up. However, when focusing on only never smokers, Lipsett et al. (2011) reported that the association between long-term $PM_{2.5}$ exposure and lung cancer mortality was positive, but imprecise (HR = 1.27 [95% CI: 0.91, 1.78]) due to the small number of lung cancer deaths (i.e., 50) in this subset of the cohort, which is consistent with never smoker analyses in both Lepeule et al. (2012) and Carey et al. (2013). Villeneuve et al. (2015) in the CNBSS cohort only reported results by smoking status in analyses of all cancers, and did not observe a similar pattern of associations as the other cohorts when stratifying by smoking status (i.e., associations larger in magnitude for never smokers).

Across the lung cancer mortality studies, the magnitude of the association was generally consistent in areas where mean $PM_{2.5}$ concentrations were generally below 15 $\mu g/m^3$ (i.e., in the U.S. and Canadian cohorts), and below 30 $\mu g/m^3$ in all studies except Wong et al. (2016) (Table 10-4). Wong et al. (2016) in a study conducted in Hong Kong that examined long-term $PM_{2.5}$ exposure and all cancers, in a model controlling for smoking status, reported an association for lung cancer mortality similar in magnitude (HR = 1.07 [95% CI: 0.98, 1.17]) to that observed in the other cohort studies. Additionally, unlike the other studies evaluated in this section where the age of study participants was broader, the cohort was limited to those 65 years of age and older. The interpretation of these results is complicated when examining associations by smoking status. For men, 85% of the lung cancer mortality cases were in ever smokers, while for women 72% were in never smokers. However, when examining associations in each subset of the cohort, no evidence of an association was observed in women that were never smokers or ever smokers, while the strongest association was in ever smoker men (HR = 1.17 [95% CI: 1.02, 1.33]). There was evidence of a positive association for never smoker men, but the 95% confidence intervals were large due to the small number of cases (HR = 1.09 [95% CI: 0.72, 1.66]).

Proxy Measures of Smoking Status

In addition to the cohorts discussed above that controlled for smoking status or examined whether there was evidence of effect measure modification by smoking status, several cohorts examined the

association between long-term $PM_{2.5}$ exposure and lung cancer mortality without the ability to account for smoking status through detailed individual-level data. In an analysis of the Canadian Census Health and Environment Cohort (CanCHEC), Crouse et al. (2015) using a 7-year moving window of $PM_{2.5}$ concentrations for each year of follow-up reported a HR = 1.03 (95% CI: 1.01, 1.05). To adjust for smoking status and obesity, the authors used ancillary data on smoking and obesity to adjust for both risk factors not included in the original data set. Applying this method to account for smoking status and obesity resulted in a slightly larger HR = 1.08 (95% CI: 1.04, 1.09). A subsequent analysis of CanCHEC conducted by Weichenthal et al. (2016) limited to Ontario and focusing on $PM_{2.5}$ oxidative potential (see Section 10.2.5) also reported results for $PM_{2.5}$ and they were larger in magnitude (HR = 1.12 [95% CI: 1.00, 1.25]) compared to those observed in the full CanCHEC study (Crouse et al., 2015). The difference in results between the Ontario and national CanCHEC studies could be attributed to several factors (e.g., demographic differences), along with the exposure assignment approach employed in each study (see Table 10-4). Similar to Crouse et al. (2015), Weichenthal et al. (2016) indirectly adjusted for smoking status and obesity, by including a variable in the statistical model that accounted for both through examination of a secondary nationally representative data set (i.e., CCHS), and found the results were relatively similar to that observed in the main model (HR = 1.09 [95% CI: 0.97, 1.22]). Cesaroni et al. (2013) in the Rome Longitudinal Study (RoLS) also used proxy measures to account for smoking status, but relied on measures of neighborhood socioeconomic level and pre-existing comorbidities, which have been shown to be associated with smoking, to develop an indicator variable meant to control for smoking status. Using time-dependent annual $PM_{2.5}$ concentrations the authors reported a positive association (HR = 1.02 [95% CI: 1.00, 1.05]) between $PM_{2.5}$ exposure and lung cancer mortality.

While the previous studies detailed within this section focused specifically on ambient $PM_{2.5}$ exposure and lung cancer mortality in the general population, Hart et al. (2011) examined ambient air pollution exposures and cause-specific mortality, including lung cancer, in an occupational cohort from the Trucking Industry Particle Study (TrIPS). The TrIPS cohort consisted of men employed in the trucking industry, and similar to the CanCHEC and RoLS cohorts the authors did not have individual-level data to account for smoking status. However, unlike the CanCHEC and RoLS cohorts the authors did not attempt to indirectly adjust for smoking status. While most of the studies detailed in this section relied on multiple years of $PM_{2.5}$ data, only data from the year 2000 was available. In analyses focusing on the full cohort, the authors reported a positive association between $PM_{2.5}$ exposure and lung cancer mortality (HR = 1.03 [95% CI: 0.94, 1.12]). To further assess the association between $PM_{2.5}$ exposure and cause-specific mortality, Hart et al. (2011) conducted a sensitivity analysis that excluded long haul truckers, which potentially reduces exposure misclassification by focusing on those truckers that return home nightly due to $PM_{2.5}$ exposures being assigned at the residential address. In the subset analysis, the authors tended to observe associations larger in magnitude across mortality outcomes compared to the full cohort although confidence intervals were larger (lung cancer; HR = 1.08 [95% CI: 0.97, 1.21]).

Summary

In summary, results from recent epidemiologic studies that examined the association between long-term $PM_{2.5}$ exposure and lung cancer mortality are generally consistent with those studies evaluated in the 2009 PM ISA (Figure 10-3). Additional reanalyses of the ACS cohort using different years of $PM_{2.5}$ data and follow-up along with exposure assignment approaches and geographic extent of the cohort continue to provide evidence of consistent positive associations between long-term $PM_{2.5}$ exposure and lung cancer mortality. Additional epidemiologic studies that used individual-level data to control for smoking status conducted both within the U.S. and internationally, also provide evidence of generally consistent positive associations. The positive associations observed across studies are further supported by studies that conducted analyses focusing on never smokers that also reported positive associations, albeit with wide confidence intervals due to the small number of lung cancer mortality cases within the population of never smokers. There was no evidence of an association between long-term $PM_{2.5}$ exposure and lung cancer mortality in two cohorts of women (i.e., CTS and CNBSS cohorts). However, an analysis of never smokers in the CTS cohort reported evidence of a positive association that was consistent with the other studies evaluated within the section that conducted analyses of never smokers. The results across studies that had individual-level data on smoking status are supported by additional epidemiologic studies in cohorts that relied upon proxy measures to account for smoking status.

10.2.5.1.2 Lung Cancer Incidence

Although there is a high case-fatality rate for lung cancer, at the completion of the 2009 PM ISA (U.S. EPA, 2009), an uncertainty identified was the limited number of studies that examined lung cancer incidence. These studies did not provide evidence of an association between long-term $PM_{2.5}$ exposure and lung cancer incidence. Since the completion of the 2009 PM ISA, a larger number of studies have examined lung cancer incidence, but overall the total number of studies remains small compared to lung cancer mortality. Similar to some of the lung cancer mortality studies, the lung cancer incidence studies also conducted stratified analyses by smoking status, which can contribute to assessing whether a relationship exists between long-term $PM_{2.5}$ exposure and lung cancer by focusing on never smokers. A unique feature of lung cancer incidence studies that also allows for further assessment of the $PM_{2.5}$-lung cancer relationship is their ability to examine associations by the histological subtype of lung cancer. Specifically, an assessment of adenocarcinoma, the only subtype that develops in nonsmokers, can contribute to further accounting for residual confounding due to smoking (Hystad et al., 2013). The following lung cancer incidence studies examine both associations stratified by smoking status, and in most cases also histological subtype.

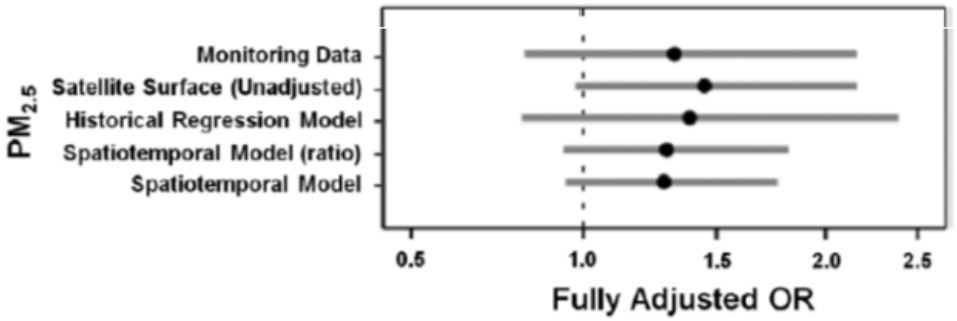
Within the U.S., the Nurses' Health Study (NHS) cohort (Puett et al., 2014) and the AHSMOG-2 cohort (Gharibvand et al., 2016) both examined the association between long-term $PM_{2.5}$ exposure and lung cancer incidence. In the NHS cohort, Puett et al. (2014) used 72-month average predicted $PM_{2.5}$ concentrations as the exposure metric, but due to the lack of $PM_{2.5}$ monitors prior to 1999, $PM_{2.5}$

concentrations for earlier time periods of the study were estimated from PM_{10}. The authors reported evidence of a small positive association with wide confidence interval for lung cancer incidence in the full cohort when adjusting for smoking status and SHS exposure (HR = 1.03 [95% CI: 0.95, 1.12] when examining 72-month average $PM_{2.5}$ concentrations). In a subset analysis of only never smokers the authors reported an association larger in magnitude (HR = 1.12 [95% CI: 0.87, 1.44]), which was also observed when combining never smokers and former smokers that had quit more than 10 years ago (HR = 1.17 [95% CI: 1.03, 1.33]). There was no evidence of an association when examining the combination of current smokers and former smokers that stopped smoking within the last 10 years. Lung cancer incidence was further evaluated through an examination of histological subtypes, specifically adenocarcinomas which comprise 44% of all lung cancer cases (Puett et al., 2014). Compared to the full cohort, when examining adenocarcinomas, the authors observed associations larger in magnitude for both the full cohort and the subset of never smokers and former smokers that had quit more than 10 years ago with HRs ranging from 1.15−1.29, but across categories confidence intervals were wide.

Gharibvand et al. (2016) within the AHSMOG-2 cohort examined mean monthly $PM_{2.5}$ concentrations over a 24-month period. In the cohort approximately 80% of the participants were never smokers, and they represented 46% of the lung cancer cases. In the full cohort, Gharibvand et al. (2016) reported evidence of a positive association when examining monthly average $PM_{2.5}$ concentrations (HR = 1.20 [95% CI: 1.02, 1.42]), which was similar in magnitude when examining both never (HR = 1.15 [95% CI: 0.95, 1.39]) and ever (HR = 1.22 [95% CI: 1.01, 1.48]) smokers. Overall, the lung cancer incidence associations in the AHSMOG-2 cohort are larger in magnitude than those observed in Puett et al. (2014), which could be attributed to the larger percentage of never smokers or long-term former smokers in the study population. On average, within the cohort, ever smokers quit smoking 24 years ago (Gharibvand et al., 2016). In an attempt to assess the influence of differences in time-activity on the observed associations, the authors examined average daily time spent outdoors and time lived at each residential location and found in both instances associations were similar in magnitude to the full cohort for those people that spent more than 1 hour per day outdoors and resided at their current address for more than 5 years. Of the lung cancer cases, approximately 66% were adenocarcinomas, which is a much larger percent than was observed in the NHS cohort, but the authors did not examine associations by histological subtype.

Additional national cohorts conducted in Canada, provide evidence of an association between long-term $PM_{2.5}$ exposure and lung cancer incidence that is similar in magnitude to that observed in AHSMOG-2 (Gharibvand et al., 2016). Hystad et al. (2013) used a case-control study with participants identified through the National Enhanced Cancer Surveillance System (NECSS) project. To reduce exposure misclassification and account for time-activity, the study was limited to cases and controls that had complete 20-year residential histories. In fully adjusted models that accounted for smoking status, the authors reported evidence of a positive association between annual $PM_{2.5}$ concentrations and lung cancer incidence (OR = 1.14 [95% CI: 0.97, 1.33]). Hystad et al. (2013) further assessed whether the exposure assignment approach used influenced the $PM_{2.5}$-lung cancer incidence association observed, and found

that across exposure assignment approaches which included using fixed-site monitoring data, satellite data, a historical regression model, and two different versions of a spatiotemporal model, the magnitude of associations was generally consistent (Figure 10-4). In additional analyses stratified by smoking status, the authors observed the strongest association among former smokers (OR = 1.20 [95% CI: 0.98, 1.48]), with no evidence of an association in never smokers (0.97 [95% CI: 0.62, 1.53]), which could be attributed to only 6% of all lung cancer cases in this population being never smokers. In histological subtype analyses, Hystad et al. (2013) did not observe a clear relationship between long-term $PM_{2.5}$ exposure and one subtype, which differs from the results of Puett et al. (2014), which indicated associations larger in magnitude for adenocarcinomas.



Source: Permission pending, Hystad et al. (2013).

Figure 10-4 $PM_{2.5}$—lung cancer incidence odds ratios (OR) for a 10 µg/m^3 increase in $PM_{2.5}$ concentrations from sensitivity analyses using different exposure assignment approaches in the Canadian National Enhanced Cancer Surveillance System (NECSS) project.

The main results of Hystad et al. (2013) are consistent with those observed in another Canadian cohort (CNBSS) by Tomczak et al. (2016), which is the same cohort that was examined for lung cancer mortality by Villeneuve et al. (2015) detailed above. In a model controlling for smoking status and other SES-related variables, the authors observed evidence of an increase in lung cancer incidence in this cohort of women (HR = 1.16 [95% CI: 1.05, 1.28]). In analyses stratified by smoking status, no association was observed for never smokers, while the association for ever smokers was consistent with that observed in the full cohort, indicating that this subset of the cohort is responsible for the overall association (HR = 1.18 [95% CI: 1.06, 1.32]). Tomczak et al. (2016) also conducted histological subtype analyses and observed evidence of a positive association for small cell carcinoma and adenocarcinoma. Although the 95% confidence intervals for the histological subtype analyses in Hystad et al. (2013) were large resulting in the inability to clearly identify differences across subtypes, the central estimates were also largest in magnitude for small cell carcinoma and adenocarcinoma.

The examination of $PM_{2.5}$ and lung cancer incidence in the European Study of Cohorts for Air Pollution Effects (ESCAPE) study resulted in an association similar in magnitude to that observed in the AHSMOG-2, NECSS, and CNBSS cohorts discussed above (HR = 1.18 [95% CI: 0.96, 1.46]) (Raaschou-Nielsen et al., 2013). The results of Raaschou-Nielsen et al. (2013) are the same as those reported by Raaschou-Nielsen et al. (2016) as part of the European Study of Transport-related Air Pollution and Health Impacts-Integrated Methodologies for Assessing Particulate Matter (TRANSPHORM) project, which also used data from the ESCAPE study, but focused on associations between long-term $PM_{2.5}$ component exposures and lung cancer incidence. In additional analyses conducted by Raaschou-Nielsen et al. (2013) that attempted to reduce the impact of exposure misclassification by focusing on those residents who did not change residence during the follow-up period, the authors reported an association similar in magnitude to the full cohort (HR = 1.20 [95% CI: 0.96, 1.51]), which is consistent with the analysis focusing on people that resided at their residential location for over 5 years conducted by Gharibvand et al. (2016) in the AHSMOG-2 cohort. Analyses stratified by smoking status did not provide strong evidence for differences among never, former, and current smokers, but associations were largest in magnitude for never (HR = 1.21) and former (HR = 1.41) smokers although 95% confidence intervals were large. When examining histological subtypes, Raaschou-Nielsen et al. (2013) observed a positive association for only adenocarcinomas (HR = 1.51 [95% CI: 1.10, 2.08]).

In another study conducted in Europe, Hart et al. (2015), in a cohort in the Netherlands (NLCS-Air), also observed evidence of a positive association between long-term $PM_{2.5}$ exposure and lung cancer incidence in models that included a variable to adjust for smoking status (HR = 1.08 [95% CI: 0.96, 1.21] for 1987−1996). Within this study a case-cohort approach was used as detailed in the original NCLS-Air cohort (Brunekreef et al., 2009; Beelen et al., 2008a). Interestingly the results of Hart et al. (2015) differ from those observed in the original NCLS-Air cohort analysis where no evidence of an association was reported with lung cancer incidence (Figure 10-3). Although not explicitly detailed in Hart et al. (2015) there are differences with the original NLCS-Air studies that could contribute to the disparate results observed between the original and extended analyses, specifically (1) an additional 6 years of follow-up, (2) the transition of some individuals to being classified as cases, (3) the exclusion of individuals without exposure or smoking status information, and (4) the use of age in years as the timescale instead of time in study (Hart, 2017b). In addition to providing overall results, Hart et al. (2015) also attempted to adjust the observed association to account for exposure measurement error by using information from a validation study involving personal and near-home outdoor measurements of 47 nonsmokers from 2004−2005. After adjusting for exposure measurement error using a regression calibration analysis the $PM_{2.5}$-lung cancer incidence association increased in magnitude, but had larger confidence intervals (1.17 [95% CI: 0.93, 1.47]). The approach by Hart et al. (2015) along with those less computationally intensive approaches detailed in Raaschou-Nielsen et al. (2013) in the ESCAPE study and Gharibvand et al. (2016) in the AHSMOG-2 cohort consistently demonstrate that $PM_{2.5}$-lung cancer incidence associations are robust when trying to account for or reduce the potential impact of exposure measurement error. However, it should be noted that in Hart et al. (2015) residential address information was only available at baseline and the validation study was conducted after the follow-up period ended,

both of which contribute some level of uncertainty in adjusting the association to account for exposure measurement error. Hart et al. (2015) also conducted histological subtype analyses, and observed positive associations across all subtypes, but no clear difference in associations between subtypes existed.

Summary

Recent epidemiologic studies build upon the limited number of studies evaluated in the 2009 PM ISA that examined the association between long-term $PM_{2.5}$ exposure and lung cancer incidence, and provide evidence of consistent positive associations (Figure 10-3). Consistent with lung cancer mortality studies, studies that conducted analyses focusing on the subset of the cohort that were never smokers generally reported evidence of positive associations, albeit with wide confidence intervals due to the small number of never smokers within the cohorts. A subset of the studies focusing on lung cancer incidence also examined histological subtype, which provided some evidence of positive associations for adenocarcinomas, the only subtype of lung cancer observed in never smokers. However, in some studies the examination of associations by histological subtype were limited due to the small number of never smokers included within the cohort (e.g., NECSS cohort). In several studies, the $PM_{2.5}$-lung cancer incidence associations observed were further evaluated in sensitivity analyses that attempted to reduce exposure measurement error by accounting for length of time at residential address, examining different exposure assignment approaches, and conducting regression calibration to account for exposure measurement error. Across all approaches, associations between long-term $PM_{2.5}$ exposure and lung cancer incidence were found to remain relatively unchanged, but in some cases confidence intervals increased in width.

10.2.5.1.3 Copollutant Models

Across the epidemiologic studies that examined associations between long-term $PM_{2.5}$ exposure and lung cancer incidence and mortality, only a few examined potential copollutant confounding. Jerrett et al. (2013) in the ACS-CPS II cohort conducted copollutant analyses with NO_2 and O_3. Within the study, estimated O_3 concentrations at the residential address were derived from IDW, while the NO_2 concentrations were estimated using the same LUR model as $PM_{2.5}$. $PM_{2.5}$ was similarly correlated with both NO_2 and O_3 ($r = 0.55$). In a copollutant model with NO_2, the $PM_{2.5}$-lung cancer mortality association was attenuated and became null (HR = 0.99 [95% CI: 0.87, 1.11]), but remained relatively unchanged from the single-pollutant model result in a copollutant model with O_3 (HR = 1.10 [95% CI: 0.99, 1.22]). These results are consistent with those observed in Lipsett et al. (2011) in the CTS cohort. The authors reported that $PM_{2.5}$ was moderately to highly correlated with NO_X, CO, NO_2, and PM_{10} with correlations ranging from 0.52−0.91, but in copollutant models with O_3 the $PM_{2.5}$-lung cancer mortality association was relatively unchanged (HR = 1.04 [95% CI; 0.70, 1.53]) compared to the single-pollutant model result. The authors did not present results for copollutant models with the other pollutants examined.

Whereas the lung cancer mortality studies tended to report results for copollutant models with O_3, only Gharibvand et al. (2016) examined $PM_{2.5}$-lung cancer incidence associations in models with O_3. Within the AHSMOG-2 cohort, Gharibvand et al. (2016) observed that the $PM_{2.5}$-lung cancer incidence association was unchanged in copollutant models with O_3 (HR = 1.21 [95% CI: 1.02, 1.43]). Raaschou-Nielsen et al. (2013) within the ESCAPE study, also examined potential copollutant confounding of the $PM_{2.5}$-lung cancer incidence association, and did not find any evidence of confounding in models with NO_2 and $PM_{10-2.5}$ (quantitative results not presented).

Across the small number of studies that examined potential copollutant confounding of the relationship between long-term $PM_{2.5}$ exposure and lung cancer mortality and incidence, there is little evidence of copollutant confounding by O_3 with more limited information available to assess potential copollutant confounding for the other gaseous pollutants and particle size fractions. However, to date, studies have not systematically evaluated copollutant confounding across the gaseous pollutants.

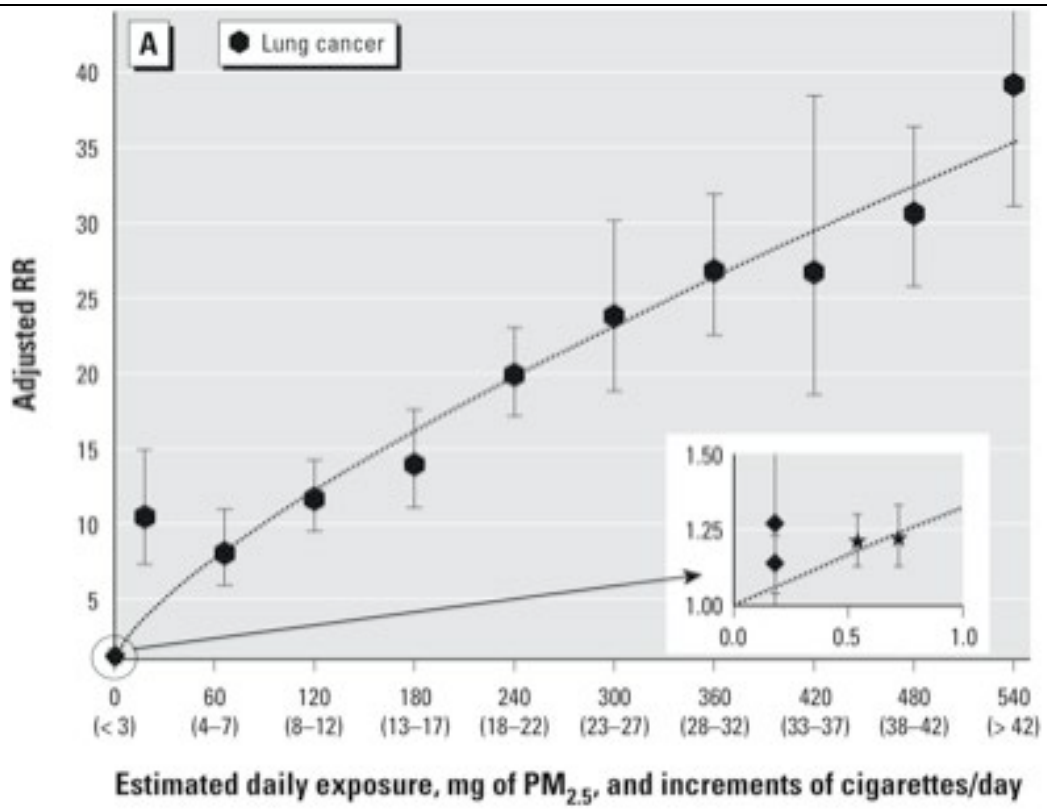
10.2.5.1.4 Concentration-Response (C-R) Relationship

Epidemiologic studies that examined the C-R relationship between long-term $PM_{2.5}$ exposure and mortality have generally found evidence of a linear, no threshold relationship (Section 11.2.4). However, fewer studies have examined the C-R relationship for cause-specific mortality outcomes, including lung cancer. Recent cohort studies of both lung cancer mortality and incidence have examined both the shape of the C-R relationship along with whether there is evidence of a threshold, or level below which there is no effect.

Across the studies evaluated, a few provided information on the shape of the $PM_{2.5}$-lung cancer mortality (Lepeule et al., 2012) and lung cancer incidence (Puett et al., 2014; Raaschou-Nielsen et al., 2013) C-R relationship, but did not extensively discuss the results. Lepeule et al. (2012) in the HSC cohort along with Puett et al. (2014) in the NHS cohort and Raaschou-Nielsen et al. (2013) in the ESCAPE study reported no evidence for deviations from linearity in the shape of the C-R relationship when examining alternative models. Additionally, Cesaroni et al. (2013) in the RoLS cohort examined a 20% random sample of the full cohort to assess the C-R relationship, but the small sample size resulted in an underestimation of the $PM_{2.5}$-lung cancer mortality association and an inability to fully characterize the C-R relationship. Although these studies provide limited information on the shape of the $PM_{2.5}$-lung cancer mortality and incidence C-R relationship, studies by Pope et al. (2011) using the ACS cohort and Tomczak et al. (2016) using the CNBSS cohort conducted more extensive analyses.

Pope et al. (2011) examined lung cancer mortality, but to convey the public health burden associated with exposures to $PM_{2.5}$ of ambient origin compared the shape of the C-R relationship for lung cancer mortality across three different exposures: active smoking, SHS, and ambient $PM_{2.5}$ exposures. For this analysis the authors focused on only 6 years of follow-up due to the lack of smoking information after initial enrollment. Pope et al. (2011) calculated adjusted relative risks (RRs) for lung cancer

mortality due to smoking status using the ACS cohort data, and relied upon RRs from other cohort studies of lung cancer mortality due to long-term $PM_{2.5}$ exposure and SHS. Using the adjusted RRs and estimates of: average inhaled dose of $PM_{2.5}$ from active smoking; average daily dose of inhaled $PM_{2.5}$ based on the range of $PM_{2.5}$ concentrations from recent U.S.-based cohort studies and average inhalation rates; and dose from SHS exposure based on approximate $PM_{2.5}$ exposures and average inhalation rates, Pope et al. (2011) fit an integrated-exposure response function using a simple power function. This functional form was selected because it allows for nonlinearity in the C-R relationship (Pope et al., 2011). In a plot of the relative risks for lung cancer mortality for ambient $PM_{2.5}$ exposure, SHS, and active smoking in relation to the estimated daily dose of $PM_{2.5}$ from different increments of cigarettes per day in smokers compared to never smokers, the authors observed evidence of a nearly linear relationship (Figure 10-5). This relationship persisted when examining lung cancer mortality in both men and women, and when accounting for smoking duration.

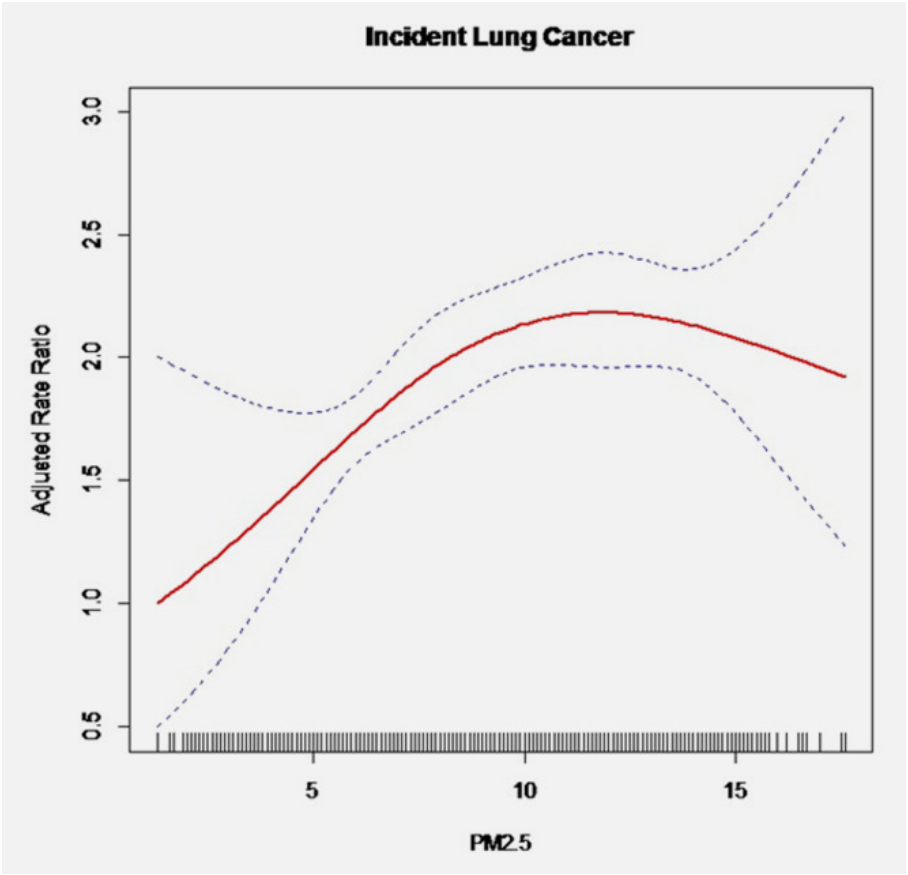


Note: Inset represents RR due to ambient $PM_{2.5}$ exposure and SHS. Diamonds = RR from studies of long-term $PM_{2.5}$ exposure and lung cancer mortality; stars = pooled RR estimates from studies of SHS and lung cancer mortality.

Source: Permission pending, Pope et al. (2011).

Figure 10-5 Adjusted relative risk (RR) for lung cancer mortality plotted over estimated daily dose of $PM_{2.5}$ (milligrams) and increments of cigarette smoking (cigarettes per day) compared to never smokers.

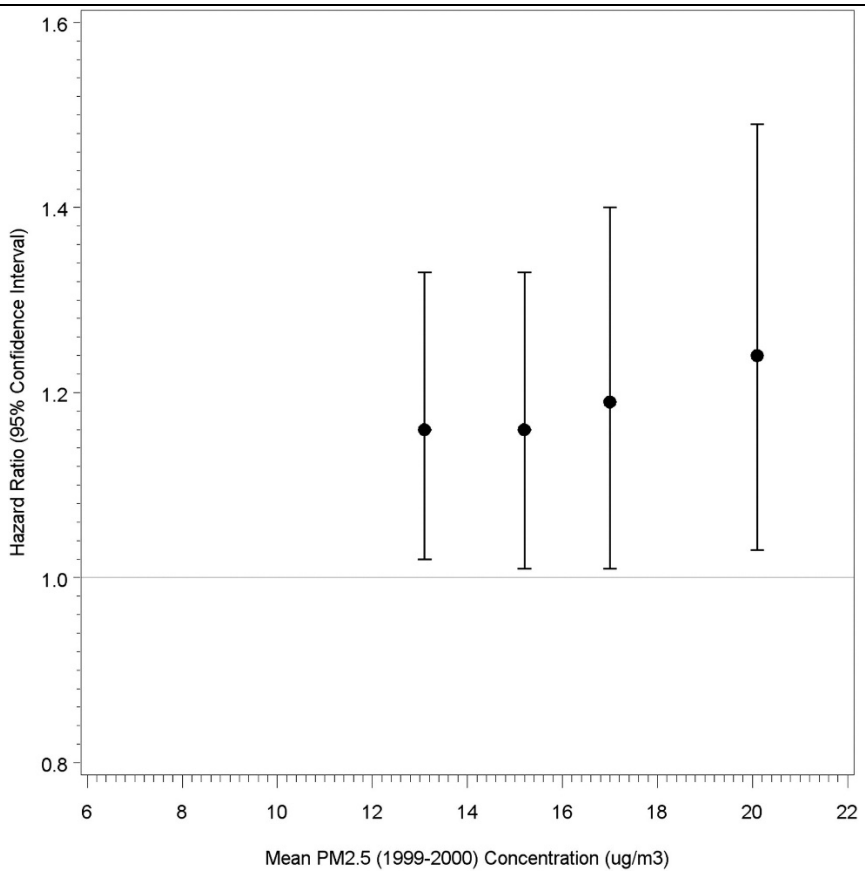
Tomczak et al. (2016) examined the shape of the C-R relationship for lung cancer incidence using the CNBSS. To examine whether there was evidence of nonlinearity in the C-R relationship, the authors considered a model with a natural cubic spline and 3 df. As depicted in Figure 10-6, Tomczak et al. (2016) observed evidence of nonlinearity in the $PM_{2.5}$-lung cancer incidence C-R relationship, which was depicted by a linear relationship up until approximately 12 µg/m^3 which then flattened out. The results of Tomczak et al. (2016) in this cohort of women differs from the examination of the C-R relationship in women by Pope et al. (2011) where the shape was found to be linear, which was consistent with the results of the full cohort. Although there is ambiguity in the shape of the C-R relationship above 12 µg/m^3 both Tomczak et al. (2016) and Pope et al. (2011) provide evidence of a linear C-R relationship in the range of $PM_{2.5}$ concentrations observed in the U.S.



Source: Permission pending, Tomczak et al. (2016).

Figure 10-6 Concentration-response (C-R) relationship between long-term $PM_{2.5}$ exposure and lung cancer incidence using a natural cubic spline and 3 degrees of freedom (df) in the Canadian National Breast Cancer Screening Survey (CNBCSS) cohort.

In addition to the studies that formally evaluated the C-R relationship, other studies used cut point analyses to examine whether there was evidence of a threshold or if the risk of lung cancer mortality or incidence varied across the range of $PM_{2.5}$ concentrations in each study. Turner et al. (2011) in the analysis of never smokers in the ACS-CPS II cohort examined the lung cancer mortality association across percentiles of the $PM_{2.5}$ distribution. When examining each percentile to the referent category, i.e., $PM_{2.5}$ concentrations less than 11.8 μg/m^3, the authors found relatively consistent associations with 95% confidence intervals increasing at higher concentrations, which is indicative of lower data density within those ranges of $PM_{2.5}$ concentrations (Figure 10-7).



Note: Cut-points represent the 25th (11.8 μg/m^3), 50th (14.3 μg/m^3), 75th (16 μg/m^3), and 90th (17.9 μg/m^3) percentiles.
Source: Permission pending, Turner et al. (2011).

Figure 10-7 Fully adjusted hazard ratios (95% confidence intervals) for lung cancer mortality in categorical analyses of mean $PM_{2.5}$ (1999−2000) concentrations in never smokers in the American Cancer Society-Cancer Prevention Study II (ACS-CPS II) cohort.

The results of Turner et al. (2011) in an analysis of lung cancer mortality, are consistent with those of Hystad et al. (2013) when examining lung cancer incidence in the NECSS cohort. In quintiles

that encompassed $PM_{2.5}$ concentrations less than those observed in Turner et al. (2011), ranging from less than 9.0 μg/m^3 for the referent category and above 14.7 μg/m^3 for the 5th quintile, the OR for long-term $PM_{2.5}$ exposure and lung cancer incidence ranged from 1.09−1.18, while the full cohort observed an OR = 1.14.

Instead of comparing $PM_{2.5}$-lung cancer incidence associations across a range of concentrations, Raaschou-Nielsen et al. (2013) in the ESCAPE study conducted a cut-point analysis to examine whether there was evidence of an association between long-term $PM_{2.5}$ exposure and lung cancer incidence below defined $PM_{2.5}$ concentrations. In the cut-point analysis, the authors excluded all participants with assigned $PM_{2.5}$ exposures that were above designated values (i.e., 10, 15, 20, and 25 μg/m^3). Across each of the cut-point values, Raaschou-Nielsen et al. (2013) reported consistent positive associations across each cut-point although confidence intervals were large due to the limited sample size for each cut-point value (HRs: 10 μg/m^3: 1.20 [95% CI: 0.55, 2.66]; 15 μg/m^3: 1.11 [95% CI: 0.85, 1.45]; 20 μg/m^3: 1.14 [95% CI: 0.90, 1.45]; 25 μg/m^3: 1.13 [95% CI: 0.90, 1.43]). The combination of results from cut-point analyses by Turner et al. (2011), Hystad et al. (2013), and Raaschou-Nielsen et al. (2013) collectively provide evidence indicating no threshold down to the lowest cut-point examined in each study (e.g., 9−11.8 μg/m^3).

Across the studies that examined long-term $PM_{2.5}$ exposure and lung cancer mortality and incidence, evidence from analysis of the shape of the C-R relationship, cut point analyses, and threshold analyses all support a no-threshold, linear relationship across the range of $PM_{2.5}$ concentrations observed in the U.S. Although Tomczak et al. (2016) observed a potentially nonlinear C-R relationship, this plateauing of the $PM_{2.5}$ association occurred at concentrations higher than those observed in many areas of the U.S., and was not consistent with the results of Pope et al. (2011) when focusing on women in the ACS-CPS II cohort.

10.2.5.1.5 Summary

Since the completion of the 2009 PM ISA there has been a dramatic increase in the number of studies that examined the relationship between long-term $PM_{2.5}$ exposure and lung cancer mortality and incidence using both previously examined cohorts as well as new cohorts. Collectively, these studies provide evidence of generally consistent, positive associations with both lung cancer mortality and incidence (Figure 10-3). These associations were observed across studies that adjusted for smoking status and exposure to SHS as well as those studies that had no direct measures of smoking status or used proxy measures to adjust for smoking.

In studies that conducted analyses on never smokers almost all of the studies, except a few conducted in Canada (Tomczak et al., 2016; Hystad et al., 2013) provided evidence of consistent positive associations. The positive associations for lung cancer in never smokers were confirmed by Turner et al. (2011) in a study of only never smokers in the ACS-CPS II cohort. The limited number of studies that

examined potential copollutant confounding reported that $PM_{2.5}$-lung cancer mortality and incidence associations remained relatively unchanged, specifically for O_3, with less evidence for other pollutants. Additionally, an examination of the C-R relationship and whether a threshold exists provided evidence that supports a no-threshold, linear relationship along the $PM_{2.5}$ concentrations observed in most locations within the U.S., specifically at concentrations representative of the lowest cut-point examined in studies, 9−11.8 μg/m^3, and where analyses of the C-R curve depict a widening of confidence intervals, ≈6 μg/m^3.

The collective body of evidence for lung cancer mortality and incidence detailed within this section, forms a substantial portion of the evidence included in recent meta-analyses of $PM_{2.5}$ and lung cancer risk, i.e., the meta-analyses did not delineate between lung cancer mortality and incidence in estimating the overall lung cancer risk (Chen et al., 2015; Yang et al., 2015; Cui et al., 2014; Hamra et al., 2014). Although the criteria for study inclusion varied across each of these meta-analyses they all reported evidence of a positive association between long-term $PM_{2.5}$ exposure and lung cancer risk (Figure 10-3). Specifically, the Hamra et al. (2014) meta-analysis, which formed a strong basis for the IARC conclusion on PM and lung cancer, included the majority of the studies evaluated within this section, the sole difference being this section did not focus on those studies that did not directly measure $PM_{2.5}$.

10.2.5.2 Other Cancers

The 2009 PM ISA concluded that there was no epidemiologic evidence supporting associations between long-term PM exposure in organs or systems other than the lung. However, the overall body of evidence was extremely limited. Since the completion of the 2009 PM ISA a number of studies have explored the relationship between long-term $PM_{2.5}$ exposure and other cancers including, but not limited to the breast and brain, with the majority focusing on cancer incidence. Of these studies, some had inherent limitations, such as an ecologic study design, and, therefore, are not the focus of this section and are available at: https://hero.epa.gov/hero/particulate-matter. Study characteristics including $PM_{2.5}$ concentrations, study population, and exposure assignment approach for the studies that examined other cancer sites are detailed in Table 10-6.

Table 10-6 Study specific details and $PM_{2.5}$ concentrations from recent that examined long-term $PM_{2.5}$ exposure and cancer in other organs or systems.

Study Years	Cohort Location	Years Air Quality/Follow-up	Events/ Population	Mean Concentration µg/m^3	Exposure Assessment
Breast cancer					
†Hart et al. (2016)[a]	NHS II (U.S.)	$PM_{2.5}$: 1988−2007 Follow-up: 1993−2011	Cases: 3,416 Pop: 115,921	12.6[b]	Monthly spatiotemporal prediction model to geocoded residential address as detailed in Yanosky et al. (2014)
†Reding et al. (2015)[a]	Sister study (U.S.)	$PM_{2.5}$: 2006 Follow-up: 2003−2013	Cases: 1,749 Controls: 47,591	10.5	Regionalized universal kriging model, as detailed in Sampson et al. (2013), to baseline home address
†Andersen et al. (2016)	DNC (Denmark)	$PM_{2.5}$: 1990−2013 Follow-up: 1993 or 1999−2013	Cases: 1,145 Pop: 22,877	19.7	Danish air pollution dispersion modelling system to estimate concentrations at residential address as detailed in Jensen et al. (2001)
†Wong et al. (2016)[c,f]	(Hong Kong)	$PM_{2.5}$: 1998−2011 Follow-up: 1998−2011	Deaths: 111 Pop: 66,820	33.7	Combination of monitoring data, geospatial height information, and satellite data to estimate concentrations at geocoded residential address as detailed in Li et al. (2005) and Lai et al. (2010)
Brain cancer					
†Jørgensen et al. (2016)[a]	DNC (Denmark)	$PM_{2.5}$: 1990−2013 Follow-up: 1993 or 1999−2013	Cases: 121 Pop: 25,143	19.7	Danish air pollution dispersion modelling system to estimate concentrations at residential address as detailed in Jensen et al. (2001)
†McKean-Cowdin et al. (2009)[c]	ACS-CPS II (U.S.)	$PM_{2.5}$: 1979−1983/ 1999−2000 Follow-up: 1982−2000	Deaths: 1,284 Pop: 630,487	1979−1983: 21.1 1999−2000: 14.0 Average: 17.7	Average of all monitoring sites in each MSA

Table 10-6 (Continued): Study specific details and $PM_{2.5}$ concentrations from recent that examined long-term $PM_{2.5}$ exposure and cancer in other organs or systems.

Study Years	Cohort Location	Years Air Quality/Follow-up	Events/ Population	Mean Concentration µg/m^3	Exposure Assessment
Liver cancer					
†Pan et al. (2016)	REVEAL-HBV (Taiwan)	$PM_{2.5}$: 2006−2009 Follow-up: 1991−2009	Cases: 464 Population: 23,820	Main Island: 32.2 Penghu Islets: 24.2	Ambient monitoring data from 75 fixed-site monitors across the study locations and modified ordinary kriging as detailed in Liao et al. (2006). R^2 = 0.73
†Pedersen et al. (2017)[h]	ESCAPE (Europe)	$PM_{2.5}$: 2008−2011 Follow-up: 1985−2005	Cases: 256 Population: 156,211	DCH: 11.3 VHM and PP: 13.6	LUR model as detailed in Beelen et al. (2013) to home address
Leukemia					
†Winters et al. (2015)[a]	(Canada)	$PM_{2.5}$: 1975−1994 Follow-up: 1975−1994	Cases: 1,064 Controls: 5,039	11.4−11.7[e]	Combination of satellite and monitoring data at postal code of residential address as detailed in as detailed in Hystad et al. (2012)
†Badaloni et al. (2013)[a]	SETIL (Italy)	$PM_{2.5}$: 2005 Follow-up: 1998−2001	Cases: 620 Controls: 957	20.6−21.1[d]	National Integrated Model (MINNI), a dispersion model, to 4 km grid cell and estimated for each geocoded residence
†Heck et al. (2013)[a,g]	(California)	$PM_{2.5}$: 1998−2007 Follow-up: 1998−2007	Cases: 479[i] Controls: 26,159	17.2	Monitoring station within 5 miles from address at birth

Table 10-6 (Continued): Study specific details and $PM_{2.5}$ concentrations from recent that examined long-term $PM_{2.5}$ exposure and cancer in other organs or systems.

Study Years	Cohort Location	Years Air Quality/Follow-up	Events/ Population	Mean Concentration µg/m^3	Exposure Assessment
Multiple cancers					
†Heck et al. (2013)[a,g]	(California)	$PM_{2.5}$: 1998−2007 Follow-up: 1998−2007	Cases: 397 Controls: 26,159	17.2	Monitoring station within 5 miles from address at birth
†Lavigne et al. (2017)	(Canada)	$PM_{2.5}$: 1998−2012 Follow-up: 1998−2012	Cases: 2,044 Pop: 2,350,898	1st, 2nd, and 3rd trimester; entire pregnancy, 1st year: 9.6	Satellite-derived estimates to 1 km resolution then adjusted based on GWR to centroid of residential 6-digit postal code as detailed in van Donkelaar et al. (2015)
†Wong et al. (2016)[c,f]	(Hong Kong)	$PM_{2.5}$: 1998−2011 Follow-up: 1998−2011	Deaths: 1,408 Pop: 66,820	33.7	Combination of monitoring data, geospatial height information, and satellite data to estimate concentrations at geocoded residential address as detailed in Li et al. (2005) and Lai et al. (2010)

ACS-CPS = American Cancer Society-Cancer Prevention Study; DCH = Diet, Cancer and Health Study; DNC = Danish Nurse Cohort; GWR = geographically weighted regression; NHS II = Nurses' Health Study-II; REVEAL-HBV = Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus; SETIL = Study on the aetiology of malignancies in children; VHM and PP = Vorarlberg Health Monitoring and Promotion Program.

[a]Cancer incidence.

[b]Mean concentration obtained from Hart (2017a).

[c]Cancer mortality.

[d]Range of mean concentration across analyses conducted.

[e]Range of $PM_{2.5}$ concentrations across cases and controls.

[f]Wong et al. (2016) examined a range of cancers including all malignant, all digestive organs, lung, breast, female genital, male genital, urinary, and lymphohematopoietic.

[g]Heck et al. (2013) examined a number of types of childhood cancers including leukemia.

[h]Only 2 (DCH, Denmark [1993−1997] and VHM and PP, Austria [1985−2005]) of the 4 escape cohorts examined measured $PM_{2.5}$.

[i]397 cases of acute lymphoblastic leukemia and 82 cases of acute myeloid leukemia.

†Studies published since the 2009 PM ISA.

10.2.5.2.1 Breast Cancer

Hart et al. (2016) and Reding et al. (2015) examined the association between long-term $PM_{2.5}$ exposure and breast cancer incidence in two U.S.-based cohorts, NHS II and Sister Study cohorts, respectively. In both studies, the authors observed relatively little evidence of an association overall for

breast cancer incidence or by hormone receptor subtype. Hart et al. (2016) using a 48-month average of $PM_{2.5}$ concentrations reported a HR = 0.95 (95% CI: 0.89, 1.01) for breast cancer incidence, which is similar to the results observed using a cumulative exposure metric (quantitative results not reported). Reding et al. (2015) also reported relatively little evidence for an association with breast cancer incidence using annual average $PM_{2.5}$ concentrations, HR = 1.04 (95% CI: 0.94, 1.16). The results of both U.S.-based studies are consistent with Andersen et al. (2016) in Denmark within the Danish Nurse Cohort (DNC) study, which provided no evidence of an association between 3-year running mean of $PM_{2.5}$ concentrations and breast cancer incidence (HR = 1.00 [95% CI: 0.87, 1.14]). However, in a study conducted at much higher $PM_{2.5}$ concentrations (>30 μg/m^3) in Hong Kong, Wong et al. (2016) reported a positive association with breast cancer mortality (HR = 1.34 [95% CI: 1.12, 1.60]).

10.2.5.2.2 Brain Cancer

The examination of long-term $PM_{2.5}$ exposure and brain cancer consisted of studies focusing on both incidence (Jørgensen et al., 2016) and mortality (McKean-Cowdin et al., 2009). In the DNC study, which consisted of female nurses over the age of 44, Jørgensen et al. (2016) used a 3-year running average of $PM_{2.5}$ concentrations and found evidence of a weak positive association for brain tumor incidence (HR = 1.09 [95% CI: 0.72, 1.65]), but no evidence of an association when focusing on malignant brain tumors (HR = 0.97 [95% CI: 0.47, 2.05]). The lack of an association with brain cancer incidence was supported by the results of McKean-Cowdin et al. (2009), using the ACS-CPS II cohort, when examining brain cancer mortality. When using three different exposure metrics representing $PM_{2.5}$ concentrations from 1979−1983 (RR = 0.94 [95% CI: 0.87, 1.01]), 1999−2000 (RR = 0.98 [95% CI: 0.89, 1.09]), and the average of the two time periods (RR = 0.95 [95% CI: 0.86, 1.05]), the authors reported no evidence of an association with brain cancer mortality.

10.2.5.2.3 Liver Cancer

Recent studies conducted in Taiwan (Pan et al., 2016) and Europe (Pedersen et al., 2017) have examined the relationship between long-term $PM_{2.5}$ exposure and liver cancer incidence. Pan et al. (2016) within the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) cohort in Taiwan examined long-term $PM_{2.5}$ exposure based on 4-year average concentrations and liver cancer incidence on both the Main Islands and Penghu Islets. Additionally, the authors examined whether there was evidence of a direct or indirect effect of long-term $PM_{2.5}$ exposure on serum alanine transaminase (ALT) levels, which is a marker of chronic liver tissue inflammation, and subsequently liver cancer incidence. During the course of the study, new cases of liver cancer were identified during follow-up by pathological examination. Between the two locations, the distribution of $PM_{2.5}$ concentrations varied dramatically with an IQR of 0.73 μ/m^3 on the Penghu Islets and 13.1 μg/m^3 the Main Islands, therefore, results are not standardized to a 5 μg/m^3 increase, which as noted previously

is the convention for the rest of the epidemiologic study results for $PM_{2.5}$ presented within this section. Based on an IQR increase, Pan et al. (2016) reported a HR = 1.22 (95% CI: 1.02, 1.47) on the Penghu Islets and HR = 1.21 (95% CI: 0.95, 1.52) on the Main Islands. In the mediation analysis, there was evidence of an indirect effect of long-term $PM_{2.5}$ exposure on liver cancer incidence through elevated ALT levels, as well as some evidence of a potential direct effect. This initial evidence of a potential association between long-term $PM_{2.5}$ exposure and liver cancer is consistent with the results of Pedersen et al. (2017) in the ESCAPE study, which used a more rigorous exposure assignment method than Pan et al. (2016). Focusing on the two cohorts conducted in Denmark and Italy that reported $PM_{2.5}$ concentrations, the authors reported a positive association with new liver cancer cases diagnosed during follow-up (HR = 1.34 [95% CI: 0.76, 2.35]), but the 95% confidence intervals were large.

10.2.5.2.4 Leukemia

The association between long-term $PM_{2.5}$ exposure and incident leukemia was examined in cohorts consisting of children in Italy (Badaloni et al., 2013) and the U.S. (Heck et al., 2013), and adults in Canada (Winters et al., 2015). Badaloni et al. (2013) in the SETIL study (i.e., Study on the aetiology of lymphohematopoietic malignancies in children), examined incident leukemia in children ≤10 years of age in a case-control study. In quartile analyses using the entire cohort, as well as analyses limited to children between the ages of 0−4, and those children that did not change residence during the course of the study, the authors observed no evidence of an association between long-term $PM_{2.5}$ exposure and incident leukemia. Heck et al. (2013) examined incident childhood cancer (ages <6 years) from the California Cancer Registry. In a case-control study, the authors did not observe clear evidence of an association between $PM_{2.5}$ and acute lymphoblastic leukemia (OR = 1.06 [95% CI: 0.95, 1.18], n = 397) no evidence of an association with acute myeloid leukemia (OR = 0.90 [95% CI: 0.70, 1.16], n = 82). A similar result was observed by Winters et al. (2015) also using a case-control study design to examine incident leukemia in adults across Canadian provinces (except for Quebec and New Brunswick). The authors reported no evidence of an association between long-term $PM_{2.5}$ exposure and incident leukemia as well as chronic lymphocytic leukemia.

10.2.5.2.5 Multiple Cancers

Although most of the studies that examine long-term $PM_{2.5}$ exposure and cancer focused on specific cancer types, a few studies examined a number of different cancer types. Wong et al. (2016) in a study conducted in Hong Kong examined mortality attributed to a variety of cancers as detailed in Table 10-6. Within this study $PM_{2.5}$ concentrations were much higher (mean = 33.7 $\mu g/m^3$) compared to the other studies evaluated in this section. Across mortality outcomes attributed to cancer types, the authors observed strong positive associations (i.e., in terms of magnitude and precision) for all malignant,

all digestive organs, and female genital cancers with HRs ranging from 1.10 to 1.32. There was no evidence of an association for male genital, urinary, or lymphohematopoietic cancer mortality.

Whereas Wong et al. (2016) focused on cancer mortality, Heck et al. (2013) and Lavigne et al. (2017) examined incident childhood cancers in California and Ontario, Canada, respectively. Heck et al. (2013) in a case-control study, examined associations between $PM_{2.5}$ exposure during the entire pregnancy and childhood cancer (ages <6 years). There was not clear evidence of an association between $PM_{2.5}$ and cancer risk for any of the cancer sites except for retinoblastoma (OR = 1.33 [95% CI: 1.06, 1.67], n = 87). Lavigne et al. (2017) also examined multiple childhood cancers, but included cancer diagnoses up to age 14. In addition to examining exposures during the entire pregnancy, the authors also examined trimester specific exposures as well as those during the first year of life. Focusing on cancers with greater than 200 cases during the study period (i.e., acute lymphoblastic leukemia, astrocytoma, and Wilms tumor) the authors reported evidence of a number of positive associations across trimesters, the entire pregnancy, and the first year of life for each of these cancers, but 95% confidence intervals were large for all except astrocytoma (HR = 1.80 [95% CI: 1.09, 2.92] for the 1st trimester and HR = 1.68 [95% CI: 1.00, 2.89] for the entire pregnancy). These results are inconsistent with Heck et al. (2013), which also examined astrocytoma and found no evidence of an association with $PM_{2.5}$ exposure during the entire pregnancy.

10.2.5.2.6 Summary

Compared to the 2009 PM ISA, more recent studies have examined associations between long-term $PM_{2.5}$ exposure and cancer incidence and mortality beyond the respiratory system. Across the cancers examined, which includes breast cancer, brain cancer, liver cancer, and leukemia there is inconsistent evidence of an association with long-term $PM_{2.5}$ exposure. In addition to the cancers evaluated within this section, there are a few individual studies that examined ovarian cancer (Hung et al., 2012) and bladder cancer (Liu et al., 2009). Collectively, there are a small number of studies that examined other cancers and this evidence does not clearly depict an association between long-term $PM_{2.5}$ and cancer in other sites.

10.2.5.3 Cancer Survival

The majority of air pollution epidemiologic studies focusing on cancer tend to examine whether long-term exposures are associated with cancer incidence or mortality, as previously detailed within this section. Recently, studies have also examined whether exposure to air pollutants, such as $PM_{2.5}$, can have a detrimental impact on cancer survival. Study characteristics for the studies that examined cancer survival in response to long-term $PM_{2.5}$ exposures are detailed in Table 10-7.

Table 10-7 Study specific details and $PM_{2.5}$ concentrations from recent studies that examined cancer survival.

Study Location, Years, Data	Population/Cancer	Mean Concentration µg/m^3	Exposure Assessment	Results
†Xu et al. (2013) Los Angeles, CA; Honolulu, HI 1992−2008 SEER	58,586 respiratory cancer cases among whites LA: 56,193 Honolulu: 2,393	LA: 18.1 Honolulu: 4.3	Average of all monitors in the county where the case resided to calculate county-level monthly mean, each case assigned monthly mean concentration for each month after diagnosis.	Kaplan-Meier Survival Analysis: Higher mortality rate for respiratory cancer cases in areas with high $PM_{2.5}$ concentrations (LA) vs. low (Honolulu) Cox Proportional Hazards Model: Categorical analysis (LA only):[a] Overall mortality: HR = 1.07 (95% CI: 1.02, 1.13) Respiratory cancer mortality: HR = 1.08 (1.02, 1.14) Continuous variable analysis (per 5 µg/m^3): Overall mortality: HR = 1.57 (95% CI: 1.53, 1.61) Respiratory cancer mortality: HR = 1.49 (1.45, 1.53)

Table 10-7 (Continued): Study specific details and $PM_{2.5}$ concentrations from recent studies that examined cancer survival.

Study Location, Years, Data	Population/Cancer	Mean Concentration µg/m^3	Exposure Assessment	Results
†Eckel et al. (2016) 1988−2009[b] California CCR	352,053 lung cancer cases	13.7	Monthly average concentrations interpolated to residential address using IDW of up to four closest monitors within 50 km radius; however, cases excluded if nearest monitor was >25 km away. Each case assigned monthly mean for each month after diagnosis.	Cox Proportional Hazards Model (per 5 µg/m^3): All-cause mortality: HR = 1.15 (95% CI: 1.15, 1.16) Lung cancer mortality: HR = 1.14 (95% CI: 1.13, 1.15)
†Hu et al. (2013) California 1999−2009 CA SEER	255,128 female breast cancer cases	—	Average of all monitors in the county where the case resided to calculate county-level monthly mean, each case assigned monthly mean concentration for each month after diagnosis. Cases excluded if any missing PM data during any month.	Kaplan-Meier Survival Analysis: Higher mortality rate for breast cancer cases living in counties with high $PM_{2.5}$ concentrations vs. low Cox Proportional Hazards Model: Breast cancer mortality: Categorical analysis:[d] 11.64−15.04 µg/m^3: 1.24 (95% CI: 0.79, 1.94) ≥15.04 µg/m^3: 1.76 (95% CI: 1.24, 2.49) Continuous analysis (per 5 µg/m^3): HR = 1.86 (95% CI: 1.12, 3.10)

Table 10-7 (Continued): Study specific details and $PM_{2.5}$ concentrations from recent studies that examined cancer survival.

Study Location, Years, Data	Population/Cancer	Mean Concentration µg/m^3	Exposure Assessment	Results
†Deng et al. (2017) California 2000−2009 CCR	22,221 HCC liver cancer patients	Total: 13.3 Local: 12.9 Regional: 13.3 Distant: 14.0	Same approach as described in Eckel et al. (2016) above.	Kaplan-Meier Survival Analysis: Median survival (years) was higher for all-cause mortality for liver cancer patients overall, and specifically for local and regional stage patients. Cox Proportional Hazards Model: Categorical Analysis:[e] Overall Results: 10−15 µg/m^3: 15−20 µg/m^3: 1.18 (95% CI: 1.12, 1.24) 20−25 µg/m^3: 1.46 (95% CI: 1.36, 1.57) 25−30 µg/m^3: 2.40 (95% CI: 2.14, 2.69) ≥30 µg/m^3: 4.61 (95% CI: 3.87, 5.50) Continuous Analysis (per 5 µg/m^3): 1.18 (95% CI: 1.16, 1.20)

CA SEER = California Surveillance Epidemiology and End Results cancer registry; CCR = California Cancer Registry; HHC = hepatocellular carcinoma; SEER = Surveillance Epidemiology and End Results cancer registry.

[a]Honolulu cases were the referent, for both categorical and continuous analysis results are for the fully adjusted model.

[b]For $PM_{2.5}$ analysis, only cases diagnosed in 1998 or later included.

[c]Mean $PM_{2.5}$ concentration not reported, but study conducted categorical analysis with $PM_{2.5}$ tertiles of <11.64 µg/m^3, 11.64−15.04 µg/m^3, and ≥15.04 µg/m^3.

[d]11.64 µg/m^3 was the referent, results are for the fully adjusted mode.

[e]<10 µg/m^3 was the referent.

†Studies published since the 2009 PM ISA.

Xu et al. (2013) and Eckel et al. (2016) examined cancer survival by focusing on both the influence of $PM_{2.5}$ concentrations on overall survival as well as the risk of death or cancer-related death in individuals with any respiratory cancer or lung cancer, respectively. Xu et al. (2013) focused on two areas representative of high (Los Angeles) and low (Honolulu) $PM_{2.5}$ concentrations, while Eckel et al. (2016) focused specifically on whether lung cancer cases resided in areas with higher and lower $PM_{2.5}$ concentrations. In Xu et al. (2013) and Eckel et al. (2016), cancer survival was found to decrease in areas with higher $PM_{2.5}$ concentrations, which was further supported by the categorical analysis conducted in Xu et al. (2013) where there was evidence of increased risk of mortality among people with cancer when comparing the higher polluted area (Los Angeles) with the lower polluted area (Honolulu). Additionally, in analyses in both studies where $PM_{2.5}$ was included as a continuous variable there was evidence of positive associations between long-term $PM_{2.5}$ exposure and overall mortality and respiratory/lung cancer mortality (Table 10-7).

Additional evidence indicating a potential relationship between cancer survival and long-term $PM_{2.5}$ concentrations was provided by studies conducted in California that examined breast cancer survival (Hu et al., 2013) and liver cancer survival (Deng et al., 2017). Hu et al. (2013) reported evidence of higher breast cancer mortality in cases living in counties with higher $PM_{2.5}$ concentrations as well as a high overall risk of breast cancer death. In the study of liver cancer survival, Deng et al. (2017) observed an overall increase in the risk of all-cause mortality as well as evidence that mortality risk increases in liver cancer patients as $PM_{2.5}$ concentrations increased (Table 10-7). Both of these studies provide initial evidence that although long-term $PM_{2.5}$ exposure has not been associated with breast cancer incidence, and only a few studies have examined liver cancer incidence (see Section 10.2.5.3), underlying cancer may contribute to increasing the risk of death after diagnosis.

In addition to examining overall cancer survival, Eckel et al. (2016), Hu et al. (2013), and Deng et al. (2017) examined whether the stage of cancer diagnosis modified survival. In each of these studies there was initial evidence, through categorical analyses, of a nonlinear relationship between $PM_{2.5}$ exposure and cancer survival, where patients with less advanced cancer at diagnosis (i.e., local or regional) had lower survival if they resided in locations with higher compared to lower $PM_{2.5}$ concentrations (Table 10-7). This pattern of associations was not observed in patients diagnosed with distant (i.e., late) stage cancer likely due to the advanced stage of cancer and overall lower survival rate. Collectively, these studies provide initial evidence that exposure to long-term $PM_{2.5}$ concentrations may contribute to reduced cancer survival. However, caution is warranted in the interpretation of the results from these studies because they are all conducted in one location, California.

10.2.6 Associations between $PM_{2.5}$ Sources and Components and Cancer

As characterized throughout this ISA, PM itself is a complex mixture consisting of numerous individual components derived from a variety of sources (see Chapter 2). It has been well characterized over the years that a number of these individual components are mutagenic, and carcinogenic (Claxton and Woodall, 2007; Claxton et al., 2004). The 2009 PM ISA noted that animal toxicological studies did not focus on specific PM size fractions, but instead emissions from various sources. The 2009 PM ISA concluded that ambient urban PM, emissions from wood smoke and coal combustion, and gasoline exhaust and DE are mutagenic, while PAHs are genotoxic. This conclusion is consistent with previous studies that demonstrated ambient PM and PM from specific combustion sources are mutagenic and genotoxic (U.S. EPA, 2009). Recent studies examined specific $PM_{2.5}$ components and in some cases related those components to specific sources to evaluate whether individual $PM_{2.5}$ components or sources are more closely related to lung cancer mortality and incidence, as well as DNA methylation, than $PM_{2.5}$ mass.

Thurston et al. (2013) in the National Particle Component and Toxicity (NPACT) study, which focused on the ACS-CPS II cohort, examined associations with individual $PM_{2.5}$ components and lung cancer mortality, and only observed evidence of positive associations with Se, a coal combustion tracer, and S. The authors used factor analysis and absolute principal component analysis (APCA) to identify source-related groupings and source categories, respectively. The results of the factor and source-apportionment analyses, which found positive associations with a Coal Combustion source, are consistent with the single-pollutant $PM_{2.5}$ component analyses. Thurston et al. (2013) did not observe evidence of clear associations with lung cancer mortality for any of the other source categories or tracer elements. (quantitative results not presented). The ESCAPE study also examined associations between long-term exposure to $PM_{2.5}$ components and lung cancer mortality. Raaschou-Nielsen et al. (2016) examined associations with eight $PM_{2.5}$ components (Cu, Fe, K, Ni, S, Si, V, and Zn) estimated using LUR methods. Positive associations were observed with all $PM_{2.5}$ components (with the exception of V), albeit with wide confidence intervals, with HR ranging from 1.02 to 1.34 for an IQR increase in $PM_{2.5}$ component concentrations.

Instead of focusing on traditional $PM_{2.5}$ components, Weichenthal et al. (2016) in the CanCHEC cohort examined the association between $PM_{2.5}$ oxidative burden (the product of mass concentration and oxidative potential) and lung cancer mortality. Regional time-weighted $PM_{2.5}$ (2012−2013) average oxidative potential was assessed according to the ability of filter extracts to deplete glutathione and ascorbate in synthetic respiratory tract lining fluid (percent depletion/μg). As detailed previously, there was a positive association with $PM_{2.5}$ mass that was found to be stronger in terms of magnitude and precision when using the glutathione-related $PM_{2.5}$ oxidative burden exposure metric (HR per IQR change in $PM_{2.5}$ and glutathione-related oxidative potential = 1.12 [95% CI: 1.05, 1.19]). There was no

association with ascorbate-related $PM_{2.5}$ oxidative burden (HR per IQR change in $PM_{2.5}$ and ascorbate-related oxidative potential = 0.97 [95% CI: 0.93, 1.01]).

In addition to studies that examined associations between $PM_{2.5}$ components and lung cancer mortality and incidence, a few studies examined whether specific $PM_{2.5}$ components are more strongly related to DNA methylation. Madrigano et al. (2011) within the Normative Aging Study discussed previously, also examined associations between individual $PM_{2.5}$ components and DNA methylation. In addition to $PM_{2.5}$ mass, the authors also observed associations for a reduction in methylation when examining BC and SO_4, particularly in LINE-1, but 95% confidence intervals were large. Additional studies conducted within the Beijing Truck Driver Air Pollution Study cohort detailed previously, also examined the influence of individual $PM_{2.5}$ components on DNA methylation. Hou et al. (2014) examined whether specific $PM_{2.5}$ components (i.e., Al, Ca, Fe, K, S, Si, Ti, and Zn) altered methylation of the same tandem repeats examined in Guo et al. (2014). The authors observed when examining associations for 10% increase in each component that there was evidence of an increase in SATα methylation for S in office workers and in NBL2 methylation for Si and Ca in truck drivers. However, Hou et al. (2014) did not examine components that comprised a larger percentage of $PM_{2.5}$ mass. For example, both Si and Ca represented less than 2 and 1% of the total $PM_{2.5}$ mass exposure for truck drivers and office workers, respectively. The authors reported no evidence of associations with other elemental components (Al, K, Ti, Fe, and Zn) or a difference in the methylation of the tandem repeat D4Z4. Sanchez-Guerra et al. (2015) also examined the Beijing Truck Driver Air Pollution Study cohort, but as detailed above focused on methylation of both 5mC and 5hmC. The authors did not report any evidence of an increase in 5hmC for the components examined in Hou et al. (2014) as well as BC.

Overall, the studies that examined associations between long-term exposure to $PM_{2.5}$ components and sources and lung cancer mortality are consistent with previous evaluations that have indicated that components and sources related to combustion activities are mutagenic and genotoxic and provide biological plausibility for PM-related lung cancer incidence and mortality (U.S. EPA, 2009). Additionally, initial evidence indicates that $PM_{2.5}$ oxidative potential may be an important metric to consider in the future. The limited number of studies that examined associations between exposure to $PM_{2.5}$ components and DNA methylation as well as the limited number of components examined, did not provide consistent evidence that any one component altered DNA methylation.

10.2.7 Summary and Causality Determination

It has been well characterized in toxicological studies that ambient air has mutagenic properties (Claxton et al., 2004) and that extracts of PM from ambient air have carcinogenic properties (Claxton and Woodall, 2007). However, at the completion of the 2009 PM ISA, little information was available from studies employing specific PM size fractions, such as $PM_{2.5}$, or inhalation exposure. The evidence indicating that PM was both a mutagen and carcinogen was supported by epidemiologic evidence of

primarily positive associations in studies of lung cancer mortality, with limited evidence for lung cancer incidence and other cancers. Since the 2009 PM ISA, a larger number of cohort studies using both traditional and more refined exposure assignment approaches provide evidence that primarily consists of positive associations between $PM_{2.5}$ exposure and both lung cancer mortality and lung cancer incidence, which is supported by subset analyses focusing on never smokers. In addition, $PM_{2.5}$ exhibits several key characteristics of carcinogens (Smith et al., 2016), as shown in toxicological studies demonstrating genotoxic effects, oxidative stress, electrophilicity, and epigenetic alterations, with supportive evidence provided by epidemiologic studies. Furthermore, $PM_{2.5}$ has been shown to act as a tumor promoter in a rodent model of urethane-initiated carcinogenesis. This biological plausibility, in combination with the epidemiologic evidence for $PM_{2.5}$ and lung cancer mortality and incidence, contributes to the conclusion of a likely to be causal relationship between long-term $PM_{2.5}$ exposure and cancer. This section describes the evaluation of evidence for cancer, with respect to the causality determination for long-term exposure to $PM_{2.5}$ using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015). The key evidence, as it relates to the causal framework, is summarized in Table 6-34.

Table 10-8 Summary of evidence for a likely to be causal relationship between long-term $PM_{2.5}$ exposure and cancer.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{2.5}$ concentrations	Increases in lung cancer mortality and incidence in cohort studies conducted in the U.S., Canada, Europe, and Asia. Supported by subset analyses reporting positive associations in never smokers.	Section 10.2.5.1.1 Figure 10-3	Annual: U.S. and Canada: 6.3−23.6 Europe: 6.6−31.0 Asia: 33.7 Table 10-4
Limited epidemiologic evidence from copollutant models for an independent $PM_{2.5}$ association	Potential copollutant confounding for lung cancer mortality and incidence examined in a few studies with initial evidence that associations remained robust in models with O_3, with more limited information for other gaseous pollutants and particle size fractions.	Section 10.2.5.1.3	—
Epidemiologic evidence supports a linear, no-threshold concentration-response (C-R) relationship	Recent multicity studies conducted in the U.S., Canada, and Europe provide evidence of a linear, no-threshold C-R relationship for annual $PM_{2.5}$ concentrations observed within the U.S., but extensive systematic evaluations of alternatives to linearity have not been conducted.	Section 10.2.5.1.4	—

Table 10 8 (Continued): Summary of evidence for a likely to be causal relationship between long term $PM_{2.5}$ exposure and cancer.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Extensive evidence for biological plausibility	Experimental studies provide evidence for oxidative stress in human subjects while in vivo inhalation studies in rodents indicate oxidative DNA damage and methylation of a tumor suppressor gene promotor in the lung, upregulation of enzymes involved in biotransformation, and tumor promotion in a model of urethane-induced tumor initiation. Studies conducted in vitro show formation of DNA adducts, DNA damage, formation of micronuclei, oxidative stress, altered methylation of repetitive elements and miRNAs, increased telomerase activity, mutagenicity, and increased metastatic potential. Additionally, there is supporting epidemiologic evidence for micronuclei formation.	Liu et al. (2015) Soberanes et al. (2012) Yoshizaki et al. (2016) Cangerana Pereira et al. (2011) Section 10.2.1 Section 10.2.2 Section 10.2.3 Section 10.2.4 Section 10.2.5	238 µg/m^3 100−120 µg/m^3 594 µg/m^3 17.66 µg/m^3
Coherence of cancer-related effects across disciplines	Epidemiologic evidence that is coherent with experimental evidence for DNA adduct formation, DNA damage, cytogenetic effects, and altered DNA methylation	Li et al. (2014); Rossner et al. (2013b) Chu et al. (2015) Rossner et al. (2011) O'Callaghan-Gordo et al. (2015) Section 10.2.3	115.4 12.0−78.9 68.4−146.6 26.1−28.4 14.4

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

Experimental and epidemiologic studies provide evidence indicating the potential role of $PM_{2.5}$ exposure in genotoxicity through an examination of cancer-related biomarkers, such as mutagenicity, DNA damage, and cytogenetic endpoints. Decades of research has laid a foundation supporting the mutagenic potential of PM. It has been clearly demonstrated in the Ames *Salmonella*/mammalian-microsome mutagenicity assay that PM contains mutagenic agents (Section 10.2.2.1). Although mutagenicity does not necessarily equate to carcinogenicity, the ability of PM to elicit mutations provides support for observations of an association with lung cancer mortality and incidence in epidemiologic studies. Both in vitro and in vivo toxicological studies indicate the potential for $PM_{2.5}$ exposure to result in DNA damage (Section 10.2.2.2), which is supported by limited evidence from epidemiologic panel studies (Chu et al., 2015) and findings of oxidative stress in a controlled human exposure study (Liu et al., 2015). When examining cytogenetic effects, a limited number of epidemiologic

and toxicological studies provides coherence for micronuclei formation and chromosomal abnormalities (Section 10.2.2.3). Additionally, there was limited evidence for differential expression of genes that may be relevant to cancer pathogenesis. Across scientific disciplines, a broad array of biomarkers of genotoxicity were examined, which complicates the assessment of whether there was evidence for coherence of effects, but overall these studies provide some evidence of a relationship between $PM_{2.5}$ exposure and genotoxicity. Similarly, experimental and epidemiologic studies that examined epigenetic effects indicate changes in methylation, both hyper- and hypomethylation, globally as well as in some specific genomic sites, providing some support for $PM_{2.5}$ exposure contributing to genomic instability (Section 10.2.3). Toxicological evidence that the promoter region of a tumor suppressor gene, p16, was methylated in lung tissue as a result of inhalation exposure to $PM_{2.5}$ is consistent with one of the hallmarks of cancer (Hanahan and Weinberg, 2000); (Hanahan and Weinberg, 2011), i.e., the evading of growth suppressors (Section 10.2.3.1).

The experimental and epidemiologic evidence for genotoxicity and mutagenicity, as well as epigenetic effects, provides biological plausibility for a relationship between exposure to $PM_{2.5}$ and cancer development. In addition, $PM_{2.5}$ exposure enhanced tumor formation in an animal model of urethane-induced tumor initiation (Cangerana Pereira et al., 2011). This study supports a role for $PM_{2.5}$ exposure in tumor promotion, which is a measure of carcinogenic potential. Further substantiating the link between $PM_{2.5}$ exposure and cancer development are epidemiologic studies demonstrating primarily consistent positive associations between long-term $PM_{2.5}$ exposure and lung cancer mortality and incidence across studies using different exposure assignment methods (Section 10.2.5.1). The evidence of $PM_{2.5}$-related lung cancer mortality and incidence is further supported by a number of studies that examined associations by smoking status and reported generally positive associations in never smokers. Across studies, potential confounding by smoking status and exposure to SHS was adequately controlled through either direct measures of smoking status or by using proxy measures to adjust for smoking. Of those studies that did not report evidence of a positive association, only Lipsett et al. (2011) in the CTS cohort examined associations by smoking status for lung cancer mortality and also reported evidence of a positive, albeit imprecise, association in never smokers. A number of the studies focusing on lung cancer incidence examined associations by histological subtype, which allows for an assessment of adenocarcinoma, the only lung cancer subtype found in nonsmokers. Across studies that examined histological subtypes, there was some evidence of positive associations with adenocarcinomas, but associations were imprecise (i.e., wide confidence intervals) and often also observed for other subtypes.

A limited number of recent lung cancer mortality and incidence studies conducted analyses to assess potential copollutant confounding and reported that $PM_{2.5}$ associations were relatively unchanged in models with O_3. However, there was a more limited assessment of potential copollutant confounding by other gaseous pollutants and particle size fractions (Section 10.2.5.1.3). Recent assessments of the C-R relationship between long-term $PM_{2.5}$ exposure and lung cancer mortality and incidence provide evidence of a linear, no-threshold relationship, specifically at concentrations representative of the lowest cut-point examined in studies, 9−11.8 $\mu g/m^3$, and where analyses of the C-R curve depict a widening of confidence

intervals, ≈6 μg/m^3. However, in assessing the C-R relationship, epidemiologic studies have not conducted empirical evaluations of potential alternatives to linearity (Section 10.2.5.1.4).

In addition to lung cancer mortality and incidence, a number of recent studies examined cancers of other sites including breast cancer, brain cancer, liver cancer, and leukemia. Across the studies, the evidence does not clearly depict an association with other types of cancers (Section 10.2.5.2). However, emerging evidence examining cancer survival in people diagnosed with various stages of different types of cancers including respiratory cancer, lung cancer, breast cancer, and liver cancer indicate that long-term $PM_{2.5}$ exposure may contribute to reduced cancer survival, particularly in individuals with less advanced cancer diagnoses (Section 10.2.5.3).

Collectively, experimental and epidemiologic studies provide evidence for a relationship between $PM_{2.5}$ exposure and genotoxicity, epigenetic effects, and carcinogenic potential. Uncertainties exist due to the lack of consistency in specific cancer-related biomarkers associated with $PM_{2.5}$ exposure across both experimental and epidemiologic studies, however $PM_{2.5}$ exhibits several characteristics of carcinogens. This provides biological plausibility for $PM_{2.5}$ exposure contributing to cancer development. **Overall, the combination of this evidence is sufficient to conclude that a causal relationship is likely to exist between long-term $PM_{2.5}$ exposure and cancer**.

10.3 $PM_{10-2.5}$ Exposure and Cancer

The 2009 PM ISA concluded that the overall body of evidence was "inadequate to assess the relationship between long-term $PM_{10-2.5}$ exposures and cancer" (U.S. EPA, 2009).[77] This conclusion was based on the lack of epidemiologic studies that examined $PM_{10-2.5}$ exposure and cancer in both the 2004 PM AQCD and the 2009 PM ISA.

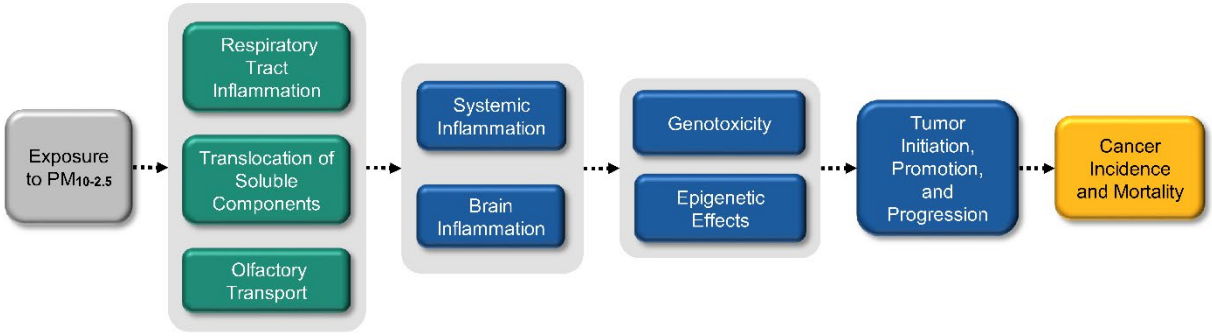
Consistent with the 2009 PM ISA, there remains a limited number of both experimental and epidemiologic studies that examined $PM_{10-2.5}$ exposure and whether it can lead to mutagenicity, genotoxicity, and carcinogenicity, as well as to cancer mortality. Although there is some evidence that $PM_{10-2.5}$ exposure can lead to changes in cancer-related biomarkers, there is a lack of epidemiologic evidence to support the continuum of effects to cancer incidence and mortality. The following sections evaluate studies published since completion of the 2009 PM ISA that focus on the mutagenicity, genotoxicity, and capability of long-term exposures to $PM_{10-2.5}$ to induce epigenetic changes all of which may contribute to cancer incidence and mortality.

[77] As detailed in the Preface, risk estimates are for a 5 μg/m^3 increase in annual $PM_{10-2.5}$ concentrations unless otherwise noted.

10.3.1 Biological Plausibility

This section describes biological pathways that potentially underlie the development of cancer resulting from exposure to $PM_{10-2.5}$. Figure 10-8 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" exposure to $PM_{10-2.5}$ may lead to the development of cancer contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 10.3.

Once $PM_{10-2.5}$ deposits in the respiratory tract, it may be retained, cleared, or solubilized (see Chapter 4). $PM_{10-2.5}$ and its soluble components may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate ROS and this capacity is termed "oxidative potential". Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see Chapter 4). Immune system responses due to the presence of particles in the interstitial space may contribute to chronic health effects. Inflammatory mediators may diffuse from the respiratory tract into the systemic circulation and lead to inflammation in extrapulmonary compartments (see Chapter 6). Although $PM_{10-2.5}$ is mostly insoluble, it may contain some soluble components such as endotoxin and metals. Soluble components of $PM_{10-2.5}$ may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments. A fraction of $PM_{10-2.5}$ may deposit on the olfactory epithelium. Soluble components of $PM_{10-2.5}$ may be transported via the olfactory nerve to the olfactory bulb of the brain. The extent to which translocation into the systemic circulation or transport to the olfactory bulb occurs is currently uncertain. For further discussion of translocation and olfactory transport, see Chapter 4. The potential contribution of olfactory transport to brain inflammation or to upregulation of gene expression in the brain is discussed in Chapter 8.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 10-8 Potential biological pathways for the development of cancer following exposure to $PM_{10-2.5}$.

Evidence is accumulating that exposure to $PM_{10-2.5}$ may lead to carcinogenesis by a genotoxic pathway that may result in mutational events or chromosomal alterations. Carcinogenesis due to dysregulated growth may follow. Compared with $PM_{2.5}$, there is less evidence that $PM_{10-2.5}$ exhibits characteristics of carcinogens (Smith et al., 2016). However, exposure to $PM_{10-2.5}$ has been shown to result in genotoxic effects and to induce oxidative stress. Currently, epidemiologic evidence is limited to studies linking $PM_{10-2.5}$ exposure to lung cancer incidence. Evidence for these pathways and cancer-related biomarkers is described below.

Genotoxicity

Genotoxicity may occur as a result of DNA damage and subsequent introduction of mutations into the genome, and as a result of cytogenetic effects at the level of the chromosome. $PM_{10-2.5}$ exposure is associated with mutagenicity, DNA damage, and cytogenetic effects. Oxidative stress is one mechanisms involved in genotoxicity resulting from $PM_{2.5}$ exposure.

Mutations are considered biomarkers of early biological effect (Demetriou et al., 2012). Indirect evidence is provided by the Ames *Salmonella*/mammalian-microsome mutagenicity assay in one study. It can identify the presence of species that can result in mutations as the result of direct interactions with DNA as well as those that require metabolic activation to elicit genotoxicity. As the most widely accepted theory of cancer etiology is the accumulation of mutations in critical genes, the presence of mutagens within PM provides biological plausibility for observations made in epidemiological studies. While this assay has several technical limitations and is criticized due to its use of bacteria as a model species, four

decades of published results from this assay have clearly demonstrated the presence of mutagenic agents in PM collected from ambient air (U.S. EPA, 2009). A new study published since the 2009 PM ISA provides evidence to support mutagenicity resulting from $PM_{10–2.5}$ exposure (Kawanaka et al., 2008).

DNA damage is a biomarker of genotoxicity (Demarini, 2013). Evidence of DNA damage following $PM_{10–2.5}$ exposure was found using the comet assay in in vitro toxicological studies (Jalava et al., 2015; Wessels et al., 2010). The identification of oxidized DNA bases suggests a role for oxidative stress in the DNA lesions. These oxidized DNA nucleobases are considered a biomarker of exposure (Demetriou et al., 2012). Exposure to PM can result in oxidative stress either through the direct generation of ROS, or indirectly, through the induction of inflammation. Other in vitro studies demonstrated an increase in ROS production as a result of exposure to $PM_{10–2.5}$ (Section 10.3.2). A study in human subjects also found increased oxidized DNA bases in urine in association with $PM_{10–2.5}$ exposure (Liu et al., 2015). The presence of oxidative stress-mediated DNA lesions and adducts can lead to the introduction of fixed mutations into the genome after incorrect repair of the damaged base or replication past the base by low fidelity DNA polymerases. The potential for oxidative stress to result in mutagenesis is underscored by the DNA repair mechanisms that have evolved to protect the genome from mutagenesis caused by these lesions.

Cytogenetic effects, such as micronuclei formation and chromosomal aberrations, are biomarkers of genotoxicity (Demarini, 2013). Micronuclei are nuclei formed as a result of chromosomal damage, while chromosomal aberrations are modifications of the normal chromosome complement (Demetriou et al., 2012). Epidemiologic studies provide supportive evidence of micronuclei formation in association with $PM_{10–2.5}$ exposure (O'Callaghan-Gordo et al., 2015).

Summary of Biological Plausibility

As described here, there is one proposed pathway by which exposure to $PM_{10–2.5}$ may lead to the development of cancer. It involves genotoxicity, including DNA damage that may result in mutational events and cytogenetic effects that may result in effects at the level of the chromosome. While experimental studies in animals and humans contribute most of the evidence of upstream events, epidemiologic studies found associations between exposure to $PM_{10–2.5}$ and micronuclei formation. This proposed pathway provides biological plausibility for epidemiologic results of cancer incidence and mortality and will be used to inform a causality determination, which is discussed later in the chapter (Section 10.3.4).

10.3.2 Genotoxicity

In the 2009 PM ISA, there were a limited number of epidemiologic studies that examined molecular and cellular markers often associated with cancer, which includes both DNA damage and

cytogenetic effects. No studies specifically examined the effects of exposure to $PM_{10-2.5}$. Recent experimental and epidemiologic studies provide a limited body of evidence for genotoxicity due to $PM_{10-2.5}$ exposure.

10.3.2.1 Toxicological Evidence

Very few studies evaluating the genotoxicity and carcinogenicity of $PM_{10-2.5}$ have been published since the 2009 PM ISA. More common are reports detailing the effects in response to PM_{10}. However, as given the scope of the current ISA, only studies detailing the effects of $PM_{10-2.5}$ exposure are summarized here. While the Ames *Salmonella*/mammalian-microsome mutagenicity test was the most common method for analysis of genotoxicity in response to $PM_{2.5}$, the use of human cell culture and other in vitro assays were the primary method for the study of $PM_{10-2.5}$. No new studies published since the 2009 PM ISA that evaluated endpoints related to epigenetic changes in response to ambient air $PM_{10-2.5}$ exposure were identified.

Kawanaka et al. (2008) investigated the mutagenicity of roadside PM organic extracts from Saitama City, Japan. Using a cascade impactor, 12 fractions of varying aerodynamic diameters were collected including $PM_{10-2.5}$ (<0.12, 0.12−0.20, 0.20−0.30, 0.30−0.50, 0.70−1.2, 1.2−2.1, 2.1−3.5, 3.5−5.2, 5.2−7.8, 7.8−11, >11 μm). The authors used the *Salmonella* assay to determine the mutagenic activity of each fraction as well as GC/NCI/MS/MS and known quantities of select nitroaromatic compounds to determine the mass contribution of those compounds to the total PM collected and to estimate the contribution of each species to the total mutagenicity, respectively. Using this approach, it was reported that quantity of nitro-PAHs per unit mass in the ultrafine fraction was greater than that of $PM_{2.5}$ or $PM_{10-2.5}$. In addition, the authors determined that mutagenicity per unit mass of $PM_{10-2.5}$ was less than that of UFP (both TA98 and YG1024 S. Typhimurium strains) and that, of the six nitroaromatic compounds evaluated, the contribution to mutagenic activity calculated was greatest for 1,8-dinitropyrene in all three fractions of PM extracts evaluated. As a result of the variability of the *Salmonella* assay as well as incomplete details regarding the statistical analysis of the data collected, it is difficult to calculate definitive values for these contributions.

Jalava et al. (2015) used the alkaline comet assay to measure DNA damage after exposure to PM suspensions in mouse macrophages (RAW 264.7). They evaluated four size fractions including $PM_{10-2.5}$ collected at Nanjing University in China. The authors observed an increase in damage compared with controls ($p \leq 0.05$), however, the increase was observed only following exposure to the PM suspension of greatest concentration.

Wessels et al. (2010) also characterized the effect of exposure to $PM_{10-2.5}$ in cultured human cells. To represent and compare diverse PM mixture profiles, the authors collected PM from four locations including a rural location and three urban locations that varied in the extent to which vehicle traffic would contribute to the PM mixture sampled. Five size fractions were collected and that with the largest

particles comprised PM with aerodynamic diameters in the range of 3−7 μm. To evaluate the genotoxicity of aqueous PM suspensions, human lung carcinoma epithelial cells (A549) were cultured and used in the formamido-pyrimidine-glycosylase (fpg)-modified comet assay. No differences were observed in the amount of DNA damage induced after exposure to $PM_{10–2.5}$ collected from any of the urban locations compared to that of equal mass collected from the rural location. This is in contrast to the smaller diameter fractions collected for which more DNA damage was observed for several of the urban roadside PM suspension exposures compared to PM collected from the rural site. In addition, the authors determined that, after adjusting for sampling site, the amount of DNA damage measured in response to exposure to different particle size fractions was similar.

Mirowsky et al. (2015), investigated the effects of exposure to aqueous suspensions of both soluble and insoluble material from $PM_{10–2.5}$ as well as $PM_{2.5}$ collected at two rural and three urban sites in California. Using cultured human pulmonary microvasculature endothelial cells (HPMEC-ST11.6R), they measured ROS with 2′,7′-dichlorofluorescein diacetate (DCFH-DA). DCFH-DA, after removal of the acetate groups by cellular esterases, can be oxidized to highly fluorescent DCF that can then be used to quantify the amount of intracellular ROS. The results identified two variables. That is, both the size fraction and location at which the PM was collected can affect the amount of intracellular ROS generated after exposure to aqueous PM suspension. Suspensions from $PM_{10–2.5}$ collected at urban sites were characterized by greater ROS activity than those from $PM_{2.5}$ collected at the same sites ($p < 0.001$). The same disparity was not observed, however, between the $PM_{10–2.5}$ and $PM_{2.5}$ suspensions from the rural sites as the ROS activity generated by both was similar. When comparing the same size fractions between urban and rural sites, greater ROS activity was observed in experiments with $PM_{10–2.5}$ from the urban sites than $PM_{10–2.5}$ collected at the rural sites, while there was not any difference reported between sites for the $PM_{2.5}$ suspensions (*p*-value not provided).

In the same study, Mirowsky et al. (2015) also used oropharyngeal aspiration to assess the response to aqueous PM suspension exposure in mice (FVB/N). As inflammation and ROS generated by infiltrating polymorphonuclear cells (PMNs) has also been proposed as a pathway that may result in genotoxicity, the authors compared the effect of exposure on the percent of PMNs in lavage fluid for the various sampling locations and PM size fractions. With the exception of one rural location, the increase in percentage of PMNs engendered by exposure to $PM_{10–2.5}$ suspensions was greater than that after exposure to $PM_{2.5}$ ($p < 0.001$).

Gordon et al. (2013) also used the DCFA-FA assay to assess intracellular ROS after exposure to PM. The authors exposed BEAS-2B and HBEpC cells to suspensions of size-fractionated PM from ambient air collected from five diverse sampling locations across the U.S. The PM size fractions collected were described as $PM_{2.5–0.2}$, $PM_{10–2.5}$, and $PM_{0.2}$. Similar to several other findings already highlighted, the authors reported variation in ROS production as a result of sampling site, season, and particle size and noted that exposure to $PM_{10–2.5}$ resulted in ROS production that was less than that of the ultrafine fraction, but greater than that of $PM_{2.5}$ on an equal mass exposure when sampling locations were combined.

10.3.2.2 Evidence from Controlled Human Exposure Studies

A controlled human exposure study by Liu et al. (2015) measured MDA in blood and urine and 8-oxo-dG in urine. The former is a lipid peroxidation product capable of reacting with DNA bases, while the latter is excreted after oxidized dGTP molecules in cellular dNTP pools used for nuclear and mitochondrial DNA replication throughout the cell are acted upon by MTH1 followed by 8-oxo-dGMPase in the process of dNTP pool sanitization. In this single-blind randomized crossover study, nonsmoking adults were exposed for 130 minutes to $PM_{10–2.5}$, $PM_{2.5}$, and UFP CAPs drawn from a downtown street in Toronto, Canada. Participant blood and urine were collected before exposure and after exposure at two-time points (1 hour, 21 hour). A positive association was observed between urinary 8-oxo-dG concentration and concentration of $PM_{10–2.5}$ ($p < 0.1$) at 1-hour post-exposure. Urinary creatinine was used to normalize biomarker concentrations. No association was observed between blood MDA concentration and $PM_{10–2.5}$ concentration.

10.3.2.3 Epidemiologic Evidence

In the Rhea cohort previously detailed in Section 10.2.2, the frequency of micronuclei was examined in 136 mother-child pairs in Crete, Greece (O'Callaghan-Gordo et al., 2015). Within the study, $PM_{10–2.5}$ concentrations (median = 22.5 μg/m^3) were estimated by taking the difference between PM_{10} and $PM_{2.5}$ from monitors at the same location. The pattern of associations observed for exposure to $PM_{10–2.5}$ and micronuclei frequency was similar to that for $PM_{2.5}$, but the magnitude of the association was smaller for $PM_{10–2.5}$. Overall, there was some evidence of a higher micronuclei frequency in maternal blood for an exposure over the entire pregnancy (RR = 1.14 [95% CI 0.94−1.38]), but no evidence of an association for cord blood (RR = 0.96 [95% CI 0.79−1.17]) (O'Callaghan-Gordo et al., 2015). Similar to $PM_{2.5}$, when stratifying by smoking status, an association larger in magnitude was observed in smoking mothers (RR = 1.4 [95% CI: 0.94, 2.1]) compared to nonsmokers (RR = 1.1 [95% CI: 0.86, 1.3]), but 95% confidence intervals crossed the null for both. Additionally, there was evidence that the association between $PM_{10–2.5}$ and micronuclei frequency was increased among women with a lower intake of vitamin C during pregnancy (i.e., <85 ng/day).

10.3.2.4 Summary of Genotoxicity

Evidence that $PM_{10–2.5}$ exposure induces mutagenicity, DNA damage, oxidative DNA damage, and oxidative stress is provided by a limited number of in vitro animal toxicological studies and a single controlled human exposure study. Liu et al. (2015) found oxidative DNA damage following an approximately 2-hour exposure of human subjects to $PM_{10–2.5}$, with rapid but transient increase in a urine biomarker. The tissue source of this marker cannot be discerned so it is unclear where in the body the

DNA damage occurred. Additionally, an epidemiologic study reported evidence of increased micronuclei formation in relation to $PM_{10-2.5}$ exposure (O'Callaghan-Gordo et al., 2015).

10.3.3 Cancer Incidence and Mortality

10.3.3.1 Lung Cancer

At the completion of the 2009 PM ISA, no epidemiologic studies had been conducted that examined the association between long-term $PM_{10-2.5}$ exposure and cancer. Since then, a few studies have examined cancer, but overall the body of evidence is small. As detailed previously, additional studies have examined the overall relationship between long-term exposure to PM and lung cancer by focusing on PM_{10}. However, these PM_{10} studies are not the focus of this evaluation due to their inability to attribute any cancer effects to a specific PM size fraction, such as $PM_{10-2.5}$. A full list of PM_{10} and lung cancer mortality and incidence studies are available at: https://hero.epa.gov/hero/particulate-matter.

10.3.3.1.1 Lung Cancer Incidence

Recent studies that examined the association between long-term $PM_{10-2.5}$ exposure and lung cancer are limited to studies of lung cancer incidence. There were no epidemiologic studies that examined exposures to $PM_{10-2.5}$ and lung cancer mortality. In addition to examining $PM_{10-2.5}$, the studies by Raaschou-Nielsen et al. (2013) in the ESCAPE study and Puett et al. (2014) in the NHS cohort also examined associations with $PM_{2.5}$ as detailed in Section 10.2.2. Study specific details including $PM_{10-2.5}$ concentrations, study population, and exposure assignment approach are presented in Table 10-9.

Table 10-9 Study specific details and $PM_{10-2.5}$ concentrations from recent studies that examined lung cancer incidence.

Study Years	Cohort Location	Years Air Quality/Follow-up	Events/Population	Mean Concentration µg/m³	Exposure Assessment
Lung cancer incidence					
North America					
†Puett et al. (2014)	NHS (U.S.)	$PM_{10-2.5}$: 1988−2007 Follow-up: 1994−2010	Cases: 2,155 Pop: 103,650	8.5[a]	GIS-based spatiotemporal model to each residential address as detailed in Yanosky et al. (2008); $PM_{10-2.5}$ calculated by subtracting monthly PM_{10} and $PM_{2.5}$ estimates
Europe					
†Raaschou-Nielsen et al. (2013)	ESCAPE (Europe)	$PM_{10-2.5}$: 2008−2011 Follow-up: 1990s[b]	Cases: 2,095 Pop: 312,944	Across sites: 4.0−20.8	LUR at geocoded addresses as detailed in Eeftens et al. (2012a); $PM_{10-2.5}$ calculated as the difference between PM_{10} and $PM_{2.5}$ estimates

ESCAPE = European Study of Cohorts for Air Pollution Effects; GIS = Geographic Information System; LUR = Land-Use Regression; NHS = Nurses' Health Study.

[a]Overall 72-mo cumulative average $PM_{10-2.5}$ concentration.

[b]Only 14 or the 17 cohorts were examined for lung cancer, of the cohorts examined initial recruitment started generally in the 1990s with an average follow-up time of 12.8 years.

†Studies published since the 2009 PM ISA.

Both Raaschou-Nielsen et al. (2013) and Puett et al. (2014) estimated $PM_{10-2.5}$ concentrations by subtracting the difference between LUR estimates of PM_{10} and $PM_{2.5}$. As detailed in Section 3.3.2.3, estimating $PM_{10-2.5}$ concentrations by subtracting modeled PM_{10} and $PM_{2.5}$ estimates do not result in the same issues that could occur when subtracting PM_{10} and $PM_{2.5}$ concentrations from collocated monitors. In the ESCAPE study Raaschou-Nielsen et al. (2013) reported an imprecise positive association with $PM_{10-2.5}$ (HR = 1.09 [95% CI 0.88, 1.33]). Puett et al. (2014) in the NHS cohort, which consisted only of women, also reported an imprecise positive association with lung cancer incidence (HR = 1.02 [95% CI: 0.96, 1.10]). Compared to the $PM_{2.5}$ results in both studies, the magnitude of the association was similar for Puett et al. (2014), but for Raaschou-Nielsen et al. (2013) the $PM_{2.5}$ effect was larger in magnitude and more indicative of a relationship with lung cancer incidence.

For Raaschou-Nielsen et al. (2013), unlike the analysis of $PM_{2.5}$ that examined a subset of the cohort that did not change residence during follow-up, a sensitivity analysis was not conducted for $PM_{10-2.5}$ to assess the potential influence of exposure measurement error. Additionally, an analysis by

histological cancer subtype was not conducted for $PM_{10–2.5}$. However, Puett et al. (2014) in the NHS cohort examined associations by smoking status and histological cancer subtype. The authors observed that the association between long-term $PM_{10–2.5}$ exposure and lung cancer incidence was larger in magnitude among never smokers, but 95% confidence intervals were still large (HR = 1.05 [95% CI: 0.86, 1.30]). When focusing specifically on those lung cancer cases defined as adenocarcinoma in the full cohort, the magnitude of the association was larger (HR = 1.11 [95% CI: 0.94, 1.30]) than that observed when focusing on all lung cancer incidence cases.

10.3.3.2 Other Cancers

A few recent studies have examined associations between long-term $PM_{10–2.5}$ exposure and cancer incidence and mortality beyond the respiratory system. This includes individual studies examining breast cancer (Hart et al., 2016) and liver cancer (Pedersen et al., 2017) that reported positive associations, (HR = 1.03 [95% CI: 0.96, 1.10]) and (HR ranging from 1.26−1.86 depending on the ESCAPE cohort), respectively, but with large 95% confidence intervals. Collectively, there are a limited number of studies that examined other cancers and this evidence does not clearly depict an association between long-term $PM_{10–2.5}$ and other cancer sites.

10.3.3.3 Summary

Overall, there is limited evidence of a positive association between long-term $PM_{10–2.5}$ exposure and lung cancer incidence, with no studies examining lung cancer mortality. In both studies that examined lung cancer incidence, $PM_{10–2.5}$ concentrations were estimated by taking the difference between PM_{10} and $PM_{2.5}$ estimates, but these estimates were derived from an LUR model (see Section 3.3.2.3). A few recent studies examined associations with cancers in other sites, but the limited number of studies prevents a full assessment of the relationship between long-term $PM_{10–2.5}$ exposure and cancers in other sites.

10.3.4 Summary and Causality Determination

It has been well characterized in toxicological studies that ambient air has mutagenic properties (Claxton et al., 2004) and that extracts of PM from ambient air have carcinogenic properties (Claxton and Woodall, 2007). However, at the completion of the 2009 PM ISA, little information was available from studies employing specific PM size fractions, such as $PM_{10–2.5}$, or inhalation exposure. Since the 2009 PM ISA, the assessment of long-term $PM_{10–2.5}$ exposure and cancer remains limited with a few recent epidemiologic studies of large and diverse cohorts providing evidence of imprecise positive associations of $PM_{10–2.5}$ with lung cancer incidence. However, uncertainty remains with respect to exposure measurement error due to the methods employed to estimate $PM_{10–2.5}$ concentrations (Section 3.3.2.3),

specifically the use of $PM_{10-2.5}$ predictions that have not been validated by monitored $PM_{10-2.5}$ concentrations. Experimental studies are more limited in number compared with the evaluation of $PM_{2.5}$ and consist of a controlled human exposure study and several in vitro animal toxicological studies demonstrating DNA damage, oxidative stress, and mutagenicity. $PM_{10-2.5}$ exhibits two key characteristics of carcinogens (Smith et al., 2016), as shown in experimental studies demonstrating genotoxic effects and oxidative stress, providing some biological plausibility for epidemiologic findings. The small number of epidemiologic and experimental studies. along with the uncertainty with respect to exposure measurement error, contribute to the determination of the relationship between long-term $PM_{10-2.5}$ exposure and cancer using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015). The key evidence, as it relates to the causal framework, is summarized in Table 10-10. **Overall, the evidence is suggestive of, but not sufficient to infer, a causal relationship between long-term $PM_{10-2.5}$ exposure and cancer**.

Table 10-10 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between long-term $PM_{10-2.5}$ exposure and cancer.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
A limited body of epidemiologic evidence at relevant $PM_{10-2.5}$ concentrations	Positive, but imprecise, increases in lung cancer incidence in a few studies conducted in North America and Europe.	Section 10.3.3.1	U.S.: 8.5 Europe: 4.0−20.8
Uncertainty regarding exposure measurement error	$PM_{10-2.5}$ concentrations estimated by taking the difference between LUR modeled PM_{10} and $PM_{2.5}$ concentrations. Uncertainty remains because $PM_{10-2.5}$ predictions are not validated by monitored $PM_{10-2.5}$ concentrations although PM_{10} and $PM_{2.5}$ LUR model predictions are validated.	Section 3.3.2.3	
Evidence for biological plausibility	Experimental studies provide evidence for oxidative DNA damage in human subjects and DNA damage, oxidative stress, and mutagenicity in vitro. Additional epidemiologic evidence supports micronuclei formation.	Liu et al. (2015) Section 10.3.2.1 O'Callaghan-Gordo et al. (2015)	213 µg/m^3

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{10-2.5}$ concentrations with which the evidence is substantiated.

10.4 UFP Exposure and Cancer

The 2009 PM ISA concluded that the overall body of evidence was "inadequate to assess the relationship between long-term UFP exposures and cancer." This conclusion was based on the lack of epidemiologic studies that examined UFP exposure and cancer in both the 2004 PM AQCD and the 2009 PM ISA.

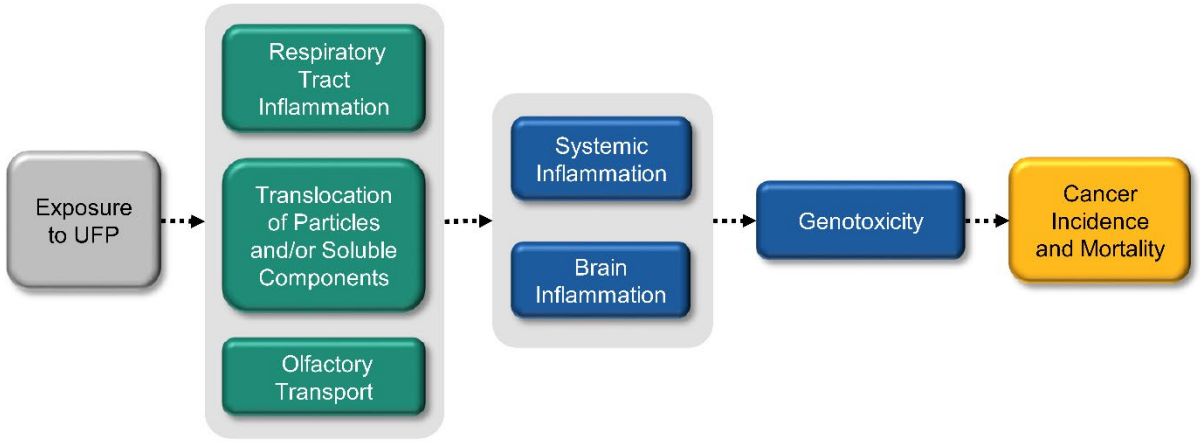
Consistent with the 2009 PM ISA, there remains a limited number of both experimental and epidemiologic studies that examined UFP exposure and whether it can lead to mutagenicity, genotoxicity, and carcinogenicity, as well as to cancer mortality, with no studies of lung cancer incidence or mortality. Although there is some evidence that UFP exposure can lead to changes in cancer-related biomarkers, there is a lack of epidemiologic evidence to support the continuum of effects to cancer incidence and mortality. The following sections evaluate studies published since completion of the 2009 PM ISA that focus on the mutagenicity and, genotoxicity of long-term exposures to UFP, which may contribute to cancer incidence and mortality.

10.4.1 Biological Plausibility

This section describes biological pathways that potentially underlie the development of cancer resulting from exposure to UFP. Figure 10-9 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" exposure to UFP may lead to the development of cancer contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 0.

Once UFP deposits in the respiratory tract, it may be retained, cleared, or solubilized (see Chapter 4). UFP and its soluble components may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate ROS and this capacity is termed "oxidative potential". Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see Chapter 4). Immune system responses due to the presence of particles in the interstitial space may contribute to chronic health effects. Inflammatory mediators may diffuse from the respiratory tract into the systemic circulation and lead to inflammation in extrapulmonary compartments (see Chapter 6). UFP and its soluble components may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments. A fraction of UFP may deposit on the olfactory epithelium. UFP and its soluble components may be transported via the olfactory nerve to the olfactory bulb of the brain. The extent to which translocation

into the systemic circulation or transport to the olfactory bulb occurs is currently uncertain. For further discussion of translocation and olfactory transport, see Chapter 4. The potential contribution of olfactory transport to brain inflammation or to upregulation of gene expression in the brain is discussed in Chapter 8.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 10-9 Potential biological pathways for the development of cancer following exposure to UFP.

Evidence is accumulating that exposure to UFP may lead to carcinogenesis by a genotoxic pathway that may result in mutational events or chromosomal alterations. Carcinogenesis due to dysregulated growth may follow. Compared with $PM_{2.5}$, there is less evidence that UFP exhibits characteristics of carcinogens (Smith et al., 2016). However, exposure to UFP resulted in genotoxic effects and oxidative stress. In addition, exposure to UFP induced genes involved in PAH biotransformation, indicating that UFP contained electrophilic species. Currently there are no epidemiologic studies evaluating the relationship between exposure to UFP and lung cancer, although breast cancer incidence has been studied. Evidence for these pathways and for cancer-related biomarkers is described below.

Genotoxicity

Genotoxicity may occur as a result of DNA damage and subsequent introduction of mutations into the genome, and as a result of cytogenetic effects at the level of the chromosome. UFP exposure is associated with mutagenicity and DNA damage. Mechanisms involved in genotoxicity resulting from UFP exposure include oxidative stress and biotransformation.

Mutations are considered biomarkers of early biological effect (Demetriou et al., 2012). Indirect evidence is provided by the Ames *Salmonella*/mammalian-microsome mutagenicity assay. It can identify the presence of species that can result in mutations as the result of direct interactions with DNA as well as those that require metabolic activation to elicit genotoxicity. As the most widely accepted theory of cancer etiology is the accumulation of mutations in critical genes, the presence of mutagens within PM provides biological plausibility for observations made in epidemiological studies. While this assay has several technical limitations and is criticized due to its use of bacteria as a model species, four decades of published results from this assay have clearly demonstrated the presence of mutagenic agents in PM collected from ambient air (U.S. EPA, 2009). A new study published since the 2009 PM ISA provides evidence to support mutagenicity resulting from UFP exposure (Kawanaka et al., 2008).

DNA damage is a biomarker of genotoxicity (Demarini, 2013). Evidence of DNA damage resulting from exposure to UFP was found using the comet assay which measures single and double DNA strand breaks in vitro (Jalava et al., 2015). The identification of oxidized DNA bases suggests a role for oxidative stress in the DNA lesions. These oxidized DNA nucleobases are considered a biomarker of exposure (Demetriou et al., 2012). Exposure to PM can result in oxidative stress either through the direct generation of reactive oxygen species (ROS), or indirectly, through the induction of inflammation. An in vitro study demonstrated an increase in ROS production as a result of exposure to UFP (Gordon et al., 2013). Studies in human subjects found increased oxidized DNA bases in urine (Liu et al., 2015) and evidence of DNA damage in peripheral blood mononuclear cells (Hemmingsen et al., 2015) in association with UFP exposure. The presence of oxidative stress-mediated DNA lesions and adducts can lead to the introduction of fixed mutations into the genome after incorrect repair of the damaged base or replication past the base by low fidelity DNA polymerases. The potential for oxidative stress to result in mutagenesis is underscored by the DNA repair mechanisms that have evolved to protect the genome from mutagenesis caused by these lesions.

Evidence that genes participating in PAH biotransformation are upregulated as a result of exposure to UFP is provided by an in vitro study (Borgie et al., 2015a). Biotransformation via Cyp1A1 may result in the production of PAH metabolites capable of reacting with DNA to form bulky DNA adducts. As in the case of oxidative stress mediated DNA adducts, when DNA repair of bulky adducts is absent or ineffective, mutational events may occur.

Summary of Biological Plausibility

As described here, there is one proposed pathway by which exposure to UFP may lead to the development of cancer. It involves genotoxicity, including DNA damage that may result in mutational events. Experimental studies in animals and humans contribute all of the evidence of upstream events. This proposed pathway provides biological plausibility for epidemiologic results of cancer incidence and mortality and will be used to inform a causality determination, which is discussed later in the section (Section 10.4.4).

10.4.2 Genotoxicity

10.4.2.1 Toxicological Evidence

Similar to $PM_{10-2.5}$ exposure, very few studies have been published since the 2009 ISA that describe effects relevant to genotoxicity resulting from exposure to UFP.

Kawanaka et al. (2008) investigated the mutagenicity of roadside PM organic extracts from Saitama City, Japan. Using a cascade impactor, 12 fractions of varying aerodynamic diameters were collected including an ultrafine fraction (<0.12). The authors used the *Salmonella* assay to determine the mutagenic activity of each fraction as well as GC/NCI/MS/MS and known quantities of select nitroaromatic compounds to determine the mass contribution of those compounds to the total PM collected and to estimate the contribution of each species to the total mutagenicity, respectively. Using this approach, it was reported that the quantity of nitro-PAHs per unit mass in the ultrafine fraction was greater than that of $PM_{10-2.5}$ or $PM_{2.5}$. In addition, the authors determined that mutagenicity per unit mass of UFP was greater than that of the other two PM size fractions in both TA98 and YG1024 S. Typhimurium strains. Of the six nitroaromatic compounds evaluated, the contribution to mutagenic activity calculated was greatest for 1,8-dinitropyrene in all three fractions of PM extracts evaluated. As a result of the variability of the *Salmonella* assay as well as incomplete details regarding the statistical analysis of the data collected, it is difficult to calculate definitive values for these contributions.

Jalava et al. (2015), as discussed earlier in the $PM_{2.5}$ and $PM_{10-2.5}$ sections, used the alkaline comet assay to measure DNA damage after exposure to PM suspensions in mouse macrophages (RAW 264.7). They evaluated four size fractions including a near ultrafine fraction described as $PM_{0.2}$ collected at Nanjing University in China. Similar to the increase observed after exposure to $PM_{10-2.5}$, the authors observed an increase in damage compared with controls ($p \leq 0.05$), however, the increase was only observed following exposure to the PM suspension of greatest concentration.

Gordon et al. (2013) measured intracellular ROS in BEAS-2B and HBEpC cells using the DCFH-DA assay after exposure to ambient UFP, as well as $PM_{10-2.5}$ and $PM_{2.5}$ size fractions collected

from five diverse sampling locations across the U.S. Similar to several other findings already highlighted, the authors reported variation in ROS production as a result of sampling site, season, and particle size and noted that exposure to the ultrafine fraction resulted in ROS production that was greater than that of both $PM_{10–2.5}$ and $PM_{2.5}$ on an equal mass exposure when sampling locations were combined.

Borgie et al. (2015a) collected ambient PM with aerodynamic diameters near those considered ultrafine (<0.3 μm) from an urban and rural location near Beirut, Lebanon and exposed cultured BEAS-2B cells to extracted organic material from the collected PM as well as intact PM suspension. The authors measured AhR, ARNT, AhRR, CYP1A1, CYP1B1, and NQO1 gene expression. They reported that, generally, an increase in CYP1A1, CYP1B1, and AhRR ($p < 0.05$) mRNA expression was observed compared to controls for both urban and rural sites. These findings are consistent with the results from their study that evaluated $PM_{2.5}$ (Borgie et al., 2015b). In that study, they also observed increases in CYP1A1, CYP1B1, and AhRR gene expression after exposure to $PM_{2.5–0.3}$ suspensions. Notably, while the current study by Borgie et al. (2015a) reported that increases in gene expression were observed for cells exposed to both EOM and aqueous suspensions, the increases in gene expression were generally greater after exposure to EOM compared with PM suspension ($p > 0.05$). This is consistent with the findings noted by Turner et al. (2015).

10.4.2.2 Evidence from Controlled Human Exposure Studies

Controlled human exposure studies have also evaluated various markers relevant to DNA damage. Hemmingsen et al. (2015) identified an association between combined DNA strand breaks and FPG sensitive sites in peripheral blood mononuclear cells and total particle number concentration using a mixed effects analysis ($p = 0.016$). These measures were representative of nonoxidative and oxidative DNA damage, respectively. In contrast, no evidence of oxidative stress or DNA damage was found in relation to $PM_{2.5}$ concentration. As described in Section 10.2.2.2, this controlled, cross-over, repeated measures human exposure study was carried out in central Copenhagen, Denmark in overweight, older adults who were exposed for 5 hours in chambers with and without high efficiency particulate adsorption filters.

A controlled human exposure study by Liu et al. (2015) measured MDA in blood and urine and 8-oxo-dG in urine. The former is a lipid peroxidation product capable of reacting with DNA bases, while the latter is excreted after oxidized dGTP molecules in cellular dNTP pools used for nuclear and mitochondrial DNA replication throughout the cell are acted upon by MTH1 followed by 8-oxo-dGMPase in the process of dNTP pool sanitization. In this single-blind randomized crossover study, nonsmoking adults were exposed for 130 minutes to $PM_{10–2.5}$, $PM_{2.5}$, and UFP CAPs drawn from a downtown street in Toronto, Canada. Participant blood and urine were collected before exposure and after exposure at two time points (1 hour, 21 hour). A positive association was observed between urinary 8-oxo-dG concentration and UFP concentration ($p < 0.05$) at 1-hour post-exposure. Urinary creatinine

was used to normalize biomarker concentrations. No association was observed between blood MDA concentration and concentration of UFP.

10.4.2.3 Summary of Genotoxicity

Evidence that UFP exposure induces mutagenicity, DNA damage, oxidative DNA damage, oxidative stress, and upregulation of enzymes involved in biotransformation is provided by a limited number of in vitro animal toxicological studies and two controlled human exposure study. Hemmingsen et al. (2015) identified an association between DNA damage in peripheral blood mononuclear cells and total particle number concentration. Liu et al. (2015) found oxidative DNA damage following an approximately 2-hour exposure of human subjects to UFP, with rapid but transient increase in a marker in urine. The tissue source of this marker cannot be discerned so it is unclear where in the body the DNA damage occurred. There were no epidemiologic studies that evaluated genotoxicity and carcinogenicity in relation to UFP exposure.

10.4.3 Cancer Incidence and Mortality

At the completion of the 2009 PM ISA, there were no studies that examined the association between long-term UFP exposure and lung cancer incidence or mortality or cancers in other sites. The only recent study that has focused on cancer and UFPs is a study conducted by Goldberg et al. (2017) in Montreal, Canada that examined postmenopausal breast cancer incidence. In a population-based, case-control study where UFP exposures from a LUR were assigned at geocoded addresses or centroids of postal codes the authors reported no evidence of an association in a model controlling for all individual-level covariates (OR = 1.02 [95% CI: 0.93, 1.13] for a 3,461.9 cm^{-3} increase in UFPs).

10.4.4 Summary and Causality Determination

It has been well characterized in toxicological studies that ambient air has mutagenic properties (Claxton et al., 2004) and that extracts of PM from ambient air have carcinogenic properties (Claxton and Woodall, 2007). However, at the completion of the 2009 PM ISA, little information was available from studies employing specific PM size fractions, such as UFP, or inhalation exposure. Since the 2009 PM ISA, a single epidemiologic study evaluated breast cancer incidence and found no evidence to support this outcome. Furthermore, no epidemiologic studies evaluated lung cancer in association with UFP exposure. Experimental studies are few in number and consist of a few controlled human exposure studies and in vitro animal toxicological studies. UFP exhibits two key characteristics of carcinogens (Smith et al., 2016) by demonstrating genotoxic effects and oxidative stress in experimental studies. While there is some biological plausibility for exposure to UFP and cancer, there is a lack of epidemiologic evidence of

cancer incidence or mortality. Additionally, there is uncertainty in the spatial variability of long-term UFP exposures, which is compounded by the relatively sparse UFP monitoring data in the U.S. This section describes the evaluation of evidence for cancer, with respect to the causality determination for long-term exposures to UFP using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015). The key evidence, as it relates to the causal framework, is summarized in Table 10-11. **Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between long-term UFP exposure and cancer**.

Table 10-11 Summary of evidence that is inadequate to infer the presence or absence of a causal relationship between long-term UFP exposure and cancer.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	UFP Concentrations Associated with Effects[c]
Lack of epidemiologic evidence at relevant UFP concentrations	Assessment of cancer limited to a study of breast cancer that reported no evidence of an association	Section 10.4.3	—
Uncertainty regarding exposure measurement error	Limited data on UFP concentrations over time and the spatial variability of UFP concentrations across urban areas	Section 2.5.1.1.5 Section 2.5.1.2.4 Section 2.5.2.2.3 Section 3.4.5	
Limited evidence for biological plausibility	Experimental studies provide evidence for oxidative DNA damage in human subjects while in vitro studies indicate DNA damage, oxidative stress, upregulation of enzymes involved in biotransformation, and mutagenicity	Hemmingsen et al. (2015) Liu et al. (2015) Kawanaka et al. (2008) Section 10.4.2	23,000/cm^2 136 µg/m^3

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the UFP concentrations with which the evidence is substantiated.

10.5 References

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CHAPTER 11 MORTALITY

Summary of Causality Determinations for Short- and Long-Term PM Exposure and Total (Nonaccidental) Mortality

This chapter characterizes the scientific evidence that supports causality determinations for short- and long-term PM exposure and total mortality. The types of studies evaluated within this chapter are consistent with the overall scope of the ISA as detailed in the Preface (see Section P.3.1). In assessing the overall evidence, strengths and limitations of individual studies were evaluated based on scientific considerations detailed in the Appendix. More details on the causal framework used to reach these conclusions are included in the Preamble to the ISA (U.S. EPA, 2015b).

Size Fraction	Causality Determination
Short-term exposure	
$PM_{2.5}$	Causal
$PM_{10-2.5}$	Suggestive of, but not sufficient to infer
UFP	Inadequate
Long-term exposure	
$PM_{2.5}$	Causal
$PM_{10-2.5}$	Suggestive of, but not sufficient to infer
UFP	Inadequate

11.1 Short-Term $PM_{2.5}$ Exposure and Total Mortality

The 2009 Integrated Science Assessment for Particulate Matter (hereafter 2009 PM ISA) concluded that "a causal relationship exists between short-term exposure to $PM_{2.5}$ and mortality" (U.S. EPA, 2009).[78] This conclusion was based on the evaluation of both multi- and single-city studies that further supported the consistent positive associations between short-term $PM_{2.5}$ exposure and mortality (i.e., total [nonaccidental] mortality) observed in the 2004 PM AQCD, with associations for total (nonaccidental) mortality ranging from 0.29% (Dominici et al., 2007) to 1.2% (Franklin et al., 2007). These associations were strongest, in terms of magnitude and precision, primarily at lags within the range of 0−1 days. Although an examination of the potential confounding effects of gaseous copollutants was

[78] As detailed in the Preface, risk estimates are for a 10 μg/m^3 increase in 24-hour avg $PM_{2.5}$ concentrations, unless otherwise noted.

limited in the studies evaluated in the 2009 PM ISA, evidence from single-city studies evaluated in the 2004 PM AQCD indicated that gaseous copollutants have minimal effect on the $PM_{2.5}$-mortality relationship. The evaluation of cause-specific mortality found that risk estimates were larger in magnitude, but also had larger confidence intervals, for respiratory mortality compared to cardiovascular mortality. Although the largest mortality risk estimates were for respiratory mortality, the interpretation of the results was complicated by the limited coherence from studies of respiratory morbidity. However, the evidence from studies of cardiovascular morbidity provided both coherence and biological plausibility for the relationship between short-term $PM_{2.5}$ exposure and cardiovascular mortality.

The multicity studies evaluated in the 2009 PM ISA provided initial information with respect to seasonal patterns of associations and city-to-city heterogeneity in $PM_{2.5}$-mortality risk estimates along with potential factors that may explain some of this heterogeneity. An evaluation of $PM_{2.5}$-mortality risk estimates by season indicated that associations tend to be largest in magnitude during the spring. Additionally, multicity studies demonstrated a regional pattern in associations with the magnitude being larger in the Eastern U.S., but also indicated that nationally, and even within a region, there are differences among city-specific $PM_{2.5}$-mortality risk estimates. Although not systematically considered across the studies evaluated in the 2009 PM ISA, several studies examined factors that provided some evidence that may explain the heterogeneity in $PM_{2.5}$-mortality risk estimates observed both within and across studies, including exposure factors (e.g., air-conditioning use), demographic differences, and $PM_{2.5}$ composition.

An evaluation of the concentration-response (C-R) relationship and whether a threshold exists was limited to multicity studies of PM_{10}. Collectively, the multicity studies that examined the C-R relationship between short-term PM_{10} exposure and mortality reported evidence of a linear, no-threshold relationship. However, some studies that also examined the C-R relationship for individual cities provided initial evidence indicating potential city-to-city differences in the shape of the C-R curve.

In addition to examining the association between short-term $PM_{2.5}$ exposures and mortality with a focus on PM mass, a few multicity studies examined whether specific $PM_{2.5}$ components modified the $PM_{2.5}$-mortality relationship while other studies focused on examining whether individual $PM_{2.5}$ components or PM sources were more strongly associated with mortality than $PM_{2.5}$ mass. In many cases, the evaluation of $PM_{2.5}$ components was limited due to the rather sparse temporal data coverage as a result of the every 3rd or 6th day sampling schedule of monitors. Collectively, these studies did not provide evidence that any one component or source is more strongly associated with mortality, which is consistent with the larger body of literature that examined the relationship between $PM_{2.5}$ components and sources and other health effects (U.S. EPA, 2009).

As detailed in the Preface, the focus of this section is on the evaluation of recently published studies that directly address policy-relevant issues, i.e., those studies where mean 24-hour average concentrations are less than 20 $\mu g/m^3$ across all cities or where at least half of the cities have mean 24-hour average concentrations less than 20 $\mu g/m^3$. Additionally, consistent with previous ISAs, this

section focuses primarily on multicity studies because they examine the association between short-term $PM_{2.5}$ exposure and a health effect over a large geographic area that consists of diverse atmospheric conditions and population demographics, using a consistent statistical methodology, which avoids the potential publication bias often associated with single-city studies (U.S. EPA, 2008). However, where applicable single-city studies, as well as multicity studies with mean 24-hour average concentrations greater than 20 $\mu g/m^3$, are evaluated when they: encompass a long study-duration; examine whether a specific population or lifestage may be at increased risk of $PM_{2.5}$-related mortality (see Chapter 12); or further characterize the relationship between short-term $PM_{2.5}$ exposure and mortality (e.g., copollutant analyses) not represented in the multicity studies with mean 24-hour average concentrations less than 20 $\mu g/m^3$ (U.S. EPA, 2016, 2015a). Other recent studies that do not fit the criteria mentioned above are not the focus of this section, and are available at: https://hero.epa.gov/hero/particulate-matter.

The following sections provide a brief overview of the consistent, positive associations observed in recent studies of mortality and short-term $PM_{2.5}$ exposures, with the main focus on assessing the degree to which these studies further characterize the relationship between short-term $PM_{2.5}$ exposure and mortality detailed in the 2009 PM ISA (U.S. EPA, 2009). The multicity, as well as single-city studies, discussed throughout this section, along with study-specific details and air quality characteristics are highlighted in Table 11-1 and represent those studies that attempt to further characterize the $PM_{2.5}$-mortality evidence by examining: potential confounding (i.e., copollutants and seasonal/temporal trends); effect modification (e.g., stressors, pollutants, season); geographic heterogeneity in associations; shape of the C-R relationship and related issues (e.g., threshold, lag structure of associations); and the relationship between $PM_{2.5}$ components and sources and mortality.

Table 11-1 Study-specific details and $PM_{2.5}$ concentrations from multicity studies in the 2004 PM Air Quality Criteria Document (AQCD) and 2009 PM ISA, and recent multicity studies.

Study/Location Years	Mortality Outcome(s)	Exposure Assessment	Mean Concentration $\mu g/m^3$	Upper Percentile Concentrations $\mu g/m^3$	Copollutant Examination
North America					
Burnett and Goldberg (2003)[a] Eight Canadian cities (1986−1996)	Total	One monitor in each of six cities and average of two monitors in two cities	13.3	98th: 38.9 99th: 45.4 Max: 86.0	Correlation (*r*): NA Copollutant models with: NA

Table 11-1 (Continued): Study-specific details and $PM_{2.5}$ concentrations from multicity studies in the 2004 PM Air Quality Criteria Document (AQCD) and 2009 PM ISA, and recent multicity studies.

Study/Location Years	Mortality Outcome(s)	Exposure Assessment	Mean Concentration µg/m^3	Upper Percentile Concentrations µg/m^3	Copollutant Examination
Klemm and Mason (2003)[a] 6 U.S. cities (1979–1988)	Total	One monitor in each city	14.7[b]	75th: 23.0 95th: 43.3	Correlation (*r*): NA Copollutant models with: NA
Burnett et al. (2004) 12 Canadian cities (1981–1999)	Total	Average of multiple monitors in each city	12.8	98th: 38.0 99th: 45.0 Max: 86.0	Correlation (*r*): 0.48 NO_2 Copollutant models with: NO_2
Ostro et al. (2006) 9 CA counties, U.S. (1999–2002)	Total Cardiovascular Respiratory	One monitor or average of multiple monitors in each county	19.9	98th: 38.9 99th: 45.4 Max: 160.0	Correlation (*r*): 0.56 NO_2; 0.60 CO; −0.14 1-h O_3; −0.22 8-h O_3 Copollutant models with: NA
Franklin et al. (2008) 25 U.S. cities (2000–2005)	Total Cardiovascular Respiratory	One monitor or average of multiple monitors in each city using method detailed in Schwartz (2000)	14.8	98th: 43.0 99th: 50.9 Max: 239.2	Correlation (*r*): NA Copollutant models with: NA
Franklin et al. (2007) 27 U.S. cities (1997–2002)	Total Cardiovascular Respiratory	One monitor or average of multiple monitors in each city using method detailed in Schwartz (2000)	15.6	98th: 45.8 99th: 54.7 Max: 239.0	Correlation (*r*): NA Copollutant models with: NA
Dominici et al. (2007) 96 U.S. cities (NMMAPS) (1999–2000)	Total Cardiovascular Respiratory	10% trimmed mean of all monitors in a city	---	---	Correlation (*r*): NA Copollutant models with: NA
Zanobetti and Schwartz (2009) 112 U.S. cities (1999–2005)	Total Cardiovascular Respiratory	One monitor or average of multiple monitors in each city using method detailed in Schwartz (2000)	13.2	98th: 34.3 99th: 38.6 Max: 57.4	Correlation (*r*): NA Copollutant models with: $PM_{10-2.5}$

Table 11-1 (Continued): Study-specific details and $PM_{2.5}$ concentrations from multicity studies in the 2004 PM Air Quality Criteria Document (AQCD) and 2009 PM ISA, and recent multicity studies.

Study/Location Years	Mortality Outcome(s)	Exposure Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
†Di et al. (2017a) U.S. (2000–2012)	All-cause	Daily predictions to 1km x 1 km grid using combination of monitoring data, satellite measurements and other data as detailed in Di et al. (2016) and Di et al. (2017b); R^2 = 0.84	---	---	Correlation (*r*): NA Copollutant models with: O_3
†Lippmann et al. (2013a) 148 U.S. cities (2001–2006)	Total Cardiovascular Respiratory	One monitor or average of multiple monitors in each city using method detailed in Schwartz (2000)	7.9[b]	---	Correlation (*r*): NA Copollutant models with: NA
†Zanobetti et al. (2014b)[d] 121 U.S. cities (1999–2010)	All-cause	One monitor or average of multiple monitors in each city using method detailed in Schwartz (2000)	4.37–17.97c	---	Correlation (*r*): NA Copollutant models with: NA
†Baxter et al. (2017) 77 U.S. Cities (2001–2005)	Total	One monitor or average of multiple monitors in each city, when multiple monitors uncorrelated monitors ($r < 0.8$) excluded	Cluster 1: 13.0 Cluster 2: 13.6 Cluster 3: 12.2 Cluster 4: 14.1 Cluster 5: 13.7	Max: Cluster 1: 19.9 Cluster 2: 16.2 Cluster 3: 22.7 Cluster 4: 16.6 Cluster 5: 14.9	Correlation (*r*): NA Copollutant models with: NA
†Dai et al. (2014) 75 U.S. cities (2000–2006)	Total Cardiovascular MI Stroke Respiratory	One monitor or average of multiple monitors in each city	13.3	---	Correlation (*r*): NA Copollutant models with: NA

Table 11-1 (Continued): Study-specific details and $PM_{2.5}$ concentrations from multicity studies in the 2004 PM Air Quality Criteria Document (AQCD) and 2009 PM ISA, and recent multicity studies.

Study/Location Years	Mortality Outcome(s)	Exposure Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
†Krall et al. (2013) 72 U.S. cities (2000–2005)	Total	One monitor or arithmetic mean of all monitors in each city	13.6	Max: 22.8	Correlation (*r*): NA Copollutant models with: NA
†Kloog et al. (2013) New England, U.S. (2000–2008)	Total	Daily predictions to 10 km × 10 km grid using combination of satellite measurements, monitor data, and LUR detailed in Kloog et al. (2011); R^2 = 0.84 (temporal)	9.8	75th: 11.9	Correlation (*r*): NA Copollutant models with: NA
†Shi et al. (2015)[d] New England, U.S. (2003–2009)	All-cause	Daily predictions to 1 km × 1 km grid using combination of satellite measurements, monitor data, and LUR detailed in Kloog et al. (2014); R^2 = 0.87 (temporal)	8.2	75th: 10.6 Max: 53.9	Correlation (*r*): NA Copollutant models with: NA
†Lee et al. (2015c) Three southeastern states, U.S. (North Carolina, South Carolina, Georgia) (2007–2011)	Total Cardiovascular Stroke CHF MI Respiratory	Daily predictions to 1 km x 1 km grid cell using combination of satellite measurements, monitor data, and LUR detailed in Lee et al. (2015b); R^2 = 0.70–0.81	11.1	Max: 86.2	Correlation (*r*): NA Copollutant models with: NA
†Young et al. (2017) California (2000−2012)[e]	Total	Highest reporting monitor on each day in each air basin	12.5−36.7[f]	NR	Correlation (*r*): NA Copollutant models with: NA

Table 11-1 (Continued): Study-specific details and $PM_{2.5}$ concentrations from multicity studies in the 2004 PM Air Quality Criteria Document (AQCD) and 2009 PM ISA, and recent multicity studies.

Study/Location Years	Mortality Outcome(s)	Exposure Assessment	Mean Concentration µg/m^3	Upper Percentile Concentrations µg/m^3	Copollutant Examination
Europe					
†Janssen et al. (2013) Netherlands (2008–2009)	Total Cardiovascular Respiratory	Nationwide average of 10 monitors	16.3	75th: 20.9 Max: 106.1	Correlation (*r*): 0.95 PM_{10}; 0.29 $PM_{10-2.5}$ Copollutant models with: $PM_{10-2.5}$
†Pascal et al. (2014) Nine French cities (2001–2006)	Total Cardiovascular Cerebrovascular Respiratory	Average of all monitors in each city	13–18[c]	Max: 68–111	Correlation (*r*): >0.80 (across cities) PM_{10}; <0.40 (across cities) $PM_{10-2.5}$; >0.7 (during summer across cities) O_3 Copollutant models with: O_3, $PM_{10-2.5}$
†Samoli et al. (2013) 10 European Mediterranean cities (MED-PARTICLES) (2001–2010)	Total Cardiovascular Respiratory	Average of all monitors in each city	13.6–27.7[b,c]	75th: 18.8–48.0	Correlation (*r*): 0.2–0.7 $PM_{10-2.5}$; 0.3–0.8 NO_2; <0.6 SO_2; <0.6 O_3 Copollutant models with: SO_2, NO_2, O_3, $PM_{10-2.5}$
†Lanzinger et al. (2016) Five Central European cities (UFIREG) (2011–2014)	Total Cardiovascular Respiratory	Average of all monitors in each city	14.9–20.7[f]	Max: 78.8–114.8	Correlation (*r*): 0.55–0.73 NO_2; 0.93–0.97 PM_{10}; 0.40–0.61 $PM_{10-2.5}$; 0.25–0.37 UFP; 0.49–0.50 PNC Copollutant models with: NA
†Stafoggia et al. (2017)[g] Eight European cities (1999–2013)	Total Cardiovascular Respiratory	Average of all monitors in each city	8.0–23.0	NA	Correlation (*r*): 0.09–0.56 UFP Copollutant models with: NA

Table 11-1 (Continued): Study-specific details and $PM_{2.5}$ concentrations from multicity studies in the 2004 PM Air Quality Criteria Document (AQCD) and 2009 PM ISA, and recent multicity studies.

Study/Location Years	Mortality Outcome(s)	Exposure Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
Asia					
†Lee et al. (2015a) 11 East Asian cities (2001–2009)	Total Cardiovascular Respiratory	Average of all monitors in each city	17.7–69.9[c]	75th: 24.1–106.8	Correlation (*r*): NA Copollutant models with: SO_2, NO_2, O_3, $PM_{10-2.5}$
†Ueda et al. (2009) 20 Japanese areas (2002–2004)	Total	1 monitor in each area	11.8–22.8[c]	90th: 21.5–38.2	Correlation (*r*): 0.55 NO_2; 0.10 O_x Copollutant models with: NA

ACE = acute coronary events; CAPES = China Air Pollution and Health Effects Study; CHF = congestive heart failure; MI = myocardial infarction; NMMAPS = National Morbidity, Mortality, and Air Pollution Study; O_x = photochemical oxidants; UFIREG = Ultrafine Particles—an evidence based contribution to the development of regional and European environmental and health policy.

[a]Multicity studies included in the 2004 PM AQCD.

[b]Median concentrations.

[c]Range of mean concentrations across all cities.

[d]Only had data for all-cause mortality including accidental mortalities, focused analyses on total (nonaccidental) mortality.

[e]Due to the sparsity of data for year 2000, it was excluded from the main analysis.

[f]Young et al. (2017) only reported average $PM_{2.5}$ concentrations for each year and not an average across all years; therefore this range represents the minimum and maximum concentration reported in any year across all air basins.

[g]Only 4 of the 5 cities had $PM_{2.5}$ data.

[h]Stafoggia et al. (2017) did not report quantitative estimates for cardiovascular and respiratory mortality.

†Studies published since the 2009 PM ISA.

11.1.1 Biological Plausibility for Short-Term $PM_{2.5}$ Exposure and Total (Nonaccidental) Mortality

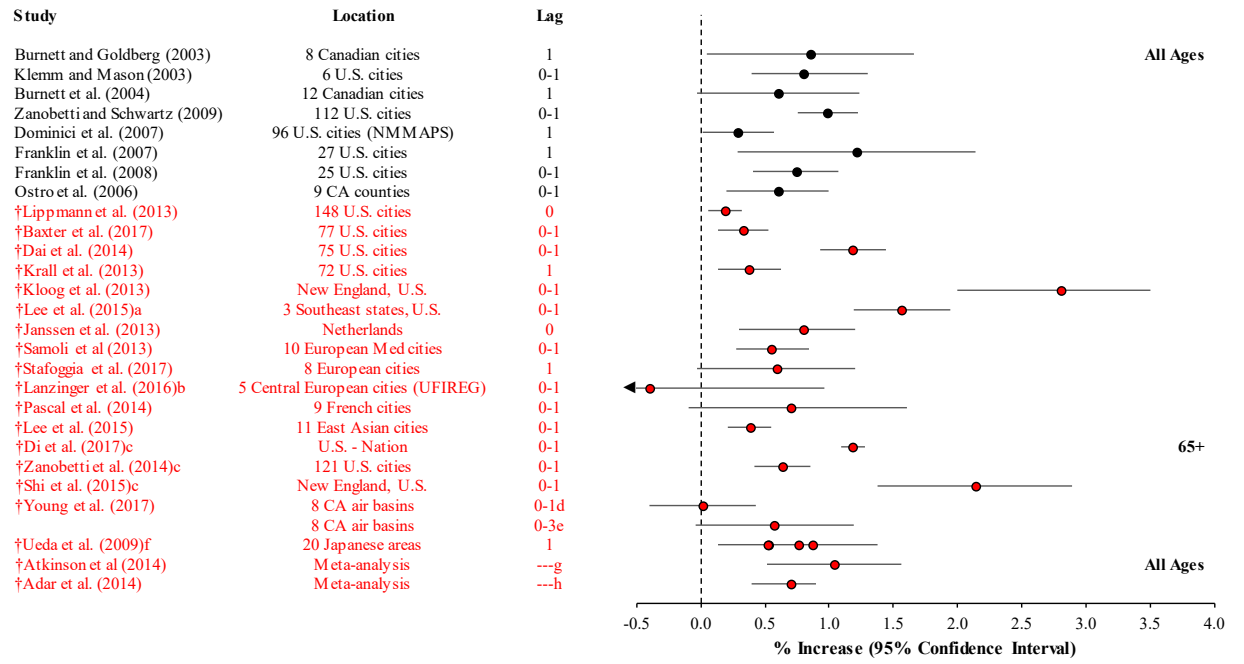
The preceding chapters characterized evidence related to evaluating the biological plausibility by which short-term $PM_{2.5}$ exposure may lead to the morbidity effects that are the largest contributors to total (nonaccidental) mortality, specifically cardiovascular and respiratory morbidity (Section 6.1.1 and Section 5.1.1, respectively). This evidence is derived from animal toxicological, controlled human exposure, and epidemiologic studies. Section 6.1.1 outlines the available evidence for plausible mechanisms by which inhalation exposure to $PM_{2.5}$ could progress from initial events to endpoints relevant to the cardiovascular system and to population outcomes such as emergency department (ED) visits and hospital admissions due to cardiovascular disease, particularly ischemic heart disease and congestive heart failure. Similarly, Section 5.1.1 characterizes the available evidence by which inhalation exposure to $PM_{2.5}$ could progress from initial events to endpoints relevant to the respiratory system.

However, the evidence for how the initial events and subsequent endpoints could lead to the observed increases in respiratory ED visits and hospital admissions, for particularly chronic obstructive pulmonary disease (COPD) and asthma, is limited. Collectively, the progression demonstrated in the available evidence for cardiovascular morbidity (and to a lesser extent, respiratory morbidity) supports potential biological pathways by which short-term $PM_{2.5}$ exposures could result in mortality.

11.1.2 Associations between Short-Term $PM_{2.5}$ Exposure and Total (Nonaccidental) Mortality in All-Year Analyses

In previous PM reviews, specifically the 2004 PM AQCD (U.S. EPA, 2004) and the 2009 PM ISA (U.S. EPA, 2009), the number of multicity studies that examined the association between short-term $PM_{2.5}$ exposure and total (nonaccidental) mortality was rather limited with the largest body of evidence encompassing single-city studies. The single-city studies evaluated in previous reviews were conducted in diverse geographic locations and reported primarily consistent positive associations between $PM_{2.5}$ exposure and daily mortality. The limited number of large multicity studies included in those reviews could be attributed to the rather small sample of ambient $PM_{2.5}$ monitoring data available at that time with the majority of monitoring being initiated in the years 1999 and 2000. Recent multicity studies encompass a larger number of years and sometimes include daily $PM_{2.5}$ concentrations, whereas previous studies were often limited to a shorter time series and $PM_{2.5}$ data that was only collected every 3rd or 6th day.

Recent multicity studies conducted across the U.S., Canada, Europe, and Asia, as well as meta-analyses (Adar et al., 2014; Atkinson et al., 2014) that examined a larger number of studies of short-term $PM_{2.5}$ exposures and mortality, primarily report consistent positive associations within the range of risk estimates reported in the 2009 PM ISA (i.e., 0.19% (Lippmann et al., 2013a) to 2.80% (Kloog et al., 2013)) (Figure 11-1). An exception to this trend across multicity studies is Lanzinger et al. (2016), which as part of the "ultrafine particles—an evidence based contribution to the development of regional and European environmental and health policy" or UFIREG study observed no evidence of an association between short-term $PM_{2.5}$ exposure and total (nonaccidental) mortality. The results of the UFIREG study may be a reflection of the short time series for each city included in the study (i.e., approximately 2 years), compared to the other multicity studies that consisted of longer study durations as summarized in Table 11-1. Additionally, in contrast to Ostro et al. (2006), a recent study by Young et al. (2017) did not provide any evidence of an association between short-term $PM_{2.5}$ exposure and mortality when examining eight air basins in California. The difference in results between these two studies could be attributed to: (1) the larger spatial domain over which exposure was assigned in Young et al. (2017), i.e., an air basin (encompassing multiple counties), compared to Ostro et al. (2006), i.e., a single county; (2) the use of only the highest monitor on each day to assign exposure Young et al. (2017) versus the averaging of all monitors over the spatial domain examined Ostro et al. (2006); and (3) the statistical models used in both studies.



NMMAPS = National Morbidity, Mortality, and Air Pollution Study; UFIREG = Ultrafine Particles—an evidence based contribution to the development of regional and European environmental and health policy.

[a]Results are from modeled $PM_{2.5}$ analysis, analysis focusing on measured $PM_{2.5}$ reported 1.21% (95% CI: 0.94, 1.47).

[b]Only four of the five cities measured $PM_{2.5}$.

[c]Shi et al. (2015) and Zanobetti et al. (2014b) only had data for all-cause mortality including accidental mortalities.

[d]Main model used in Young et al. (2017) included current and average of 3 previous days daily maximum temperature, daily minimum temperature, and maximum daily relative humidity.

[e]Sensitivity analysis in Young et al. (2017) focusing on only the San Fransisco Bay air basin, dropping out the maximum daily relative humidity term, where the shortest duration of lag days examined was 0−3 days.

[f]Ueda et al. (2009) presented results for three different modeling approaches, which are presented here: GAM, GLM, and case-crossover.

[g]Atkinson et al. (2014) primarily focused on single-day lag results.

[h]Adar et al. (2014) focused on single-day lag results, specifically lag 0, 1, or 2.

Note: †Studies published since the 2009 PM ISA. Black circles = U.S. and Canadian multicity studies evaluated in the 2004 PM AQCD and 2009 PM ISA. Red circles = Multicity studies and meta-analyses published since the completion of the 2009 PM ISA. Corresponding quantitative results are reported in the Supplemental Material for this chapter, see (U.S. EPA, 2018a).

Figure 11-1 Summary of associations between short-term $PM_{2.5}$ exposure and total (nonaccidental) mortality in multicity studies for a 10 μg/m^3 increase in 24-hour average concentrations.

11.1.2.1 Examination of $PM_{2.5}$-Mortality Relationship through Causal Modeling Statistical Approaches

In addition to traditional epidemiologic study designs (e.g., time-series, case-crossover), there has been a growing interest in applying causal modeling statistical approaches to examine the $PM_{2.5}$-mortality relationship. Within the studies that examined short-term $PM_{2.5}$ exposure and mortality, two types of

causal modeling approaches have been employed: (1) causal inference (Schwartz et al., 2017; Schwartz et al., 2015) and (2) quasi-experimental (Yorifuji et al., 2016) (Table 11-2).

Table 11-2 Methods and results from epidemiologic studies that applied causal inference statistical approaches.

Study	Method	Results
Causal inference		
†Schwartz et al. (2015) Boston, MA (2004–2009)	Instrumental variable: used back trajectories of $PM_{2.5}$ along with variables for wind speed and sea level pressure in a 2-stage approach to develop temperature independent predictions of daily $PM_{2.5}$ concentrations (the instrument). Analyses used 2-day mean instrument concentrations.	0.53% (95% CI: 0.09, 0.97) for a 1 μg/m^3 increase in the instrument for $PM_{2.5}$
	Propensity score: modeled $PM_{2.5}$ in a linear regression with variables for time, temperature, day of week, and copollutants (O_3, NO_2, SO_2, and CO). The predicted $PM_{2.5}$ concentrations from the model represent the propensity score. After trimming days with highest and lowest 5% propensity scores, divided the scores into deciles. Analyses used 2-day mean predicted $PM_{2.5}$ concentrations.	0.50% (95% CI: 0.2, 0.8) for a 1 μg/m^3 increase in $PM_{2.5}$
	Sensitivity analysis: using an approach similar to Granger causality, the instrumental variable was used to examine the association between the instrument 2 days after the day of death on today's value of daily deaths.	Failed to reject null hypothesis, (P = 0.93; 95% CI: −0.43, 0.47)
†Schwartz et al. (2017) Boston, MA (2000–2009)	Instrumental variable: planetary boundary layer (PBL) and wind speed at lag 0 and lag 1 were regressed on $PM_{2.5}$, BC or NO_2 concentrations to generate a single instrumental variable for each pollutant representative of local pollution, taking into consideration variation within month-by-year strata and within deciles of temperature. Analyses used 2-day mean instrument concentrations.	0.90% (95% CI: 0.25, 1.56) for an IQR increase in the instrument for local $PM_{2.5}$
	Sensitivity analysis: using an approach similar to Granger causality, the instrumental variable was used to examine the association between the instrument 2 and 3 days after the day of death on today's value of daily deaths.	0.18% (95% CI: −0.45, 0.81) for an IQR increase in the instrument for local $PM_{2.5}$

Table 11-2 (Continued): Methods and results from epidemiologic studies that applied causal inference statistical approaches.

Study	Method	Results
Quasi-experimental		
†Yorifuji et al. (2016) Tokyo, Japan (2000–2012)	Compared mortality rates in Tokyo, Japan, which had a strict diesel emissions control ordinance in place and Osaka, Japan, which did not. Interrupted time-series analysis used to regress log of age-standardized mortality rates in Tokyo, weighted by daily trends in Osaka, on the $PM_{2.5}$ concentrations and estimated rate ratios across 3-year intervals using the three years prior to the ordinance as a reference period.	Difference in mortality between 2000–2003 and 2009–2012: Total: −6.0% Cardiovascular: −11.0% IHD: −10.0% Cerebrovascular: −6.2% Pulmonary: −22.0%

BC = black carbon, IHD = ischemic heart disease.

†Studies published since the 2009 PM ISA.

Through causal inference statistical approaches, the goal is to "estimate the difference (or ratio) in the expected value of [an] outcome in the population under the exposure they received versus what it would have been had they received an alternative exposure" (Schwartz et al., 2015). Schwartz et al. (2015) and Schwartz et al. (2017) examined instrumental variable and propensity score approaches using data from Boston, MA. Through the instrumental variable approach, a variable is constructed that is only related to the outcome through the exposure of interest, while the propensity score approach represents the conditional probability of exposure assignment given a vector of observed covariates (Schwartz et al., 2015).

Schwartz et al. (2015) and Schwartz et al. (2017) took different approaches to constructing instrumental variables, and both reported evidence of an association between the $PM_{2.5}$ instrument and mortality (Table 11-2). In Schwartz et al. (2017) this association was found to persist when limiting the analysis to days with 24-hour average $PM_{2.5}$ concentrations <30 $\mu g/m^3$ (0.84% [95% CI: 0.19, 1.50]). Schwartz et al. (2015) and Schwartz et al. (2017) also conducted Granger-like causality tests to examine whether there was evidence of an association between mortality and $PM_{2.5}$ concentrations after the day of death, which would support the possibility that unmeasured confounders were not accounted for in the statistical model. Both Schwartz et al. (2015) and Schwartz et al. (2017) reported no evidence of an association with $PM_{2.5}$ concentrations measured after death.

While Schwartz et al. (2015) and Schwartz et al. (2017) focused on causal inference approaches that result in the development of alternative exposure variables, Yorifuji et al. (2016) conducted a quasi-experimental study that examined whether a specific regulatory action in Tokyo, Japan (i.e., a diesel emission control ordinance) resulted in a subsequent reduction in daily mortality (Table 11-2). The quasi-experimental design relies on some intervention that is meant to reduce ambient air pollution

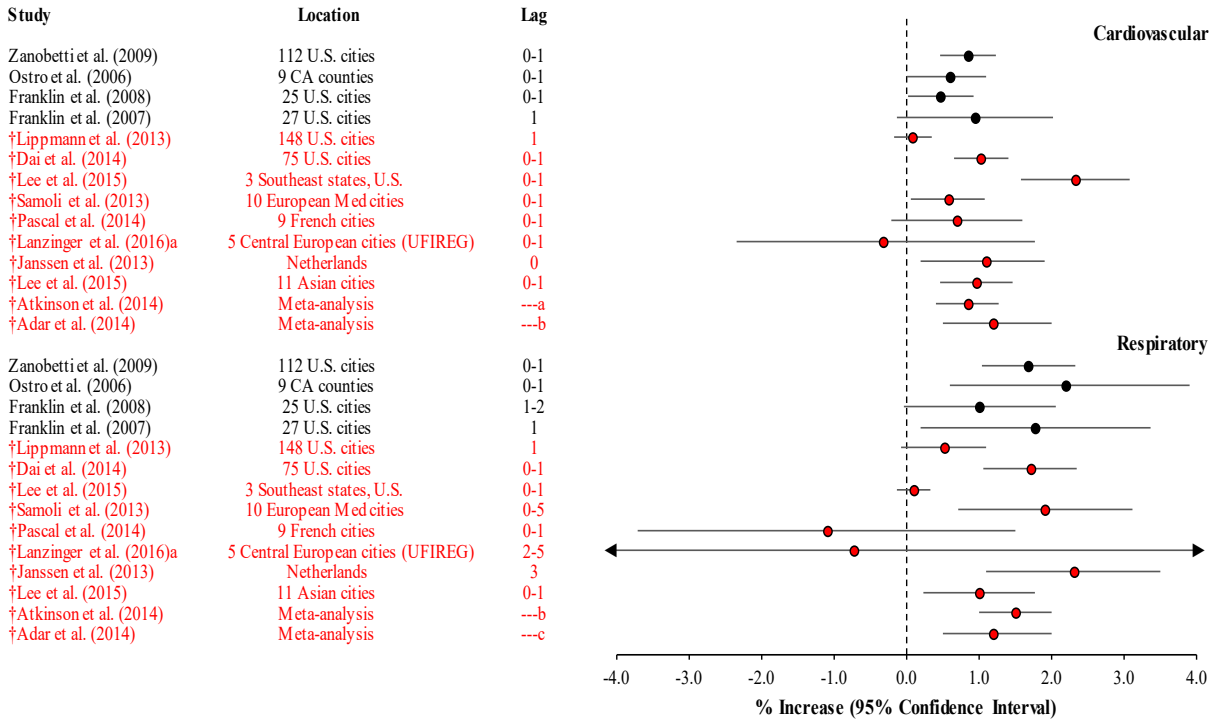
concentrations. Yorifuji et al. (2016) reported evidence of a reduction in mortality in Tokyo due to the ordinance, in comparison to Osaka, Japan, which did not have a similar diesel emission control ordinance in place.

Although the studies to date that have used causal modeling statistical approaches are limited to two locations, overall the studies provide additional support for the relationship between short-term $PM_{2.5}$ exposure and mortality described in previous and recent studies, including those highlighted in Figure 11-1. Additionally, the study by Yorifuji et al. (2016) demonstrates that improvements in air quality, including reductions in $PM_{2.5}$ concentrations, contribute to public health benefits such as reductions in daily mortality.

11.1.3 Associations between Short-Term $PM_{2.5}$ and Cause-Specific Mortality in All-Year Analyses

Single and multicity studies evaluated in the 2009 PM ISA that examined cause-specific mortality reported consistent positive associations with both cardiovascular and respiratory mortality. The magnitude of the association was larger for respiratory mortality, but also had greater confidence intervals due to the smaller number of respiratory-related deaths compared to cardiovascular-related deaths.

Recent multicity studies have further examined the relationship between short-term $PM_{2.5}$ exposure and cause-specific mortality, with some studies conducting additional examinations of specific cardiovascular or respiratory deaths (e.g., stroke, COPD as mentioned in Section 5.1.9 and Section 6.1.9). These studies generally report positive associations, which is consistent with the studies evaluated in the 2009 PM ISA. Overall, these studies report larger risk estimates for respiratory mortality, but many of the confidence intervals are larger than those for cardiovascular mortality due to cardiovascular mortality representing a greater percentage of total mortality (~35%) compared to respiratory mortality (<10%) (American Heart Association, 2011) (Figure 11-2). A more thorough discussion of cardiovascular- and respiratory-related mortality can be found in the respective cardiovascular and respiratory effects sections (Section 5.1.9 and Section 6.1.9).



UFIREG = Ultrafine Particles—an evidence-based contribution to the development of regional and European environmental and health policy.

[a]Only four of the five cities measured $PM_{2.5}$.

[b]Atkinson et al. (2014) primarily focused on single-day lag results.

[c]Adar et al. (2014) focused on single-day lag results, specifically lag 0, 1, or 2.

Note: †Studies published since the 2009 PM ISA. Studies organized by lag structure, therefore, cardiovascular and respiratory mortality results are not in the same order. Black circles = U.S. and Canadian multicity studies evaluated in the 2004 PM AQCD and 2009 PM ISA. Red circles = Multicity studies and meta-analyses published since the completion of the 2009 PM ISA.

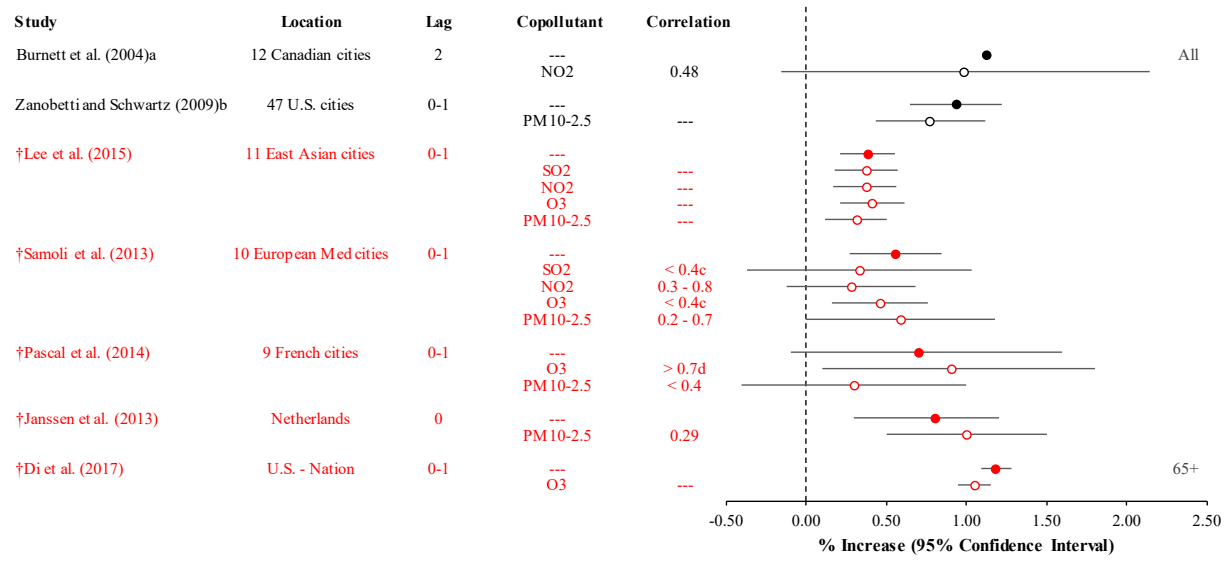
Corresponding quantitative results are reported in the Supplemental Material for this chapter, see (U.S. EPA, 2018a).

Figure 11-2 Summary of associations between short-term $PM_{2.5}$ exposure and cardiovascular and respiratory mortality in multicity studies for a 10 µg/m^3 increase in 24-hour average concentrations.

11.1.4 Potential Copollutant Confounding of the $PM_{2.5}$-Mortality Relationship

Analyses of potential copollutant confounding of the $PM_{2.5}$-mortality relationship in the 2009 PM ISA indicated that associations remain robust, and relatively unchanged in copollutant models. These conclusions were based primarily on a multicity study conducted in Canada (Burnett et al., 2004) along with single-city studies reviewed in the 2004 PM AQCD (U.S. EPA, 2004), and supporting evidence from studies that examined the PM_{10}-mortality relationship. Recent multicity studies that assess the potential for copollutant confounding of the $PM_{2.5}$-mortality relationship are limited to Europe and Asia. However, similar to the 2004 PM AQCD and 2009 PM ISA, analyses of potential confounding by gaseous pollutants (i.e., SO_2, NO_2, and O_3) were limited in number, with additional analyses focusing on copollutant models with $PM_{10-2.5}$. Overall, studies that examined potential copollutant confounding reported that $PM_{2.5}$-mortality risk estimates remained positive and relatively unchanged in models with both gaseous pollutants and $PM_{10-2.5}$, although confidence intervals increased in some cases. Across studies that examined potential confounding by gaseous copollutants (Di et al., 2017a; Lee et al., 2015a; Pascal et al., 2014; Samoli et al., 2013), the $PM_{2.5}$-mortality relationship was relatively unchanged (Figure 11-3). Those studies that present correlation coefficients provide additional information to support the results from the copollutant analyses due to the low ($r < 0.4$) to moderate correlations ($r = 0.4 < 0.7$) observed.

When assessing the evidence across the studies that examined potential copollutant confounding by $PM_{10-2.5}$, the approaches used to estimate $PM_{10-2.5}$ varied across studies, which could contribute to exposure measurement error and complicate the overall interpretation of results (Section 3.3.1.1). However, regardless of the method used to estimate $PM_{10-2.5}$ concentrations, in copollutant models the $PM_{2.5}$-mortality association was relatively unchanged, but in some cases confidence intervals were larger compared to the single pollutant models (Figure 11-3). The results from multicity studies that examined potential confounding of the $PM_{2.5}$-mortality relationship by $PM_{10-2.5}$ are further supported by a meta-analysis conducted by Adar et al. (2014). The authors focused almost exclusively on the $PM_{10-2.5}$-mortality relationship, but also examined $PM_{2.5}$. In copollutant analyses the authors observed that $PM_{2.5}$-mortality associations were relatively unchanged when including $PM_{10-2.5}$ in the model (quantitative results not presented).



[a]Data from 1998−2000 when PM measured by TEOM. Standard error for the single-pollutant $PM_{2.5}$ result was not reported in the study so only the central estimate is included.

[b]Analysis focused on 112 U.S. cities, but $PM_{10-2.5}$ only measured in 47 U.S. cities.

Note: †Studies published since the 2009 PM ISA. Closed circles = single-pollutant results. Open circles = copollutant results. Corresponding quantitative results are reported in the Supplemental Material for this chapter. See (U.S. EPA, 2018a).

Figure 11-3 Summary of association between short-term $PM_{2.5}$ exposure and total (nonaccidental) mortality for a 10 μg/m^3 increase in 24-hour average concentrations in single- and copollutant models from previous and recent multicity studies.

11.1.5 Other Potential Confounders of the $PM_{2.5}$-Mortality Relationship

11.1.5.1 Long-Term Temporal Trends and Weather

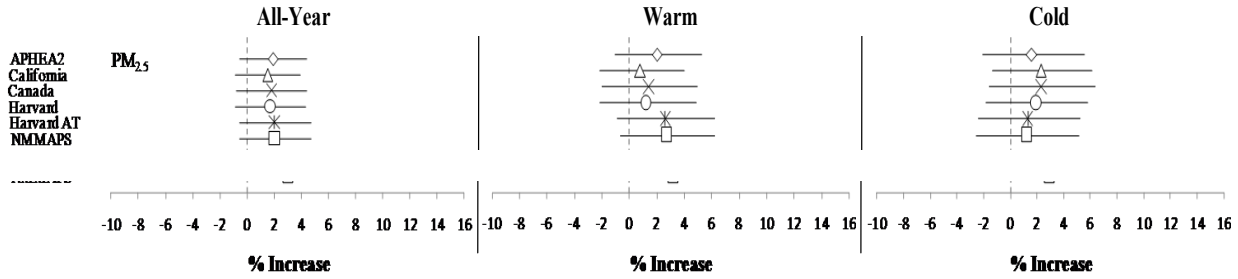
In the 2009 PM ISA, studies that examined the influence of alternative model specification, in terms of controlling for temporal trends or the confounding effects of weather were limited to studies of PM_{10}. Of these studies Welty and Zeger (2005) conducted the most systematic evaluation and found that PM_{10}-mortality risk estimates remained robust across various combinations of degrees of freedom (df) to control for temporal trends and weather covariates. At the completion of the 2009 PM ISA, there were not studies of short-term $PM_{2.5}$ exposure and mortality that conducted similar analyses to address whether the results observed in PM_{10} studies were consistent for $PM_{2.5}$. Recent multicity, as well as a few single-city, studies specifically examined the influence of model specification on the $PM_{2.5}$-mortality association

while others conducted sensitivity analyses to examine whether the primary statistical model was appropriate.

Ueda et al. (2009) in a study of 20 Japanese cities and Sacks et al. (2012) in a study in Philadelphia, PA conducted systematic evaluations of alternative models to adjust for long-term temporal trends and weather covariates. Ueda et al. (2009) examined a generalized additive model (GAM), generalized linear model (GLM), and logistic regression through a case-crossover analysis to examine the relationship between short-term air pollution exposure, including $PM_{2.5}$, and mortality. Across models, the $PM_{2.5}$-mortality association remained relatively unchanged after increasing the df employed (i.e., 3 or 6) to control for the potential nonlinear relationship between ambient temperature and mortality. These results are consistent with Lee et al. (2015c) in a study of three southeastern U.S. states where the $PM_{2.5}$-mortality association remained robust when increasing the df for the temperature covariate from 2 to 4.

In Ueda et al. (2009), the largest influence on the $PM_{2.5}$-mortality association was observed for the GLM when changing the approach to adjust for seasonality from using an indicator variable of every 2 months to the more traditional approach of using a natural spline. The results using the natural spline in the GLM (0.43% [95% CI: 0.00, 0.86]; lag 1) were more consistent with those observed in the GAM (0.53% [95% CI: 0.13, 0.94]; lag 1) where penalized splines were used to adjust for seasonality. It is worth noting that overall the results of the comparisons conducted by Ueda et al. (2009) are consistent with previous analyses that have shown that the GLM, GAM, and case-crossover approach all result in relatively consistent results (Schwartz et al., 2003).

Sacks et al. (2012) took a different approach than Ueda et al. (2009) by examining the influence of model specification using the models employed in recent multicity studies conducted by Burnett and Goldberg (2003), Zanobetti and Schwartz (2009), Zanobetti and Schwartz (2008), Ostro et al. (2008), Samoli et al. (2005), and Dominici et al. (2005) within the context of a similar data set. These models differed by the approach used to control for long-term temporal trends (i.e., number of df per year) and the potential confounding effects of weather (i.e., the weather covariate included in the model, and the accompanying lag and/or df for the covariate). Focusing on daily cardiovascular mortality and daily air pollution concentrations, including $PM_{2.5}$, the authors observed in all-year analyses that results for $PM_{2.5}$ were relatively similar across models with the percent increase in cardiovascular mortality ranging from 1.5–2.0% (Figure 11-4). In seasonal analyses there was more variability in the magnitude of the association across models (i.e., cold Season: 1.2–2.3%; warm Season: 0.8–2.7%), but the direction of the association remained consistent.



Note: APHEA2 = Samoli et al. (2005); California = Ostro et al. (2008); Canada = Burnett and Goldberg (2003); Harvard = Zanobetti and Schwartz (2009); Harvard AT = Zanobetti and Schwartz (2008); and NMMAPS = Dominici et al. (2005).
Source: Permission pending, Sacks et al. (2012).

Figure 11-4 Percent increase in cardiovascular mortality for a 10 μg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations at lag 0−1 in Philadelphia, PA (May 1992−September 1995) across statistical models used in multicity studies.

Whereas Ueda et al. (2009) and Sacks et al. (2012) conducted systematic evaluations on the influence of model specification on the $PM_{2.5}$-mortality relationship, other studies conducted more targeted analyses. Lee et al. (2015a) and Samoli et al. (2013) in 11 East Asian cities and 10 European Mediterranean cities, respectively, both examined the influence of various approaches to control for long-term temporal trends on the $PM_{2.5}$-mortality relationship. In sensitivity analyses where the df employed per year ranged from 6 to 12, Lee et al. (2015a) did not observe any evidence that $PM_{2.5}$-mortality risk estimates changed as the df increased. Samoli et al. (2013) examined alternative approaches to control for long-term temporal trends through either setting the df a priori, using absolute sum of the residuals of the partial autocorrelation function (PACF) or a case-crossover design in the context of a Poisson model with a three-way interaction. Across each approach, the authors observed that the magnitude of the association was smallest when specifying the df per year to use a priori, but a positive association persisted across all approaches ranging from 0.55 to 0.97%.

In the Denver Aerosol Sources and Health (DASH) study, Kim et al. (2015) further confirmed the results from previous studies that examined alternative specifications to account for long-term temporal trends and the confounding effects of weather. The authors examined both decreasing and increasing the df to control for long-term temporal trends, matching the lags of meteorological covariates to those of the pollutants, and a squared term and moving averages of extended days (i.e., lags 0, 1−3, and 4−7) for temperature. Across all of these alternative model specifications, Kim et al. (2015) found that results were relatively consistent with the main statistical model (2.63% [95% CI: −0.22, 5.44]; lag 0−3 days unconstrained DL). Compared to Kim et al. (2015), Lee et al. (2015c) in a study of three southeastern

U.S. states and Di et al. (2017a) a national analysis only examined the sensitivity of the $PM_{2.5}$-mortality relationship to changing the df for weather covariates. Lee et al. (2015c) observed that increasing the df from 2 to 4 for the same-day temperature covariate resulted in relatively consistent risk estimates, with the percent increase in mortality ranging from 1.57 to 1.63% at lag 0−1 days. The results of Lee et al. (2015c) are consistent with those reported in Di et al. (2017a) where it was observed that increasing the natural spline df to 6 and 9 for both the temperature and dew point temperature covariates did not change the magnitude of the $PM_{2.5}$-mortality association when compared to the main analysis that used 3 df.

The recent studies focusing on short-term $PM_{2.5}$ exposures and mortality that examined alternative approaches to controlling for long-term temporal trends and the confounding effects of weather in all-year analyses are consistent with the observations from studies focusing on PM_{10} in the 2009 PM ISA. The limited assessment of model specification when conducting seasonal analyses provides some evidence that associations may be more sensitive to model specification. Overall, the results from these studies indicate that alternative approaches may influence the magnitude of the $PM_{2.5}$-mortality association, but have not been found to influence the direction of the observed association.

11.1.5.2 Influence of Long-Term $PM_{2.5}$ Concentrations on Short-Term $PM_{2.5}$ Associations

It has often been questioned whether the associations observed in epidemiologic studies of short-term air pollution exposure reflect the impact of the short-term exposure on health or are partly a reflection of exposure to air pollution over many years. This question is often posed for $PM_{2.5}$, where a large body of epidemiologic evidence demonstrates strong associations between both short- and long-term $PM_{2.5}$ exposure and mortality. In a study of the New England area, Shi et al. (2015) attempted to address the impact of different exposure durations on the $PM_{2.5}$-mortality relationship by examining both long- and short-term $PM_{2.5}$ exposures and mortality in the same statistical model. The authors observed in analyses using the full cohort that the association between short-term $PM_{2.5}$ exposure and mortality was relatively unchanged in models without adjustment (2.14% [95% CI: 1.38, 2.89]; lag 0−1) and with adjustment (2.08 [95% CI: 1.32, 2.84]) for long-term $PM_{2.5}$ exposures. These results provide additional evidence confirming the relationship between short-term $PM_{2.5}$ exposure and mortality.

11.1.6 Effect Modification of the $PM_{2.5}$-Mortality Relationship

The examination of effect modification of the $PM_{2.5}$-mortality relationship can be divided into several categories. There are some studies that examine whether specific individual- or population-level characteristics modify the $PM_{2.5}$-mortality association, which can provide information pertaining to whether certain populations are at increased risk of a PM-related health effect. Other studies focus more

broadly on examining those factors that potentially modify that $PM_{2.5}$-mortality association, and may explain some of the observed geographic heterogeneity in risk estimates. A detailed discussion of populations potentially at increased risk of PM-related health effects can be found in Chapter 12. As a result, this subsection focuses on exploring those factors that may modify the $PM_{2.5}$-mortality association and provide insight on the heterogeneity in risk estimates.

11.1.6.1 Season

The examination of whether $PM_{2.5}$-mortality associations differ by season can provide a better understanding of the overall relationship between short-term $PM_{2.5}$ exposure and mortality. The 2009 PM ISA reported some evidence that $PM_{2.5}$-mortality associations are larger in magnitude during the warm season, specifically the spring, with the majority of this evidence coming from U.S. multicity studies (Zanobetti and Schwartz, 2009; Franklin et al., 2008). Recent multicity studies generally support the seasonal patterns of associations previously observed, and due to the larger sample size allow for a more robust evaluation of potential seasonal differences.

Among the recent U.S.-based multicity studies, Dai et al. (2014) observed a larger risk during the spring with a 2.9% (95% CI: 2.2, 3.5%) increase in total (nonaccidental) mortality at lag 0−1, but positive associations were observed across the summer, fall, and winter ranging from 0.46−1.2%. Although the magnitude of the association was larger in Dai et al. (2014), in the NPACT study, Lippmann et al. (2013a) observed a larger $PM_{2.5}$-mortality effect in the warm season (April–September) (0.35% [95% CI: 0.13, 0.58%]; lag 0) and evidence of no association in the cold season among 148 U.S. cities. Interestingly, Krall et al. (2013) observed no evidence of seasonal differences in $PM_{2.5}$-mortality associations across 72 U.S. cities, which included the same study years as Dai et al. (2014) and Lippmann et al. (2013a). Although some study design aspects differ among the studies, the overall design of Krall et al. (2013) and Lippmann et al. (2013a) are similar as are the underlying statistical models, which further complicates the interpretation of the disparate results with respect to seasonal associations between the studies. However, each of the studies reported positive associations in all-year analyses even though the magnitude varied (Figure 11-1).

European multicity studies support the results observed in Dai et al. (2014) and Lippmann et al. (2013a) of associations larger in magnitude during warmer months of the year. In a study of 20 European Mediterranean cities, Samoli et al. (2013) observed larger associations during the warm season (2.2% [95% CI: 1.5, 3.0]; lag 0−1) compared to the cold season (0.23% [95% CI: −0.08, 0.54]). Pascal et al. (2014) also observed larger associations during the summer (3.4% [95% CI: 1.8, 5.1]; lag 0−1) compared to the other three seasons with estimates ranging from −0.6 to 0.9%. However, in copollutant models with O_3 the authors observed that associations across all seasons persisted, except the summer (0.50% [95% CI: −3.3, 4.4]) indicating some evidence of potential confounding by O_3.

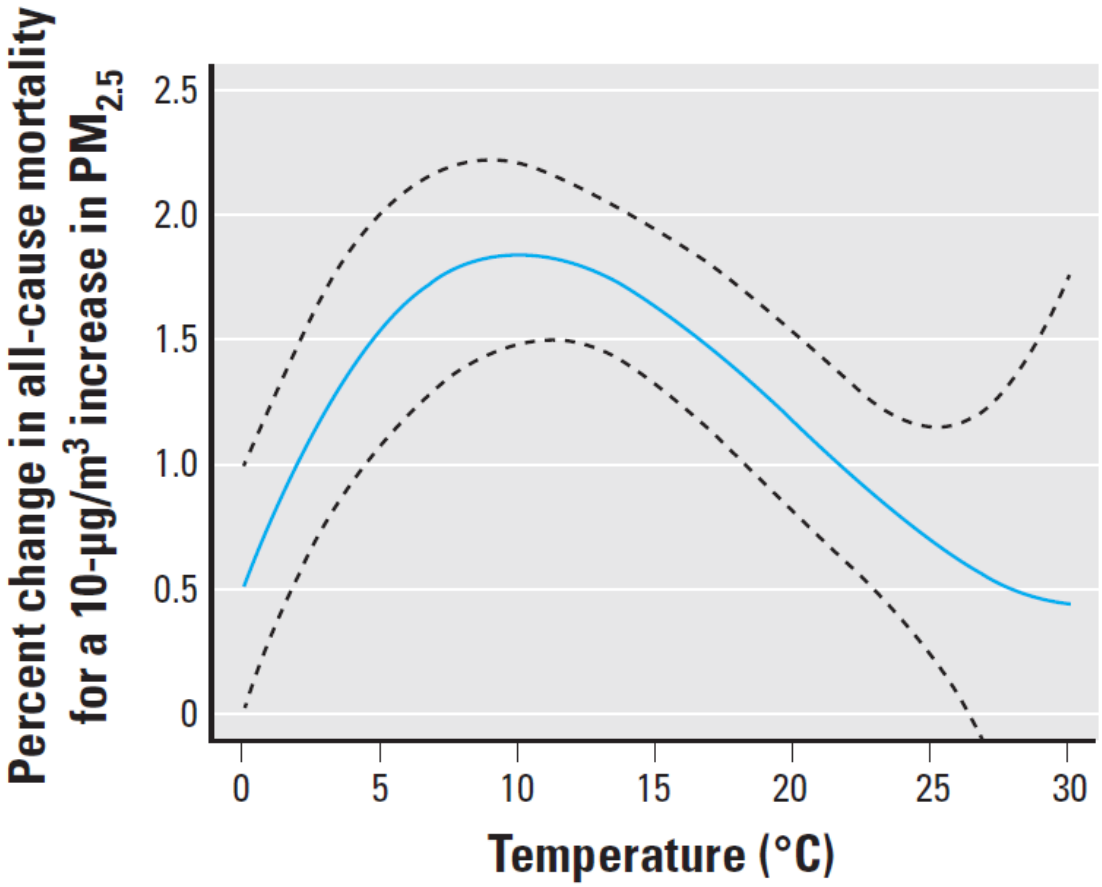
Across recent multicity studies, there was general agreement that $PM_{2.5}$-mortality associations were larger in magnitude during warmer months. However, it remains unclear if copollutants confound the seasonal patterns in associations observed. Across most studies the pattern of seasonal associations persisted using different methods to examine whether there was evidence of seasonal differences in associations with some studies relying on stratified analyses (Dai et al., 2014; Samoli et al., 2013) and others incorporating interaction terms between $PM_{2.5}$ and season (Pascal et al., 2014; Lippmann et al., 2013a).

11.1.6.2 Temperature

Seasonal analyses, such as those discussed above, indirectly take into consideration the role of temperature on the $PM_{2.5}$-mortality association. However, these studies do not directly address the question of whether higher or lower temperature days modify the $PM_{2.5}$-mortality association. Studies by Dai et al. (2014) and Pascal et al. (2014) further explore the role of temperature on the $PM_{2.5}$-mortality relationship.

Previous studies have demonstrated an inverted U-shape curve between temperature and indoor ventilation, which potentially influences exposure to $PM_{2.5}$ (Koutrakis et al., 2005). In a study of 75 U.S. cities, Dai et al. (2014) examined the influence of city-season mean temperature on the $PM_{2.5}$-mortality association. Consistent with the observations of Koutrakis et al. (2005) the authors found a smaller $PM_{2.5}$-mortality association during high and low temperatures, which could be attributed to reduced indoor penetration of $PM_{2.5}$ as a result of less ventilation (Figure 11-5).

Whereas Dai et al. (2014) focused on examining the $PM_{2.5}$-mortality relationship across the distribution of city-season temperatures, Pascal et al. (2014) focused on the "extra effect of PM during warm days." The authors defined warm days as those days "when the mean temperature equals or exceeds the 97.5th percentile of the mean temperature distribution" (Pascal et al., 2014). Stratifying on days above the 97.5th percentile, Pascal et al. (2014) reported a larger increase in nonaccidental mortality on warm days (1.4% [95% CI: −5.5, 8.9]; lag 0−1) compared to nonwarm days (0.70% [95% CI: −0.10, 1.5]); however, confidence intervals were large indicating a small number of days with temperatures within this range of the temperature distribution. The interaction term examining the additional PM-mortality effect attributed to high temperatures was similar to the warm days stratified result, i.e., indicating potential evidence of effect measure modification, but with wide confidence intervals (interaction ratio: 1.03 [95% CI: 0.97, 1.11]).



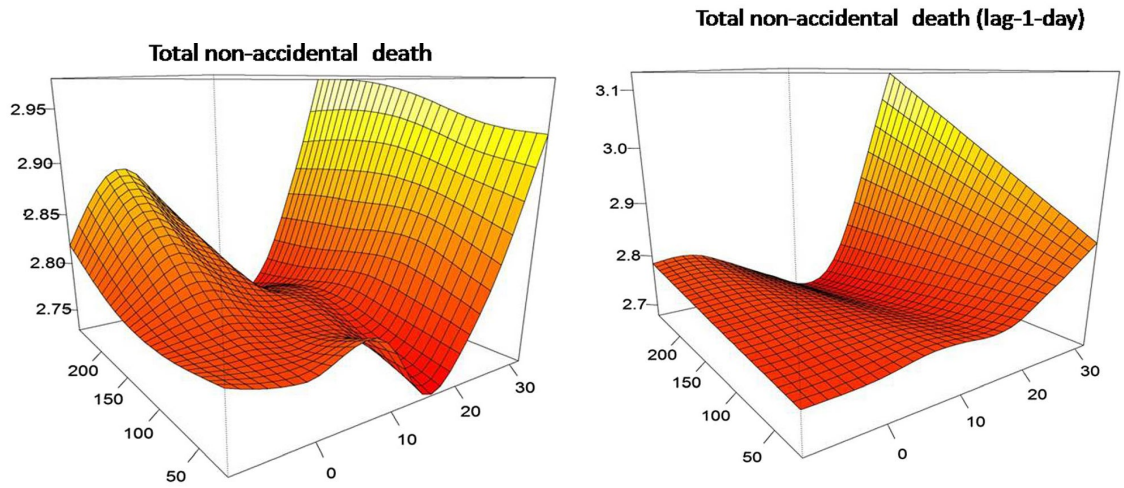
Source: Permission pending, Dai et al. (2014).

Figure 11-5 Relationship between estimated $PM_{2.5}$-mortality association and temperature.

Additional studies conducted by Sun et al. (2015) and Li et al. (2015), in Hong Kong and Beijing, respectively, had mean $PM_{2.5}$ concentrations over 20 µg/m^3 during the study duration, but used unique approaches to examine the potential interactive effect of temperature on the $PM_{2.5}$-mortality relationship. Sun et al. (2015) first identified the lag structure over which there was evidence of a temperature-mortality relationship for both cold and warm temperatures using generalized cross-validation (GCV). This process identified a 0−6-day lag for cold temperatures and a 0−1-day lag for warm temperatures. The authors then defined the cold and warm temperature cutoff by identifying the temperature at which the log relative risk of the temperature-mortality relationship was equal to zero resulting in low temperatures being defined as <22°C, medium temperatures as 22–25°C, and high temperatures as ≥25° C. In a stratified analysis, Sun et al. (2015) reported evidence of a larger association for $PM_{2.5}$ and total (nonaccidental) mortality in Hong Kong for lower temperatures (0.94% [95% CI: 0.65,

1.2]; lag 0−1) when compared to higher temperatures (0.47% [95% CI: 0.18, 0.76]). This pattern of associations persisted in copollutant models with NO_2, SO_2, and O_3.

A different pattern of $PM_{2.5}$-mortality associations was observed by Li et al. (2015) when examining the influence of temperature. The authors first visually examined the combined effects of temperature and $PM_{2.5}$ on mortality using a nonparametric bivariate response surface. Using the results of the bivariate model allowed for the identification of temperature ranges that could be examined by conducting a stratification analysis (i.e., low temperature <2.6ºC, medium temperature 2.6–23.5ºC, and high temperature >23.5ºC). Whereas Sun et al. (2015) observed larger mortality associations only at higher temperatures, in the bivariate response model Li et al. (2015) reported evidence of larger $PM_{2.5}$-mortality associations at both low and high temperatures, specifically at lag 0 (Figure 11-6). However, it is important to note that the definition of low temperature for Li et al. (2015) and Sun et al. (2015) differed, complicating the comparison of results between these two studies.



Note: *y*-axis = percent increase in mortality, *z*-axis = $PM_{2.5}$ concentrations, and *x*-axis = temperature (°C).
Source: Permission pending, Li et al. (2015).

Figure 11-6 Bivariate $PM_{2.5}$-temperature response surfaces for total (nonaccidental) mortality using same-day 24-hour mean temperature and lag 0 and lag 1 $PM_{2.5}$ concentrations.

The observation from the bivariate model was confirmed when examining $PM_{2.5}$-mortality associations at the various temperature ranges in the stratified analysis. The magnitude of the association was similar at both the low and high temperatures at both lag 0 (low temperature: 1.3 [95% CI: 0.46, 2.0]; high temperature: 1.4 [95% CI: 0.35, 2.4]) and lag 1 (low temperature: 1.1 [95% CI: 0.48, 1.7]; high temperature: 1.1 [95% CI: 0.76, 2.1]).

Overall, the examination of the potential modification of the $PM_{2.5}$-mortality relationship by temperature remains unclear. Although there is some evidence of an increase in the magnitude of the $PM_{2.5}$ association at both lower and higher temperatures in studies conducted at higher $PM_{2.5}$ concentrations, to date studies conducted within the U.S. have not provided evidence of a modification of the $PM_{2.5}$-mortality association by temperature.

11.1.6.3 City and Regional Characteristics

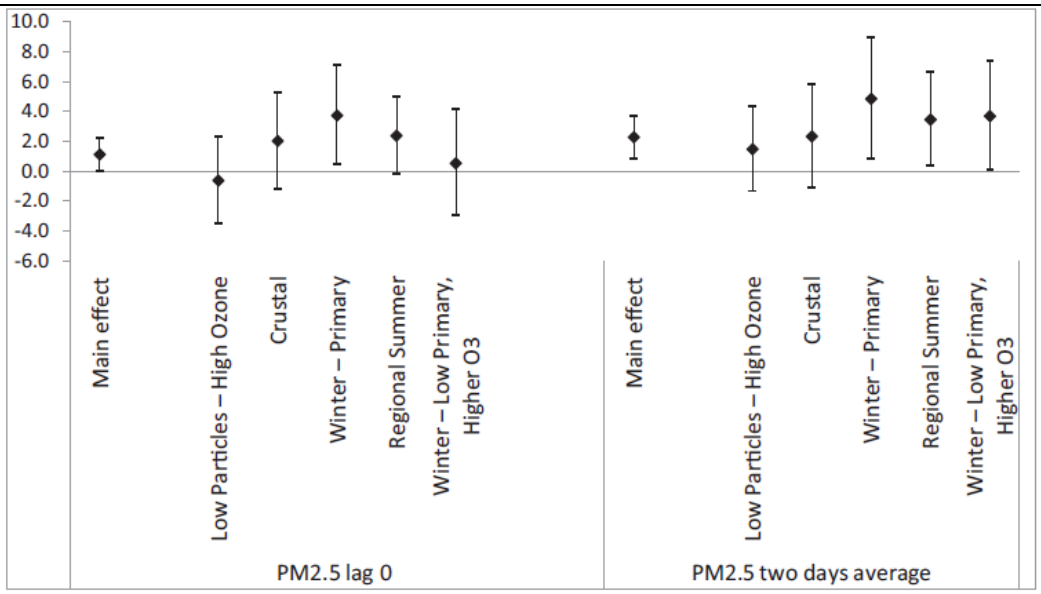
It has often been hypothesized the heterogeneity in $PM_{2.5}$-mortality associations observed across cities could be attributed to city-specific differences in population demographics, $PM_{2.5}$ composition, or exposure characteristics. Studies of population demographics often focus on whether there is evidence of effect modification and not on how risk may change between cities due to demographic differences. In the 2009 PM ISA, the evaluation of the observed heterogeneity in $PM_{2.5}$-mortality associations was limited to studies examining whether individual $PM_{2.5}$ components or the prevalence of air conditioning use, a surrogate for decreased PM penetration indoors, modified the association. Although examining the modification of the PM-mortality relationship by $PM_{2.5}$ components included studies focusing on PM_{10}, overall a number of components were found to potentially explain the city-to-city heterogeneity (U.S. EPA, 2009). Additionally, there was some evidence that the prevalence of air conditioning (AC) use across cities modifies the $PM_{2.5}$-mortality association and that $PM_{2.5}$-mortality associations vary by region of the country (i.e., east vs. west) (U.S. EPA, 2009). Although $PM_{2.5}$ composition, AC use, and geographic location may explain some of the heterogeneity in $PM_{2.5}$-mortality risk estimates, at the completion of the 2009 PM ISA it remained unclear what factors or combination of factors explain the observed heterogeneity. Recent studies discussed in the following sections have expanded upon the initial analyses detailed in the 2009 PM ISA by examining whether specific $PM_{2.5}$ components/mixtures or exposure characteristics provide information that explains the heterogeneity in $PM_{2.5}$-mortality associations observed in multicity studies.

11.1.6.3.1 Composition/Mixtures

The examination of effect modification of the $PM_{2.5}$-mortality association, by either an individual $PM_{2.5}$ component or the proportion of a $PM_{2.5}$ component to mass, is one of the traditional approaches that has been employed to examine the influence of PM composition on the $PM_{2.5}$-mortality relationship. Although detailed as one of the main approaches used to examine the association between a $PM_{2.5}$ component and a health outcome in Mostofsky et al. (2012), these studies are discussed within this section because they have primarily been used as a means to explain the heterogeneity in $PM_{2.5}$-mortality risk estimates observed between cities or regions of a country. Other studies focusing specifically on examining the effect of individual $PM_{2.5}$ components on mortality are detailed in Section 11.1.11.

As part of the NPACT study and in a study of 75 U.S. cities, Lippmann et al. (2013a) and Dai et al. (2014) conducted analyses similar to those in Franklin et al. (2008), which was evaluated in the 2009 PM ISA, to examine whether specific pollutants modify the $PM_{2.5}$-mortality relationship. Lippmann et al. (2013a) examined the modifying effect of long-term average pollutant concentrations, while Dai et al. (2014) and Franklin et al. (2008) examined the $PM_{2.5}$ component to $PM_{2.5}$ mass proportion. In a second-stage analysis, Lippmann et al. (2013a) reported evidence that as the IQR of mean concentrations of pollutants increased across cities, the $PM_{2.5}$-mortality association increased in magnitude, specifically with SO_4^{2-}, weekday excess $PM_{2.5}$, Pb, and V. There was additional evidence that other pollutants (e.g., Cu, Se) may also contribute to modifying the $PM_{2.5}$-mortality association, but to a lesser extent, as was evident by the wider confidence intervals. Dai et al. (2014) used the monthly component-to-$PM_{2.5}$ proportion in the second-stage analysis to examine effect modification and observed as the distribution of the proportion increased from the 10th to 90th percentile there was evidence of larger $PM_{2.5}$-mortality associations for Si, S, and Ca. Although Dai et al. (2014) and Lippmann et al. (2013a) did not report consistent results, Lippmann et al. (2013a) and Franklin et al. (2008) both reported some evidence that SO_4^{2-} potentially increases the magnitude of the $PM_{2.5}$-mortality relationship and may explain some of the heterogeneity in risk estimates.

In addition to the traditional effect modification approaches to examining heterogeneity, such as those used in Lippmann et al. (2013a) and Dai et al. (2014), a number of recent studies have explored alternative, and to an extent more novel approaches such as whether cities have unique pollution profiles, to examine if city or region specific pollutant characteristics help explain differences in $PM_{2.5}$-mortality risk estimates observed between cities and regions within the U.S. One such approach developed by Zanobetti et al. (2014a) explores whether distinct daily pollution profiles modify the $PM_{2.5}$-mortality relationship, and although limited to Boston, MA, could be applicable to examining heterogeneity between cities or regions. The authors used $PM_{2.5}$ component data along with gaseous pollutant data from 1999−2009 to identify five distinct pollution profiles through the use of *k*-means clustering, which was detailed in Austin et al. (2012). The five clusters identified were representative of days with low particles—high O_3; crustal; winter—primary; regional summer; and winter—low primary, higher O_3. In single-pollutant models with $PM_{2.5}$, the authors observed a 1.1% increase in mortality (95% CI: 0.0, 2.2) at lag 0 and a 2.3 % increase (95% CI: 0.9, 3.7) at lag 0−1. When examining whether days with specific pollution profiles modified the $PM_{2.5}$-mortality relationship, Zanobetti et al. (2014a) reported evidence that at lag 0 the winter—primary cluster, which has a strong contribution from traffic and oil combustion, had the largest effect, with some evidence that the crustal and regional summer clusters modified the association. A similar pattern of results was observed when examining lag 0−1, but with the magnitude of the association slightly larger for each pollution profile (Figure 11-7). Overall, this study indicates that specific pollution profiles may modify the $PM_{2.5}$-mortality relationship.

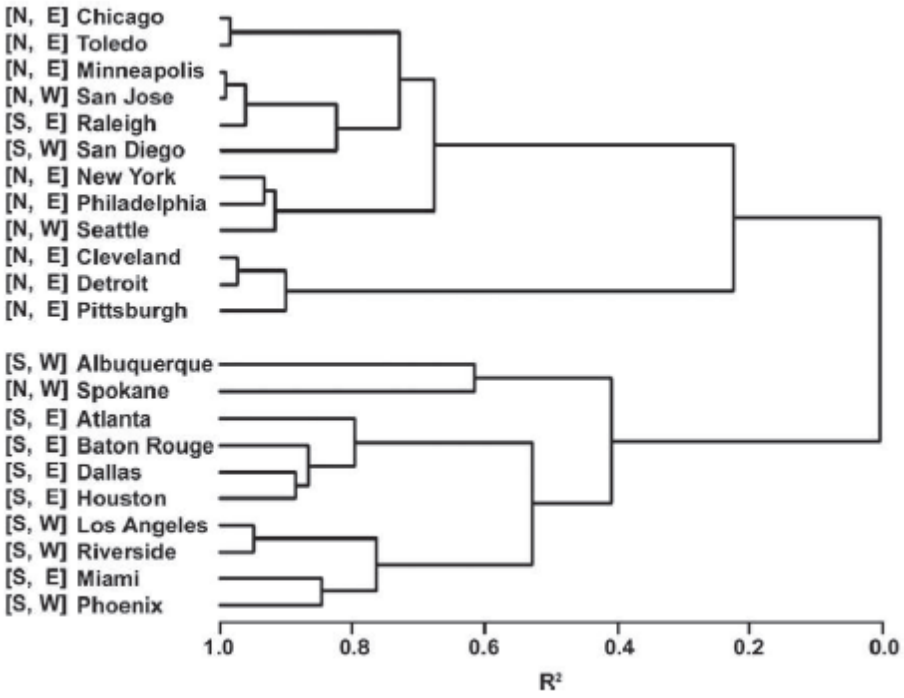


Source: Permission pending, Zanobetti et al. (2014a).

Figure 11-7 Percent increase in mortality for a 10 μg/m^3 increase in $PM_{2.5}$ concentrations at lag 0 and lag 0−1 in single-pollutant models and models containing indicator variables representative of days with specific pollution profiles.

Davis et al. (2011) approached the question of heterogeneity in $PM_{2.5}$-mortality risk estimates using a more qualitative approach. Specifically, the authors focused on whether there was evidence of broad regional patterns in $PM_{2.5}$ component concentrations by examining if groups of cities have similar $PM_{2.5}$ component profiles and if there are regional differences in individual $PM_{2.5}$ component concentrations. To conduct this analysis the authors focused on the 30 cities within the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) that represented the 20 most populated cities and 10 midsize cities that were selected to provide regional coverage across the U.S. Data for 20 $PM_{2.5}$ components from the CSN for the years 2005−2007. Of the cities included in the study, only 17 large and 5 midsize cities had sufficient monitoring data to be included in the cluster analysis. After normalizing the data across cities by calculating the coefficient of divergence (COD) between data sets in each city, a hierarchical cluster analysis was used to group cities with similarities in $PM_{2.5}$ component concentrations. Based on the clustering analysis there was evidence of a north-south delineation in cities with similar $PM_{2.5}$ component concentrations, with the exception of three cities (i.e., Raleigh, San Diego, and Spokane), and not the east-west delineation that has often been observed when examining geographic differences in $PM_{2.5}$-mortality risk estimates as detailed in the 2009 PM ISA (U.S. EPA, 2009) (Figure 11-8). This potential north-south delineation was further reflected when examining whether there are regional differences in individual $PM_{2.5}$ component concentrations using the Wilcoxon two-sample test. In east-west analyses, crustal components (e.g., Al, Si, Ti, Fe, and K) and nitrate were found to be

higher in the West, whereas higher sulfur was observed in the East. There was no evidence of east-west differences in combustion-related components. However, when examining north-south contrasts there was evidence of higher concentrations of combustion-related components, sulfate and nitrate in the North and crustal components and OC in the South. Collectively these results support regional differences in the composition of $PM_{2.5}$. However, within geographic regions there is city-to-city heterogeneity in $PM_{2.5}$ mortality risk estimates, which complicates the interpretation of the regional pattern of associations observed in studies such as Davis et al. (2011).



Note: N = north, S = south, W = west, E = east.
Source: Permission pending, Davis et al. (2011).

Figure 11-8 Dendrogram showing relationships among the 17 largest and 5 midsize National Morbidity, Mortality, and Air Pollution Study (NMMAPS) cities using $PM_{2.5}$ composition data from Chemical Speciation Network (CSN) for 2005−2007.

While Davis et al. (2011) focused on broad regional differences in the composition of $PM_{2.5}$ and its potential role in explaining the heterogeneity in $PM_{2.5}$-mortality risk estimates, Baxter et al. (2013) focused specifically in trying to identify potential contributors to the city-to-city differences in risk estimates observed in multicity epidemiologic studies. Baxter et al. (2013) conducted a semiquantitative analysis focusing on $PM_{2.5}$ component and gaseous pollutant concentrations to gain a better understanding

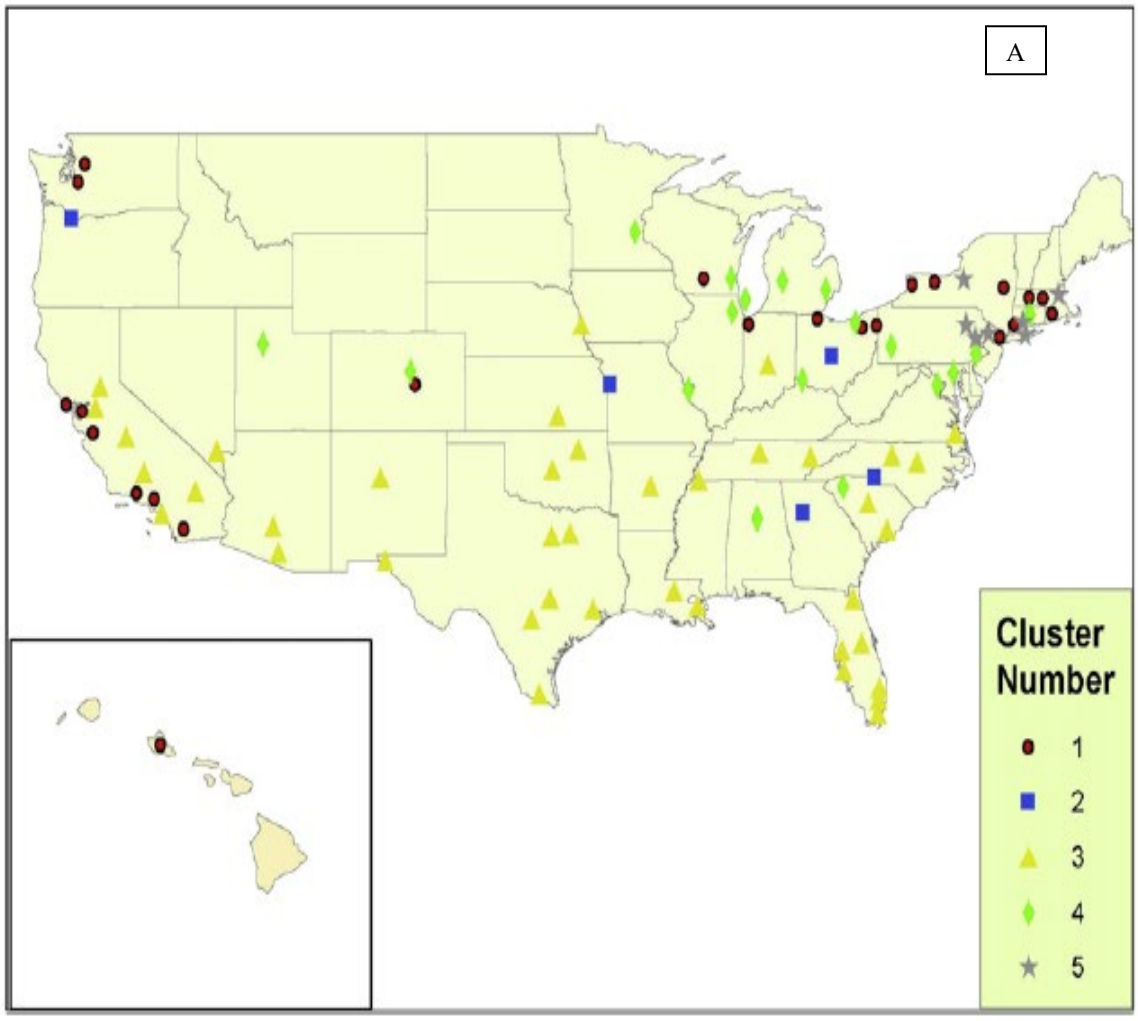
of their relationship with $PM_{2.5}$ mass, and their potential influence on $PM_{2.5}$-mortality risk estimates. Focusing on the results from a study of 27 U.S. cities conducted by Franklin et al. (2007), Baxter et al. (2013) explored city-specific air pollution characteristics for the two cities in each region of the U.S. with the largest and smallest $PM_{2.5}$-mortality risk estimates (i.e., Northeast: Boston, MA [largest] and Pittsburgh, PA; South: Memphis, TN [largest] and Birmingham, AL; Midwest: Milwaukee, WI [largest] and Detroit, MI; West: San Diego, CA [largest] and Riverside, CA). To explore air pollution characteristics of each city, the authors examined (1) percent contribution of each $PM_{2.5}$ component to $PM_{2.5}$ mass; (2 and 3) Spearman correlation and COD between each city pair and pollutant (21 $PM_{2.5}$ components, $PM_{2.5}$ mass, and gaseous pollutants); (4) Spearman correlation between each $PM_{2.5}$ component and gaseous pollutant and $PM_{2.5}$ mass in each city; and (5) composition of air pollution mixtures in each city to identify whether sources differ between cities by conducting a principal component analysis (PCA) including both PM and gaseous pollutant data. Although there were some differences between cities, this analysis did not identify one component or group of components that could explain the difference between city pairs. Additionally, in the source-based analysis, differences were observed between cities when focusing on local sources such as motor vehicle and industry, but one or more sources were not identified that could explain the difference in risk estimates between cities. Overall, the study by Baxter et al. (2013) indicates some differences in $PM_{2.5}$ composition and sources between cities, but also demonstrates that city-to-city differences in $PM_{2.5}$-mortality risk estimates are not limited to $PM_{2.5}$ source and composition differences.

11.1.6.3.2 Exposure Factors

Many studies that have examined heterogeneity in $PM_{2.5}$-mortality risk estimates often examine whether specific city characteristics modify the association. This examination occurs in a second-stage analysis that focuses on the distribution of a factor (e.g., percentage poverty) across cities and how risk changes moving from the low end to the high end of the distribution. Lippmann et al. (2013a) used this more traditional approach, but focused on a suite of city-specific variables (i.e., land-use, port-, and traffic-related data) that could reflect exposure differences. The evidence indicated that port berth volume within 60 miles of a city along with the sum of road lengths within a city increased the risk of $PM_{2.5}$-related mortality. There was also evidence that percent of a city developed and percent of a city with wetland positively increased risk, but with greater uncertainty. The relationship between $PM_{2.5}$-mortality risk and port berth volume is supported by the negative relationship with distance to large port. The results of Lippmann et al. (2013a) provides evidence that city-specific factors that may influence exposure can influence the $PM_{2.5}$-mortality relationship across cities.

Unlike Lippmann et al. (2013a) where the focus was on community-level factors that may modify the $PM_{2.5}$-mortality relationship, Baxter and Sacks (2014), which in some respect is an expansion of Baxter et al. (2013), focused on exploring whether there are city-specific exposure profiles that may have a role in explaining the observed heterogeneity. Using data from the American Housing Survey (AHS) for

94 Core-Based Statistical Areas (CBSAs) with a population greater than 500,000 from 2001−2005, the authors used k-means clustering to examine whether there were unique CBSA clusters based on residential infiltration factors (i.e., percent of homes with central AC, mean year home was built, and mean home size) and both residential infiltration factors and commuting factors (i.e., mean in-vehicle commuting time and mean in-vehicle commuting distance). The residential infiltration factor analysis identified five clusters, with a large number of the cities in clusters 1 (N = 24) and 3 (N = 40). The main difference between these clusters were the mean home age was slightly older for cluster 1, while there was a greater percent of central AC in cluster 3. There was evidence of a geographic pattern in the clustering of cities as reflected in Figure 11-9. The combination of residential infiltration and commuting factors resulted in the identification of 10 clusters. Across clusters, only two clusters had more than 11 CBSAs, clusters 8 and 9, which primarily differed by percent of homes with central AC. Cities with shorter commuting times were found to also have shorter commuting distances. Although not as pronounced as the residential infiltration analysis there tended to be a geographic pattern in the residential infiltration and commuting factor analysis (Figure 11-9). In Baxter and Sacks (2014) 66 of the CBSAs encompassed cities included in NMMAPS, therefore, the cluster analysis results were compared to city-specific PM_{10}-mortality risk estimates from NMMAPS. Recognizing the potential differences in infiltration between $PM_{2.5}$ and PM_{10}, given that $PM_{2.5}$ comprises varying proportions of PM_{10}, the results provide some evidence that cities with older homes and a smaller percent of central AC have higher risk estimates compared to cities with newer homes and a larger percent of central AC. Although the addition of commuting factors to the cluster analysis could reveal some additional exposure nuances between cities, the small number of CBSAs in each cluster complicates the interpretation of the combined analyses. Overall, the results of Baxter and Sacks (2014) provide initial evidence that certain differences in exposure characteristics between cities may also contribute to explaining the city-to-city heterogeneity in $PM_{2.5}$-mortality risk estimates.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Cluster Number
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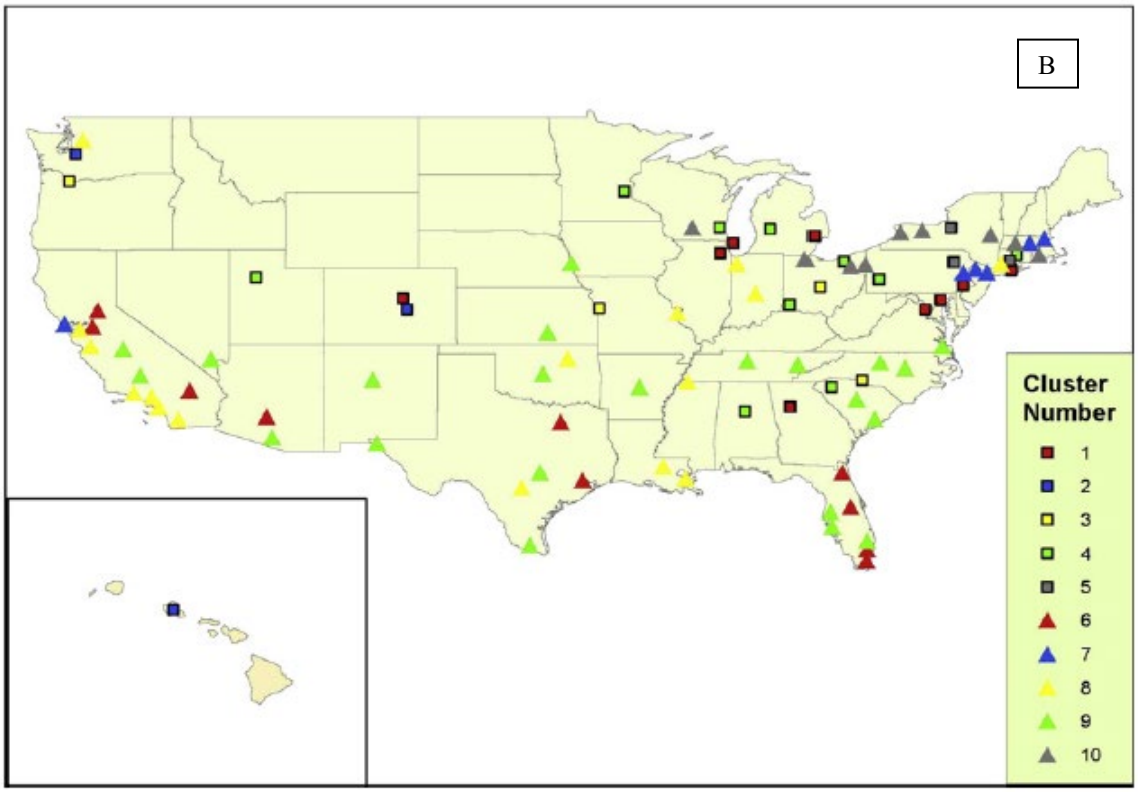


Source: Permission pending, Baxter and Sacks (2014).

Figure 11-9 Maps of Core-Based Statistical Areas (CBSAs) by cluster based on (A) residential infiltration factors and (B) residential infiltration and commuting factors.

Baxter et al. (2017) built off the cluster analysis detailed in Baxter and Sacks (2014), and used only the residential infiltration-based clusters as a means to explore whether there are differences in the $PM_{2.5}$-mortality association across clusters and if the clusters explain the observed heterogeneity. In the analysis, 77 U.S. cities were grouped into five clusters based on prevalence of central air conditioning, mean year home was built, and mean size of home. Focusing on those clusters where the number of cities included was greater than 5, there is some evidence of differences in $PM_{2.5}$ mortality risk estimates that could be attributed to differential exposure as a result of residential infiltration. For example, clusters 1 and 3 were representative of smaller homes, but with differing age and percent of air conditioning. Cluster 3 homes had a higher percentage of central air conditioning and were newer than cluster 1, but the risk estimates in both clusters were the smallest across clusters (cluster 1: −0.01% [95% CI: −0.31, 0.29]; cluster 3: 0.25 [95% CI: −0.15, 0.65]). Cluster 4, which was representative of larger homes that were older with a moderate percentage of central air conditioning (i.e., 55.7%) had the largest risk estimate (0.66% [95% CI: 0.35, 0.97]). These results are consistent with previous studies that have demonstrated that air exchange rates are higher in larger and older homes, resulting in increased exposures to ambient

PM (Section 3.4.1.1). In a second-stage analysis, the authors further examined the role of the clusters in explaining the observed heterogeneity and whether the individual residential infiltration factors alone contributed to the heterogeneity. Baxter et al. (2017) reported that cluster assignment explained 6% of the observed heterogeneity, and that only larger home size modified the $PM_{2.5}$-mortality association, which is consistent with the results of the main cluster analysis.

11.1.7 Evaluation of Exposure Assessment Techniques

As described in the previous section, a number of factors have been considered in an attempt to explain the heterogeneity in $PM_{2.5}$-mortality risk estimates. An underlying factor not discussed in the previous section is the potential role of exposure assessment and exposure misclassification (see Section 3.4.2). Traditionally, air pollution epidemiology studies have relied upon single monitors or the average of multiple monitors over some geographic extent (e.g., county) to assign exposure. Recent studies have examined the influence of distance to monitor on the $PM_{2.5}$-mortality association. Additionally, new and innovative approaches have been developed that use ensemble approaches to combine air pollution data from a number of sources including ambient monitors and satellite data, as well as model predictions in an attempt to obtain a more refined estimate of exposure. The following section discusses these approaches and how this information further informs the $PM_{2.5}$-mortality relationship.

11.1.7.1 Monitor Representativeness

Recent studies by Davis et al. (2011), Kloog et al. (2013), Kim et al. (2015), and Di et al. (2017a) conducted sensitivity analyses to examine the potential influence of distance to monitor on the relationship between short-term $PM_{2.5}$ exposure and mortality. These types of analyses can provide information on exposure assessment that may influence the city-to-city or regional heterogeneity observed in multicity epidemiologic studies.

As part of their analysis examining if there are broad $PM_{2.5}$ composition differences between regions, Davis et al. (2011) also explored the representativeness of ambient monitors to reflect population exposure. Both on an individual city level as well as the broad regional classifications identified (i.e., north versus south, and east versus west), the authors examined the percent of the population residing within 1 km, 5 km, 10 km, and 15 km from an AQS monitor. Less than 50% of the population across almost all cities resided within 5 km of a monitor. Interestingly, of the 20 cities with populations over 1 million people, almost half of the cities had up to 20% of the population residing greater than 15 km of an AQS monitor. In the regional designations, a larger percent of people was closer to monitors at all distances for both the East and North designations. The 2009 PM ISA (U.S. EPA, 2009) presented data for intermonitor correlation versus distance between monitors to examine the influence of distance to

monitor on exposure assessment (see Section 3.4.2.2). Correlations of approximately Pearson $R = 0.90$ were reported for intermonitor distances of 15 km in three cities (Boston, Pittsburgh, and Los Angeles) with correlations largely above 0.8 at distances of 50 km in Boston in Pittsburgh. These findings indicate that temporal variability of $PM_{2.5}$ concentrations are often similar over urban scales. Therefore, large errors in the exposure time-series are not anticipated across large distances for the cities included in Davis et al. (2011).

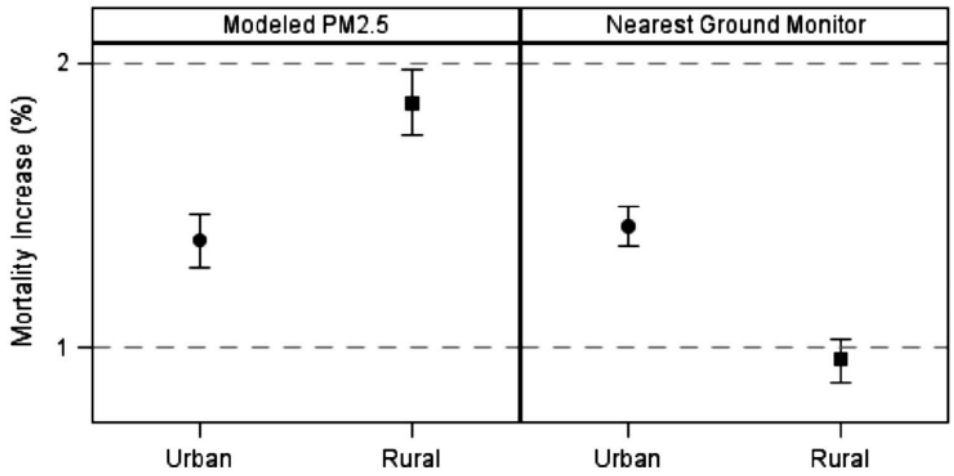
Recent studies examined the influence of distance to monitor on the association between short-term $PM_{2.5}$ exposure and mortality. Kloog et al. (2013) examined the impact of distance to monitor on the daily $PM_{2.5}$-mortality association as part of a study conducted in Massachusetts. Within this study, daily $PM_{2.5}$ concentrations were predicted to 10 × 10 km grid cells using satellite data that were calibrated with ground-level $PM_{2.5}$ measurements. Additionally, land-use regression and weather variables were used to predict $PM_{2.5}$ concentrations on days where AOD values were not available. In a sensitivity analysis, the authors examined associations based on distance to monitor, defined as greater than or less than 20 km from an ambient monitor. In models that included an interaction term for distance to monitor, Kloog et al. (2013) reported a 4.5% increase in mortality (95% CI: 2.6, 6.5) near a monitor and 1.4% increase in mortality (95% CI: 0.8, 2.0) far from a monitor at lag 0−1, compared with a 2.8% increase in mortality (95% CI: 2.0,3.5) across the study population. Di et al. (2017a) also conducted a sensitivity analysis examining $PM_{2.5}$-mortality associations based on the nearest monitor within 50 km. In the main analysis, the authors predicted $PM_{2.5}$ and O_3 concentrations to 1 km × 1 km grid cells based on the combination of ambient monitoring data, satellite measurements, land-use data, and chemical transport modeling. $PM_{2.5}$ exposures were assigned to the zip code level and in a model that adjusted for O_3, Di et al. (2017a) reported a 1.05% increase (95% CI: 0.95, 1.15) in all-cause mortality at lag 0−1 days within the Medicare population. In the nearest monitor analysis, the authors also reported a positive association, but it was smaller in magnitude (0.83% [95% CI: 0.73, 0.93]; lag 0−1), which is consistent with the results of Kloog et al. (2013) and indicative of some degree of exposure misclassification at distances further from monitors. However, Kim et al. (2015) as part of the DASH study in Denver, CO, examined the $PM_{2.5}$-mortality association at 10 km and 20 km buffers around a single monitor and found no evidence of a difference in the association across buffers. As discussed in Davis et al. (2011) and in Section 2.5.1.2.1 this could reflect the spatial and temporal characteristics of $PM_{2.5}$ in Denver, which may differ from those observed in Kloog et al. (2013) in Massachusetts and Di et al. (2017a) nationally.

11.1.7.2 Urban versus Rural Locations

As detailed in Chapter 3, new and innovative statistical approaches have been developed to obtain more refined exposure estimates, particularly in areas that do not have ambient monitors (i.e., rural locations). The studies by Kloog et al. (2013), Shi et al. (2015), and Lee et al. (2015c) all employed some derivation of a similar approach to estimate $PM_{2.5}$ concentrations that relied upon satellite measurements.

The question that often arises from studies such as these is: How well does the method employed capture $PM_{2.5}$ concentrations in areas that do not have monitors?

Of the studies conducted to date, only Lee et al. (2015c) explored the difference between urban and rural $PM_{2.5}$-mortality associations using both the modeled data, which incorporated satellite measurements, and the nearest ambient monitor across three southeastern U.S. states. Using the modeled $PM_{2.5}$ data, the authors reported evidence of a larger association in rural compared to urban locations, but when assigning exposure using data from ambient $PM_{2.5}$ monitors, the rural location association remained positive although it was attenuated (Figure 11-10). Overall, the results from Lee et al. (2015c) provide some evidence for potential differences in $PM_{2.5}$-mortality associations between urban and rural locations, but uncertainties remain due to the relative sparseness of monitors in rural locations and the known differences in $PM_{2.5}$ sources between locations.



Source: Permission pending, Lee et al. (2015c).

Figure 11-10 Percent increase in mortality at lag 0−1 for a 10 μg/m³ increase in 24-hour average $PM_{2.5}$ concentrations based on location of residence using modeled and monitored $PM_{2.5}$ concentrations.

11.1.8 Timing of Effects and Exposure Metrics

11.1.8.1 Lag Structure of Associations

Within the 2009 PM ISA, the studies evaluated indicated that the effect of short-term $PM_{2.5}$ exposure on mortality was immediate, occurring within the first few days after exposure, with the strongest evidence, in terms of magnitude and precision of the associations, in the range of 0 to 1 day.

However, these studies defined the lags to examine a priori and often in accordance with the 1-in-3 or 1-in-6 day sampling schedule of ambient $PM_{2.5}$ monitors. Additionally, these mortality studies examined associations with $PM_{2.5}$ using a 24-hour average exposure metric, resulting in the inability to determine whether subdaily exposure metrics (e.g., 1-hour max) capture other exposures of concern. Some studies published since the completion of the 2009 PM ISA have conducted more extensive examinations of the lag structure of associations for short-term $PM_{2.5}$ exposures and mortality, focused on subdaily exposure metrics to understand the role of peak $PM_{2.5}$ concentrations on the $PM_{2.5}$-mortality relationship, and examined whether the risk of mortality attributed to short-term $PM_{2.5}$ exposure has changed over time.

The studies evaluated in the 2009 PM ISA did not conduct a systematic evaluation of the lag structure of associations between short-term $PM_{2.5}$ exposure and mortality, but reported evidence of consistent, positive associations within the first few days after exposure (i.e., 0−1 lag days) (U.S. EPA, 2009). Recent studies have conducted analyses aimed at understanding the timing of effects between short-term $PM_{2.5}$ exposure and mortality. Studies have ranged in their level of evaluation from examining multiple individual or multiday lags to more systematically examining whether there is evidence of immediate (e.g., lag 0−1 days), delayed (e.g., lag 2−5 days), or prolonged (e.g., lag 0−5 days) effects. However, a number of studies do not provide the information necessary to systematically evaluate the timing of the relationship between $PM_{2.5}$ exposure and mortality. For example, in a study conducted in the Netherlands, Janssen et al. (2013) examined single-day lags ranging from 0 to 3 days, along with the inclusion of a lag encompassing the average of 0−6 days. By not including information on lag days 4, 5, and 6 only the single-day lag information can be interpreted because it is not possible to differentiate whether considering a longer lag is reasonable.

The evidence from experimental studies can provide information on the biological plausibility of the timing between exposure and effect. In the case of cardiovascular mortality, which encompasses ~33% of total (nonaccidental) mortality (NHLBI, 2017), it is well characterized that short-term $PM_{2.5}$ exposure results in rather immediate cardiovascular responses (Section 6.1.14.3), providing biological plausibility for the focus of most $PM_{2.5}$-mortality studies on shorter windows of exposure, in the range of 0 to 2 days. However, the evidence for a respiratory effect in response to short-term $PM_{2.5}$ exposure has been found to be more delayed, which provides biological plausibility for examining associations with respiratory mortality at longer lags (Section 5.1.10.3). Although the discussion of lag structure of associations for cause-specific mortality will be detailed in the respective cardiovascular and respiratory chapters, the biological plausibility of the timing of effects for cardiovascular and respiratory mortality provide the basis for focusing the discussion on the lag structure of associations on those studies that: evaluate a series of single-day lags (e.g., lags 0 to 3 days); conduct a systematic evaluation of different lags (e.g., single-day versus distributed or average of multiple days); and include all single days evaluated in the distributed or multiday average lags (i.e., if a study examines a distributed or multiday average lag of 0−6 days it also examines single-day lags of 0 to 6 days).

Most of the recent studies that examined the lag structure of associations for the $PM_{2.5}$-mortality relationship either conducted analyses of single-day lags over multiple days or various iterations of multiday lags (e.g., 0−1, 0−2, 0−3, etc.). As part of the NPACT study, Lippmann et al. (2013b) examined single-day lags ranging from 0 to 3 days. In all-year analyses, the strongest associations, in terms of magnitude and precision, with total (nonaccidental) mortality were at lags 0 and 1 day, with associations persisting in the warm season and no evidence of an association in the cold season. The results of Lippmann et al. (2013b) are consistent with the pattern of associations observed in other multicity studies that also examined a series of single-day lags (Di et al., 2017a; Stafoggia et al., 2017; Janssen et al., 2013). Di et al. (2017a) examined single-day lags of 0 to 4 days and compared these results to the main analysis that used a multiday lag of 0−1 days. It is important to note that the main analysis as well as these sensitivity analyses were based on a model that also adjusted for O_3. Across the single-day lags, results support an immediate effect as reflected by largest magnitude of an association for lag 0 and 1 day (~ 0.75% increase in all-cause mortality), but these associations were smaller in magnitude to the main analysis that used the multiday lag of 0−1 days (1.05% [95% CI: 0.95, 1.15]). When examining the other single-day lags, Di et al. (2017a) reported a much smaller association at lag 2 (~0.25% increase), with no evidence of an association at lag 3 and 4. In an examination of single-day lags (i.e., 0 to 3 days), Janssen et al. (2013) reported rather immediate effects with associations similar in magnitude (0.8−1.0%) across each of the single-day lags. An examination of single-day lags ranging from 0 to 10 days in a study of eight European cities reported the strongest association at lag 1 (Stafoggia et al., 2017). The pattern of associations observed across studies that examined a series of single-day lags is consistent with the results reported by Lee et al. (2015a) that examined a series of multiday lags and observed the strongest associations for total (nonaccidental) mortality at lag 0−1, but associations remained positive when examining multiday lags up to 0−4 days.

In the MED-PARTICLES Project, Samoli et al. (2013) conducted a systematic evaluation of the lag structure of associations by examining whether there was evidence of an immediate (lag 0−1), delayed (lag 2−5), or prolonged (lag 0−5) $PM_{2.5}$-mortality effect as well as examining the pattern of associations over lags 0 to 7 days in a polynomial distributed lag model. The authors reported a 0.55% increase in total (nonaccidental) mortality (95% CI: 0.27, 0.84) at lag 0−1, a 0.51% increase (95% CI: 0.07, 0.96) at lag 2−5, and a 0.70% increase (95% CI: 0.22, 1.18) at lag 0−5. Although the 0−5 lag shows the association largest in magnitude, the 0- to 1-day lag comprises a large amount of this effect. A closer examination of associations on a day-to-day basis through the polynomial distributed lag model shows evidence of the strongest associations within the range of 1 to 3 days (quantitative results not presented). The combination of the multi- and single-day lag analyses provides further support for the $PM_{2.5}$-mortality association being strongest within the first few days after exposure.

11.1.8.2 24-Hour Average versus Subdaily (Peak) Exposures

Most of the studies conducted to date have examined the association between short-term $PM_{2.5}$ exposure and mortality using 24-hour average exposure metrics. A few recent single-city studies examined alternative exposure metrics to further examine the relationship between short-term $PM_{2.5}$ exposure and mortality. In a study conducted in Oslo, Norway that estimated $PM_{2.5}$ concentrations using a dispersion model Madsen et al. (2012) used the traditional 24-hour average exposure metric along with one representative of peak exposures (i.e., the hourly average two daily rush hour periods; 08:00–10:00 and 15:00–17:00). Within this study mean peak concentrations were approximately 23 $\mu g/m^3$, while 24-hour average concentrations were 15.1 $\mu g/m^3$. The authors observed the same pattern of associations across the single and multiday lags examined (i.e., lags 4 and 5, and 0−4 and 0−5 days) for the 24-hour average and peak exposure metric with the magnitude being slightly larger for the 24-hour average metric (quantitative results not provided). Although Lin et al. (2016) examined peak and 24-hour average $PM_{2.5}$ exposures that were much higher (i.e., 1-hour max = 66.9 $\mu g/m^3$ and 24-hour average = 46.4 $\mu g/m^3$) than those reported in Madsen et al. (2012), the results from this study can further inform our understanding of alternative exposure metrics. Unlike Madsen et al. (2012) which used $PM_{2.5}$ concentrations predicted from a dispersion model, $PM_{2.5}$ concentrations in Lin et al. (2016) were measured over 11 ambient monitors throughout Guangzhou, China. In analyses of peak and 24-hour average $PM_{2.5}$ exposures and cardiovascular mortality at single day lags ranging from 0 to 5 days, and multiday lags from 0 to 3 days, the authors observed a consistent pattern of associations across lags for both exposure metrics, with the magnitude of the association often larger in models with the 24-hour average metric. The results of Lin et al. (2016) are consistent with those observed in Madsen et al. (2012), which collectively provide initial evidence that when comparing subdaily and 24-hour average exposure metrics, the 24-hour average exposure metric is consistently associated with mortality.

11.1.9 Alternative PM Size Fractions and Exposure Metrics

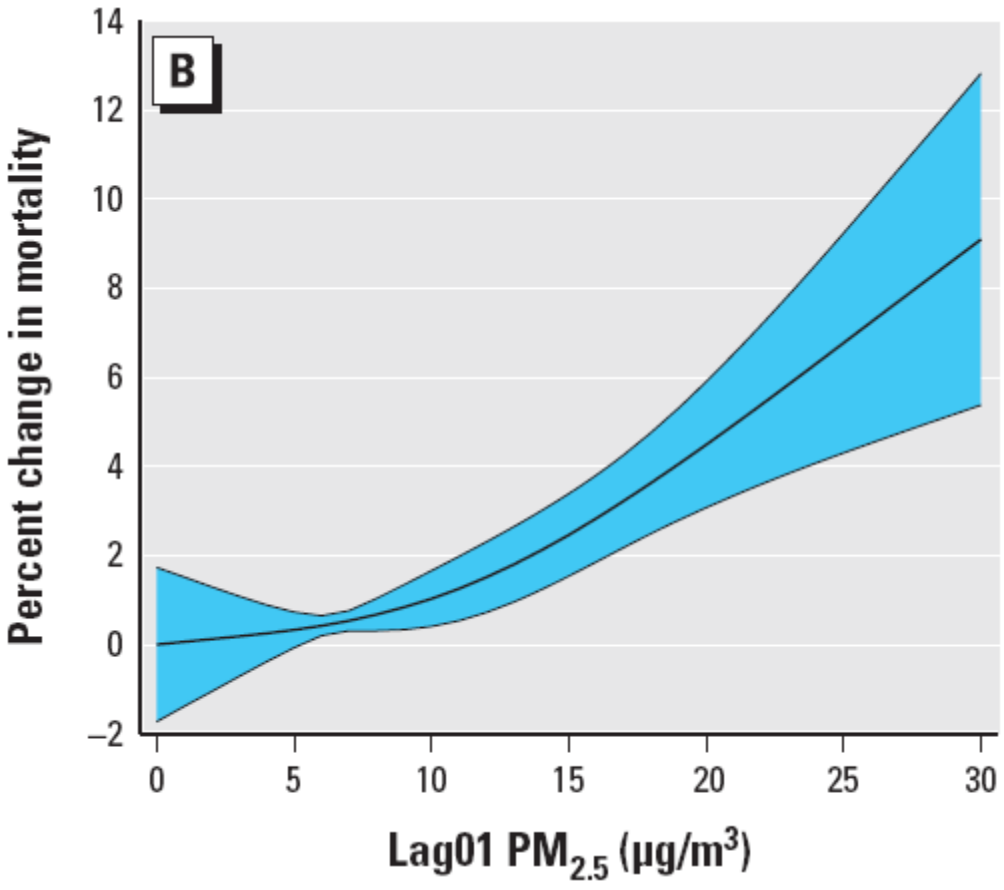
While most studies that examine the relationship between short-term $PM_{2.5}$ exposure and mortality focus on $PM_{2.5}$ mass, some studies have examined alternative exposure metrics, such as particle number concentration (NC), surface area concentration (SC), and mass concentration (MC) for PM size fractions smaller than $PM_{2.5}$ but larger than 100 nm. Particles smaller than 100 nm will be discussed in Section 11.5. To date, only a few studies examined PM size fractions smaller than 2.5 µm, and often these size fractions are included in studies that examine UFP exposure and mortality (Section 11.4.1). Across studies, generally positive associations were observed for particles >100 nm for NC, and <1.0 µm for SC and MC (See (U.S. EPA, 2018a)), which supports the larger body of evidence demonstrating a consistent, positive association between short-term $PM_{2.5}$ exposure and mortality. However, these studies are conducted over a short duration and are limited to two locations (i.e., China (Meng et al., 2013; Leitte et al., 2012; Breitner et al., 2011) and Spain (Pererz et al., 2009)). Additionally, although these studies report

generally positive associations it remains difficult to directly compare results from studies that use a NC or SC metric with the traditional mass based exposure metric.

11.1.10 Concentration-Response (C-R) Relationship and Threshold Analyses

Previous reviews of PM including the 2004 PM AQCD (U.S. EPA, 2004) along with the 2009 PM ISA (U.S. EPA, 2009) have highlighted the difficulty associated with examining the shape of the PM-mortality concentration-response (C-R) relationship and whether a threshold exists. Specifically, the 2004 AQCD and 2009 PM ISA stated that conducting C-R and threshold analyses is challenging due to the "(1) limited range of available concentration levels (i.e., sparse data at the low and high end); (2) heterogeneity of [at-risk] populations [between cities]; and (3) influence of measurement error" (U.S. EPA, 2004). Even with these inherent limitations, studies have continued to examine the PM-mortality C-R relationship and whether a threshold exists. In the 2009 PM ISA, the examination of the PM-mortality C-R relationship was limited to studies of PM_{10}. Within the multicity studies examined, there was evidence of a linear no-threshold C-R relationship between short-term PM exposures and mortality with some evidence of differences in the shape of the C-R curve across cities. A major limitation of the C-R analyses conducted to date has been the reliance on PM_{10} data and the limited amount of data available to examine the shape of the C-R curve at the low end of the concentration distribution. Recent studies conducted in the U.S. (Di et al., 2017a; Lee et al., 2015c; Shi et al., 2015) and Europe (Samoli et al., 2013) provide information specifically on the C-R relationship between short-term $PM_{2.5}$ exposures and mortality in different regions of the world and at $PM_{2.5}$ concentrations at the lower end of the distribution.

In a study of states in the New England region of the U.S., Shi et al. (2015) conducted two analyses to address (1) whether associations are observed at concentrations <30 $\mu g/m^3$ and (2) the shape of the PM-mortality C-R relationship at concentrations <30 $\mu g/m^3$. In the analysis restricted to person-time with $PM_{2.5}$ concentrations <30 $\mu g/m^3$ Shi et al. (2015) reported associations similar in magnitude (2.14% [95% CI: 1.33, 2.95]) to those observed in the full cohort that included $PM_{2.5}$ concentrations >30 $\mu g/m^3$ (2.14% [95% CI: 1.38, 2.89]). Using the restricted data set, Shi et al. (2015) then examined the shape of the C-R relationship between short-term $PM_{2.5}$ concentrations and mortality by fitting a penalized regression spline where the degrees of freedom (df) of the spline were selected by generalized cross-validation. The authors reported no evidence of deviation from linearity, but had less confidence in the shape of the curve at concentrations <5 $\mu g/m^3$ due to wider confidence intervals (Figure 11-11).

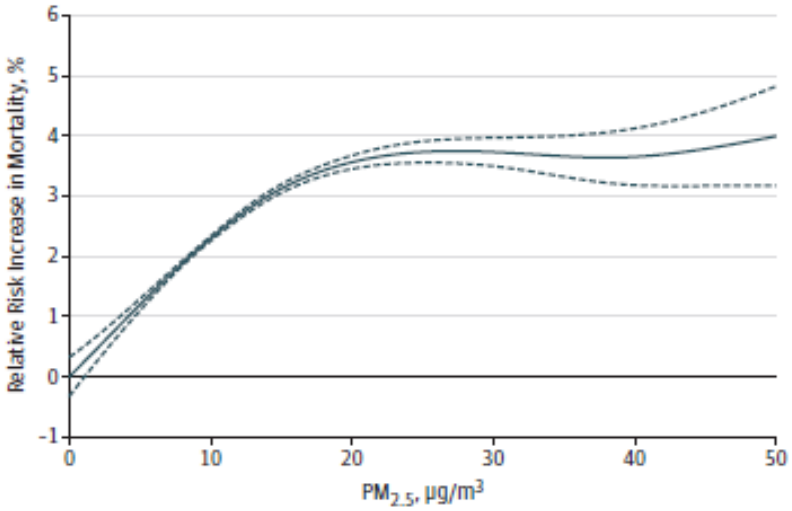


Source: Permission pending, Shi et al. (2015).

Figure 11-11 Concentration-response relationship between short-term $PM_{2.5}$ concentrations and mortality (lag 0−1) in an analysis restricted to person time with daily $PM_{2.5}$ concentrations <30 µg/m³.

Di et al. (2017a) examined the C-R relationship focusing on questions similar to those examined by Shi et al. (2015), but in a national analysis of the Medicare population. In a copollutant model with O_3 the authors examined: (1) whether associations are observed at $PM_{2.5}$ concentrations <25 µg/m³, and (2) the shape of the PM-mortality C-R relationship, particularly at concentrations <25 µg/m³. In the low exposure analysis, Di et al. (2017a) reported an association larger in magnitude (1.61 [95% CI: 1.48, 1.74]; lag 0−1) than the main analysis (1.05% [95% CI: 0.95, 1.15]; lag 0−1), indicating a steeper slope at lower $PM_{2.5}$ concentrations. The results of the low exposure analysis were confirmed when examining the shape of the C-R curve using penalized splines for both $PM_{2.5}$ and O_3, which reported evidence of an almost linear relationship with no evidence of a threshold and a steeper slope at concentrations <25 µg/m³ (Figure 11-12). While the low exposure results of Di et al. (2017a) differ from those of Shi et al. (2015),

this could be a reflection of the populations of the studies encompassing different age ranges (i.e., individuals over the age of 65, and the entire population, respectively).



Source: Permission pending, Di et al. (2017a).

Figure 11-12 Two-pollutant analysis of the $PM_{2.5}$ concentration-response (C-R) curve with penalized splines for both $PM_{2.5}$ and O_3 to examine the percent increase in daily mortality at lag 0−1 days.

Lee et al. (2015c) confirmed the findings of Shi et al. (2015) and Di et al. (2017a) that $PM_{2.5}$-mortality associations persist at low ambient $PM_{2.5}$ concentrations by conducting a subset analysis focusing on three southeastern U.S. states. The authors examined the association between short-term $PM_{2.5}$ exposure and mortality by limiting the dataset to zip codes where the predicted annual $PM_{2.5}$ concentrations were less than 12 µg/m^3 and in a separate analysis focused on ZIP codes where predicted 24-hour average $PM_{2.5}$ concentrations were less than 35 µg/m^3. In the full cohort the authors reported a 1.56% increase in mortality (95% CI: 1.19, 1.94) at lag 0−1. In the cut-point analyses focusing on the annual and daily cutpoints, Lee et al. (2015c) reported a 2.06% (95% CI: 1.97, 2.15) and 2.08% (95% CI: 1.99, 2.17) increase in mortality, respectively, providing evidence that $PM_{2.5}$-mortality associations remain and may be larger in magnitude at low $PM_{2.5}$ concentrations.

While Shi et al. (2015), Lee et al. (2015c), and Di et al. (2017a) examined the shape of the C-R relationship between short-term $PM_{2.5}$ exposure and mortality across a distribution of data, Samoli et al. (2013) focused exclusively on whether there is evidence of a threshold at specific concentrations. As part of the MED-PARTICLES project, the authors examined threshold values ranging from 0 to 35 µg/m^3 at increments of 5 µg/m^3 across the 10 Mediterranean cities included in the study. The threshold model

assumed the risk of mortality due to short-term $PM_{2.5}$ exposure was zero below the threshold value. Evidence of a threshold was examined in each city by computing the deviance of the fitted model for each threshold value, the authors then computed an average deviance across all cities. The deviance for each threshold value was then examined to determine whether any threshold values minimized the mean deviance. Samoli et al. (2013) did not observe any evidence of a threshold, with the models assuming no threshold reporting the lowest mean deviance, and subsequently being considered the "best-fitting" models. Although the 24-hour average $PM_{2.5}$ concentrations observed in the MED-PARTICLES cities were much higher than the $PM_{2.5}$ concentrations observed in Shi et al. (2015), the threshold analysis in Samoli et al. (2013) focusing on daily concentrations below 35 $\mu g/m^3$ provides additional support for a linear C-R relationship at concentrations relevant to U.S. cities.

Although difficulties remain in assessing the shape of the $PM_{2.5}$-mortality concentration-response relationship, as identified in the 2009 PM ISA, and studies have not conducted systematic evaluations of alternatives to linearity, recent studies continue to provide evidence of a no-threshold linear relationship, with less confidence at concentrations lower than 5 $\mu g/m^3$. Additionally, those studies that conducted analyses focused on examining associations at lower $PM_{2.5}$ concentrations provide initial evidence indicating that associations persist and may be larger in magnitude (i.e., a steeper slope) at lower $PM_{2.5}$ concentrations.

11.1.11 Associations between $PM_{2.5}$ Sources and Components and Mortality

The 2009 PM ISA examined the relationship between both $PM_{2.5}$ components and sources and individual health outcomes (e.g., mortality) and effects (e.g., blood pressure), as well as collectively across health outcomes, to assess whether any one source or component was more strongly related to a health outcome or effect. At the completion of the 2009 PM ISA, it was not evident that any one component or source was more strongly related to mortality, which was consistent with the broader conclusion on sources and components (U.S. EPA, 2009). Recent studies that examine both the relationship between short-term exposures to $PM_{2.5}$ components along with $PM_{2.5}$ mass provide additional evidence on whether $PM_{2.5}$ mass or an individual $PM_{2.5}$ component or source is more strongly associated with mortality.

11.1.11.1 $PM_{2.5}$ Components

The examination of the relationship between $PM_{2.5}$ components and mortality can generally be divided into two types of analyses: (1) those that examine whether specific components modify the $PM_{2.5}$-mortality association or (2) those that examine whether an individual component is associated with mortality and potentially a better indicator of PM toxicity compared to $PM_{2.5}$ mass. Although

approach (1) is considered one of the techniques used to assess component toxicity as detailed in Mostofsky et al. (2012) these studies are often used to examine heterogeneity in $PM_{2.5}$-mortality risk estimates. As a result, the focus of this section is on those techniques that fall under approach (2), which includes assessing $PM_{2.5}$ component effect by component concentration, component proportion, component concentration adjusted for $PM_{2.5}$ mass, component residual, or $PM_{2.5}$ residual (Mostofsky et al., 2012). Multicity $PM_{2.5}$ mortality studies detailed in the 2009 PM ISA examined associations with individual components (Ostro et al., 2008; Ostro et al., 2007), and indicated that a number of components are associated with mortality. However, there were limitations in the air quality data (i.e., 1-in-3 or 1-in-6 sampling of $PM_{2.5}$ components) and only a small number of studies had been conducted that examined the relationship between $PM_{2.5}$ components and mortality (U.S. EPA, 2009).

Since the completion of the 2009 PM ISA (U.S. EPA, 2009), a growing number of studies have examined the relationship between short-term exposure to $PM_{2.5}$ components and mortality. These studies continue to support the conclusions of the 2009 PM ISA that many components are associated with mortality and there is no evidence that any one component is more strongly associated with mortality than $PM_{2.5}$ mass. The recent multicity studies and U.S.-based single-city studies are detailed in Table 11-3 along with study specific details including statistical approach used to assess the $PM_{2.5}$ component effect and the $PM_{2.5}$ components examined.

Table 11-3 Study-specific details of multicity and U.S.-based single-city studies that examine the relationship between short-term exposure to $PM_{2.5}$ components and mortality.

Study	Mortality Outcome	Data/Sampling Schedule	Statistical Approach Used	Components Examined
Multicity studies				
Ostro et al. (2007) Six California counties, U.S. (2000–2003)	Cardiovascular	SLAMS; 1-in-3 or 1-in-6 day schedule	Individual components included in single pollutant model	Al, Br, Ca, Cl, Cu, EC, Fe, K, Mn, Ni, NO_3, OC, Pb, S, Si, SO_4, Ti, V, Zn
Ostro et al. (2008) Six California counties, U.S. (2000–2003)	Cardiovascular	SLAMS; 1-in-3 or 1-in-6 day schedule	Individual components included in single pollutant model	Ca, Cl, Cu, EC, Fe, K, NO_3, OC, S, Si, SO_4, Ti, Zn
†Krall et al. (2013) 72 U.S. cities (2000–2005)	Total	CSN; 1-in-3 or 1-in-6 day schedule	Individual components included in single pollutant model	EC, Na^+, NO_3, NH_4, OC, Si, SO_4

Table 11-3 (Continued): Study-specific details of multicity and U.S.-based single-city studies that examine the relationship between short-term exposure to $PM_{2.5}$ components and mortality.

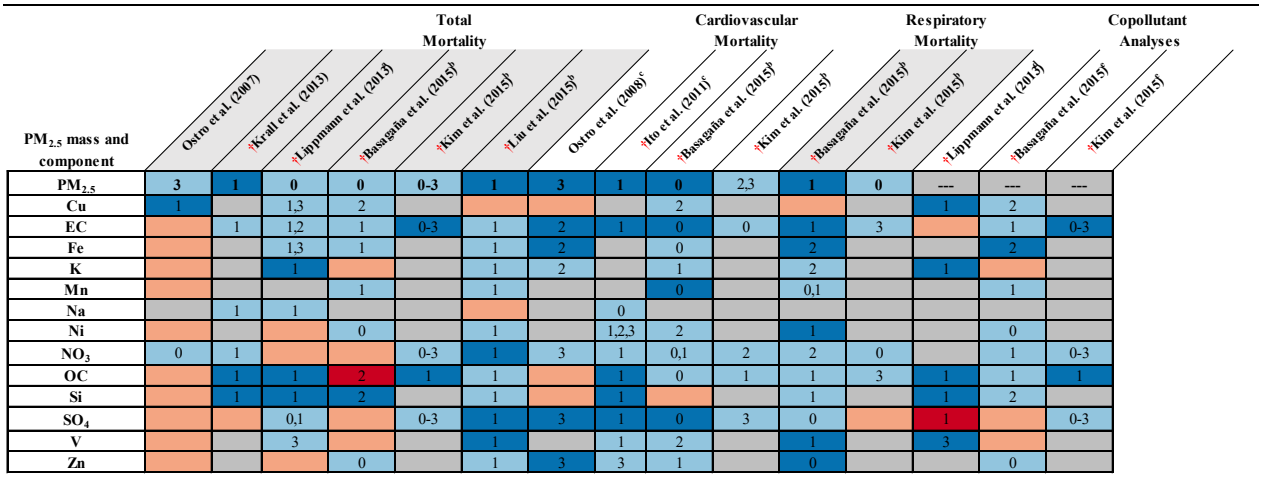
Study	Mortality Outcome	Data/Sampling Schedule	Statistical Approach Used	Components Examined
†Lippmann et al. (2013a) 64 U.S. cities (2001–2006)	Total	CSN; 1-in-3 or 1-in-6 day schedule	(1) Individual components included in single pollutant model; (2) individual components in copollutant model with $PM_{2.5}$	As, Cu, EC, Fe, K, Na, Ni, NO_3^-, OC, Pb, SO_4^{2-}, Se, Si, V, Zn
†Basagaña et al. (2015) Five South-European cities (2003–2013)	Total Cardiovascular Respiratory	One monitor in each city; daily monitoring in two cities, biweekly monitoring in two cities, and once a week monitoring in one city	(1) Individual components included in single pollutant model; (2) individual component residual	Ca, Cu, EC, Fe, K, Mg, Mn, Ni, NO_3^-, OC, SO_4^{2-}, SiO_2, TC, Ti, V, Zn
Single-city studies				
†Kim et al. (2015) Denver, CO (2003–2007)	Total Cardiovascular Respiratory	Daily measurements from one monitor (DASH site)	(1) Individual components included in single pollutant model; (2) individual component residual	EC, NO_3^-, OC, SO_4^{2-}
†Liu and Zhang (2015) Houston, TX (2000–2011)	Total	CSN; 1-in-3 or 1-in-6 day schedule	Individual components included in single pollutant model	Al, Br, Cr, Cu, EC, Fe, K, Mn, Na^+, NH_4^+, Ni, NO_3^-, OC, Si, SO_4^{2-}, V, Zn
†Zhou et al. (2011) Detroit, MI Seattle, WA (2002–2004)	Total Cardiovascular Respiratory	Daily measurements from one monitor in each city	Individual components included in single pollutant model	Al, EC, Fe, K, Na, Ni, S, Si, V, Zn
†Ito et al. (2011) New York, NY (2000–2006)	Cardiovascular	Three CSN monitors; 1-in-3 day sampling	Individual components included in single pollutant model	Br, EC, Na^+, Ni, NO_3, OC, SO_4, Se, Si, V, Zn

AQS-TTN = U.S. EPA Air Quality System Technology Transfer Network; CSN = Chemical Speciation Network; DASH = Denver Aerosol Sources and Health study; STN = Speciation Trends Network; SLAMS = State and Local Air Monitoring Stations Network.

†Studies published since the 2009 PM ISA.

As detailed in Table 11-3 and throughout the text that follows, the evaluation of the association between $PM_{2.5}$ components and mortality is complicated by the different methods applied across studies. Overall, the results for individual $PM_{2.5}$ components across studies are generally more imprecise than the results for $PM_{2.5}$ (i.e., much wider confidence intervals, often including the null value), which make the individual results, as well as results across studies, more difficult to interpret. As such, for the purposes of characterizing results with respect to $PM_{2.5}$ components a different convention is employed to evaluate the pattern of associations across studies. Specifically, risk estimates from studies are classified into four categories in Figure 11-13 and Figure 11-14: (1) statistically significant positive associations; (2) positive

associations, regardless of width of the confidence interval; (3) null or negative association; and (4) statistically significant negative association. Figure 11-13 and Figure 11-14 summarize the results from studies that examined associations between short-term $PM_{2.5}$ mass and $PM_{2.5}$ components that will be evaluated in the following section.



[a]Lippmann et al. (2013a) results representative of median interquartile range increase in individual $PM_{2.5}$ component concentrations for the 64 cities combined.

[b]Results representative of an interquartile range increase in individual $PM_{2.5}$ component concentrations.

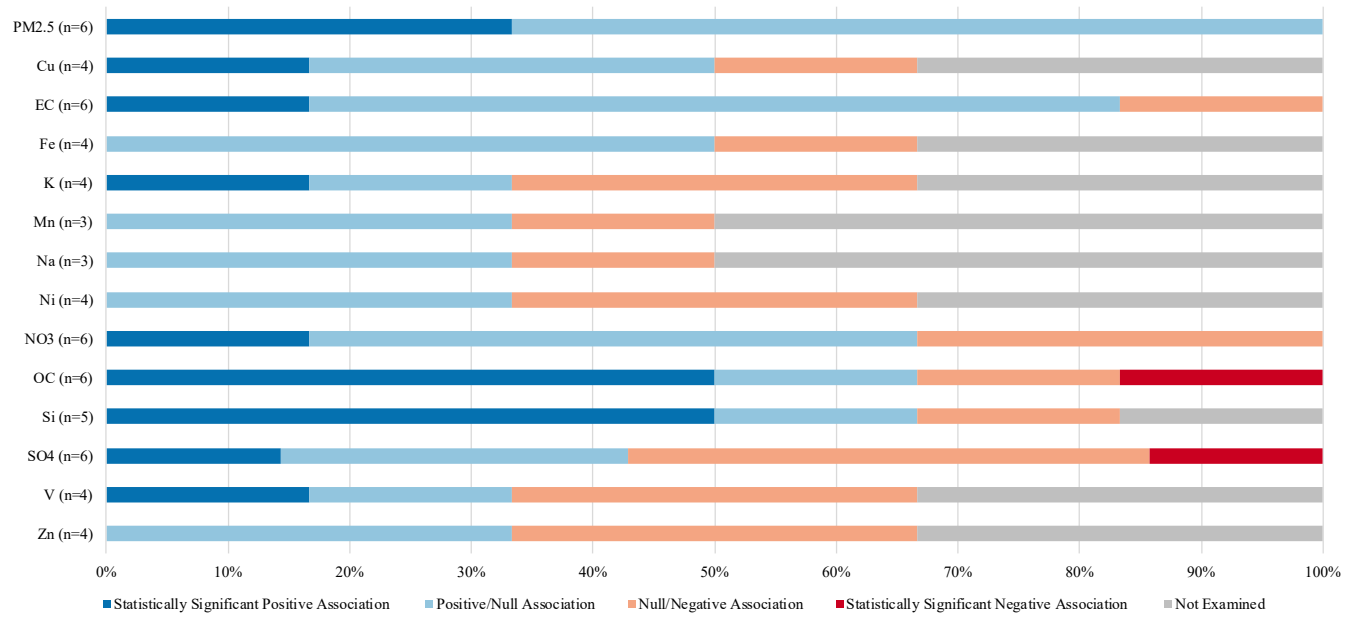
[c]Studies only examined $PM_{2.5}$ component associations with cardiovascular mortality.

[d]Lippmann et al. (2013a) results representative of median interquartile range increase in individual $PM_{2.5}$ component concentrations for the 64 cities combined in copollutant model with $PM_{2.5}$.

[e]Basagaña et al. (2015) results using the $PM_{2.5}$ component residual method detailed by Mostofsky et al. (2012).

Note: †$PM_{2.5}$ component studies published since the 2009 PM ISA. $PM_{2.5}$ row = lag(s) at which association observed between short-term $PM_{2.5}$ exposure and mortality; $PM_{2.5}$ components rows = lag(s) at which association observed. Dark blue = study reported statistically significant positive association; Light blue = study reported a positive association regardless of width of confidence intervals; Light orange = study reported null or negative association; Red = study reported statistically significant negative association; Gray = study did not examine individual component. Only those $PM_{2.5}$ components that were examined in at least three studies that included results for total (nonaccidental) mortality are included in this table.

Figure 11-13 Heat map of associations observed between short-term $PM_{2.5}$ and $PM_{2.5}$ components exposure and mortality in multi- and single-city studies.



N = number of studies that provided an estimate for $PM_{2.5}$ mass and individual $PM_{2.5}$ components.

Note: Bars represent the percent of associations across studies for $PM_{2.5}$ mass or $PM_{2.5}$ components detailed in Figure 11-13 that are statistically significant positive (dark blue), positive/null (light blue), null/negative (light orange), statistically significant negative (red), or not examined (gray).

Figure 11-14 Distribution of total (nonaccidental) mortality associations for $PM_{2.5}$ and $PM_{2.5}$ components examined in studies detailed in Figure 11-13.

Single Component Models

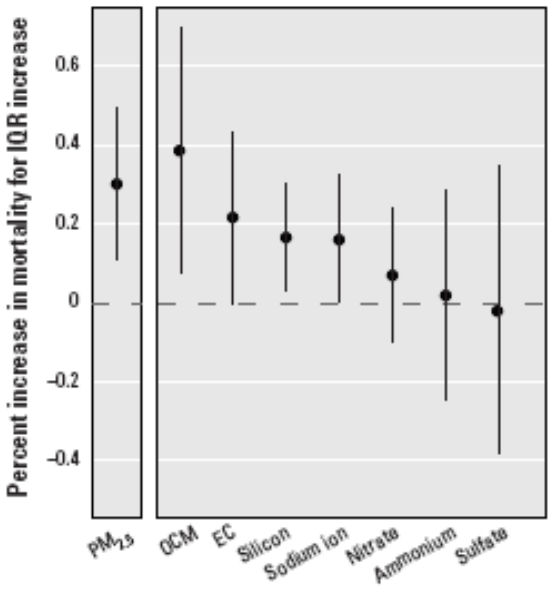
At the completion of the 2009 PM ISA, most studies that examined the association between short-term exposure to $PM_{2.5}$ components and mortality consisted of statistical models that examined component-mortality associations one at a time. Although informative, these studies are often difficult to interpret because they do not account for the individual component being part of $PM_{2.5}$ mass. Additionally, although often not reported, the correlations between individual $PM_{2.5}$ components and $PM_{2.5}$ mass are often moderate ($r = 0.4–0.7$) to high ($r > 0.7$), which complicates the interpretation of the single-component model results. Recent multi- and single-city studies have continued to examine $PM_{2.5}$ component-mortality associations in single component models, but the addition of seasonal analyses for some studies have attempted to gain a broader understanding of how $PM_{2.5}$ mass and overall composition may change over the course of the year and affect health.

Multicity studies conducted by Lippmann et al. (2013a) as part of the NPACT study and Krall et al. (2013) in 72 U.S. cities, both primarily focused on single-component models to assess the relationship between $PM_{2.5}$ components and mortality. Lippmann et al. (2013a) examined the association between short-term exposure to $PM_{2.5}$ components, along with sources (see Section 11.1.11.2), across 64 U.S. cities. The components selected to be examined were based on analyses of measurements obtained, in

reference to both the detection limit and fraction of readings equaling zero; monitor-to-monitor correlations for a subset of cities; and toxicological considerations (Lippmann et al., 2013a). In the main analyses, the authors did not use measured component data, but instead calculated the daily deviation from the monthly mean in an attempt to "reduce the influence of the seasonal cycles of pollutants on the overall associations" (Lippmann et al., 2013a). In single-component models in an all-year analysis, the strongest associations were for Cu, K, OC, Si, and V although at different lags ranging from 1 to 3 days, while the $PM_{2.5}$ association was positive at lag 0 (Figure 11-13). In seasonal analyses, the $PM_{2.5}$ association was strongest in the warm season at lag 0 with no evidence of an association in the cold season. Across components strong positive associations were only observed at lag 0 for Na, NO_3^-, and SO_4^{2-}, while other components were found to be positively associated at other lags including: EC, K, Na, OC, Pb, Si, and V. A different pattern of associations was observed in the cold season with evidence of positive associations across lags for As, Cu, EC, K, OC, Se, and Si. The different lag structure of associations for the individual components compared to $PM_{2.5}$ mass complicates the interpretation of the individual component results.

Krall et al. (2013) took a slightly different approach than Lippmann et al. (2013a) in an analysis of 72 U.S. cities, by focusing on those components that contribute the most (i.e., approximately 79−85%) of yearly and seasonal $PM_{2.5}$ mass. The authors developed city-specific component models and also examined associations by season (i.e., spring, summer, fall, and winter) and by region (i.e., Northeast, Southeast, southern Midwest, northern Midwest, Southwest, and Northwest). Krall et al. (2013) observed the strongest associations for OCM, EC, Si, and Na^+, but overall reported no evidence that any of these components is more strongly associated with mortality than $PM_{2.5}$ mass (Figure 11-15). Additionally, the authors reported no evidence that individual component associations varied by season or region.

In addition to the U.S. based multicity studies detailed above, Basagaña et al. (2015) examined the association between short-term exposure to $PM_{2.5}$ components and mortality in five cities in southern Europe as part of the MED-PARTICLES project. The components examined were selected a priori and based on their detectability in each of the five cities as well as evidence from the literature linking each of the $PM_{2.5}$ components with health. In single-component models the authors observed the strongest associations with SiO_2 and total (nonaccidental) mortality; SiO_2, Mg, and Mn and cardiovascular mortality; and SO_4^{2-}, K, and Mn and respiratory mortality.



Source: Permission pending, Krall et al. (2013).

Figure 11-15 Percent increase in mortality for $PM_{2.5}$ and $PM_{2.5}$ components for an interquartile range (IQR) increase in concentrations at lag 1 across 72 U.S. cities.

U.S.-based single-city studies conducted in locations across the country provide additional information that can aid in the interpretation of $PM_{2.5}$ component results from multicity studies. In a study conducted in New York City, NY focusing on cardiovascular mortality, Ito et al. (2011) examined associations with $PM_{2.5}$ components that were selected for inclusion in the study "based on past source apportionment studies in New York City as well as recent health effects studies". In all-year analyses, when focusing on those components that are the largest contributors to $PM_{2.5}$ mass, the authors observed the strongest associations for EC, OC, and SO_4^{2-} at lag 1. These results persisted in the warm season, but in the cold season the association remained the strongest for EC, and although the positive magnitude of the association and precision were reduced for OC and SO_4^{2-}. Among the other components examined, associations were observed in all-year and seasonal analyses for Br and Na^+, whereas for Se there was evidence of an association in all-year and warm season analyses at lag 1, but not in the cold season. For Ni, V, and Zn, there was no evidence of an association in all-year or warm season analyses, but lag 3 in the cold season, which is consistent with the burning of residual oil in NYC (see Section 11.1.11.2).

Although Ito et al. (2011) examined seasonal differences in $PM_{2.5}$ component associations, the authors were limited by the one-in-three sampling schedule of the monitors. Examining the associations between total, cardiovascular and respiratory mortality and $PM_{2.5}$ components, Zhou et al. (2011) was able to more rigorously examine potential differences in seasonal associations (i.e., examine both single and multiday lags) compared to Ito et al. (2011) due to the availability of daily $PM_{2.5}$ component data.

Similar to other component studies detailed in this section, the authors selected $PM_{2.5}$ components for inclusion in the study based on evidence from the toxicological literature. When examining the seasonal pattern of associations using a distributed lag model for 0−2 days, there was a clear difference in potential sources of $PM_{2.5}$ based on the strongest $PM_{2.5}$ associations with total and cause-specific mortality occurring in the warm season for Detroit and the cold season for Seattle (see Section 11.1.11.2). In both locations, mean 24-hour average $PM_{2.5}$ concentrations were near of below15 $\mu g/m^3$ for the duration of the study (Detroit = 15.1 $\mu g/m^3$; Seattle = 9.7 $\mu g/m^3$). The seasonal pattern in $PM_{2.5}$ mass associations observed in both cities were further reflected when examining $PM_{2.5}$ component associations. In Detroit in the warm season for total (nonaccidental) mortality there was evidence of positive associations for S and EC, with a strong negative association for Si. This pattern of associations was similar for cardiovascular mortality, although the confidence intervals for each component were larger. Wider confidence intervals were also observed for respiratory mortality, with positive associations only for Ni and S. For Seattle in the cold season, the component associations observed for total (nonaccidental) mortality and cardiovascular mortality were similar with positive associations observed for Al, Fe, K, Ni, S, Si, Zn, and EC. Additionally, there was some evidence of a positive association between only cardiovascular mortality and V. When examining respiratory mortality in Seattle there was no evidence of a positive association with any $PM_{2.5}$ components. In both the Detroit and Seattle data sets, Zhou et al. (2011) conducted sensitivity analyses focusing on model specification and did not observe any evidence that $PM_{2.5}$ component-mortality associations changed when increasing the degrees of freedom to control for temporal trends or when using alternative temperature variables, which is similar to what has been observed when examining $PM_{2.5}$ mass (see Section 11.1.5.1).

Kim et al. (2015) also used daily $PM_{2.5}$ component data in a study in Denver, CO that examined total (nonaccidental), cardiovascular, and respiratory mortality. However, unlike a number of the studies focusing on $PM_{2.5}$ components the authors only focused on a few of the main contributors to $PM_{2.5}$ mass (i.e., EC, OC, SO_4^{2-}, and NO_3^-). Across mortality outcomes, the strongest associations were observed for total (nonaccidental) mortality for the 0−3 distributed lag model results for EC and OC, with less evidence of an association for SO_4^{2-} and NO_3^-. For cardiovascular mortality there was only evidence for a positive association with OC and lag 1; whereas for respiratory mortality there was evidence of a positive association at lag 3 for both EC and OC. Similar to Zhou et al. (2011) in sensitivity analyses focusing on model specification the authors did not observe that $PM_{2.5}$ component-mortality associations changed when increasing the degrees of freedom to control for temporal trends or when using alternative temperature variables.

As detailed above, the majority of $PM_{2.5}$ component studies have examined whether one or a combination of components are driving the $PM_{2.5}$ mass associations, but Liu and Zhang (2015) examined whether associations with $PM_{2.5}$ mass and components have changed over time. The design of this study is like that of Dominici et al. (2007) which also attempted to examine whether PM-mortality risks have changed over time, but on a national scale. As detailed in the 2009 PM ISA, "a flaw in the use of the time-series study design for this type of analysis is that it adjusts for long-term trends, and therefore, does

not estimate the change in mortality in response to the gradual change in [PM]." As a result, the focus is on the $PM_{2.5}$ mass and component results detailed for the entire study period along with the seasonal analyses. Similar to previous studies, the components examined were selected a priori and based on evidence from the epidemiologic literature as well as a local source apportionment study (Liu and Zhang, 2015). When focusing on associations at lag 1, $PM_{2.5}$ mass had the strongest association, with evidence of a positive association for a number of individual components (Figure 11-13). When conducting seasonal analyses, the strongest associations tended to be observed during the winter, specifically for NH_4^+, Br, Cr, Mn, Ni, SO_4^{2-}, NO_3^-, V, EC, and OC. The seasonal component results are consistent with the $PM_{2.5}$ results where the association with the largest magnitude was also observed to be in the winter.

Additional $PM_{2.5}$ Component Analyses

The majority of $PM_{2.5}$ component studies conducted to date have focused almost exclusively on examining single-component models. However, a main limitation of single component models is their inability to account for the potential confounding effects of $PM_{2.5}$ mass or other $PM_{2.5}$ components. As detailed in Mostofsky et al. (2012) there are a number of alternative statistical approaches that can be used, each with their own strengths and limitations. A few of the studies detailed above that focused on single pollutant models also examined alternative models to further inform the $PM_{2.5}$ component-mortality relationship.

Lippmann et al. (2013a) used a traditional two-pollutant (i.e., copollutant) model in an attempt to examine whether $PM_{2.5}$ mass confounds the component associations observed for a subset of the components examined. In an all-year analysis, component results were robust to inclusion of $PM_{2.5}$ in the model for OC, V, Si, K, and Cu, with evidence of potential confounding for EC and SO_4^{2-}, but these two components contribute a large percentage to $PM_{2.5}$ mass and are often found to be highly correlated. In seasonal analyses, all components were robust to the inclusion of $PM_{2.5}$ in the model in the warm season, with some evidence of attenuation of the component association in the cold season for V, Si, K, and Cu, while SO_4^{2-} was found to be negatively associated with mortality.

Instead of applying a traditional copollutant model to examine component associations, Basagaña et al. (2015) and Kim et al. (2015) used the component residual approach. In this approach, the residuals from the regression of $PM_{2.5}$ on each component are included in the model, which provides the effect of each individual component holding $PM_{2.5}$ constant and theoretically eliminates confounding by $PM_{2.5}$ (Mostofsky et al., 2012). As detailed in Table 11-3, Basagaña et al. (2015) reported evidence that component results were relatively robust using the component residual approach to examine associations. Similarly, Kim et al. (2015) reported that individual component associations were relatively consistent with those observed in single-component models when using the component residual approach (Figure 11-13).

Summary

Since the completion of the 2009 PM ISA there has been a growing body of single and multicity epidemiologic studies that examined the association between short-term exposures to $PM_{2.5}$ components and mortality. As depicted in Figure 11-13, $PM_{2.5}$ component studies reported positive associations with multiple PM components at various lags using both single component models as well as alternative models. Studies have demonstrated positive associations with a number of $PM_{2.5}$ components, but across studies there is a varying degree to which components have been found to be positively associated with mortality. In comparison, there is evidence of consistent positive associations between $PM_{2.5}$ mass and mortality across all studies examined (Figure 11-14). As demonstrated in some studies the different pattern of component associations is reflective of the different sources of $PM_{2.5}$ across cities. Collectively, recent studies further support the conclusions of the 2009 PM ISA, indicating that many $PM_{2.5}$ components are associated with mortality, but no one component is more strongly associated with mortality than $PM_{2.5}$ mass.

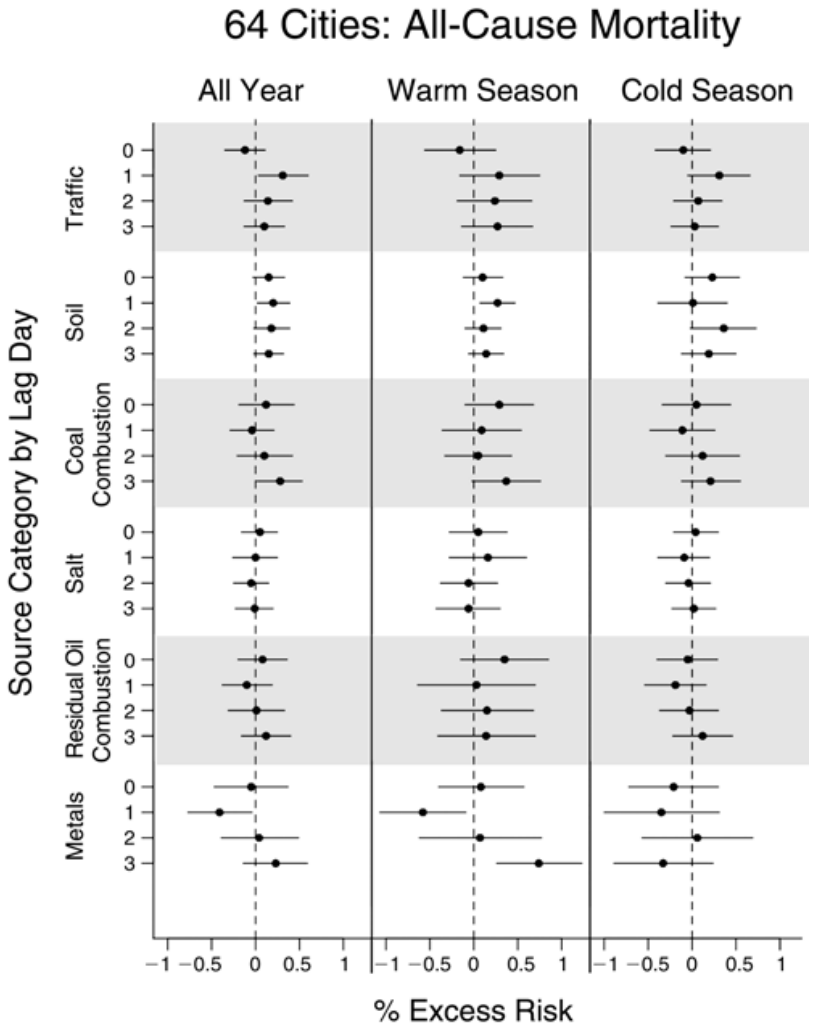
11.1.11.2 Sources

A few studies evaluated in the 2009 PM ISA conducted source apportionment analyses to examine whether specific sources of $PM_{2.5}$ are more strongly associated with mortality. These studies generally found that the most consistent associations were for $PM_{2.5}$ from combustion-related activities, which supports the results from studies evaluated in the 2004 PM AQCD (U.S. EPA, 2004). Recent studies focus primarily on examining individual $PM_{2.5}$ component associations, but also often link the components evaluated to specific $PM_{2.5}$ sources a priori. As a result, most recent studies do not rely on formal mathematical approaches, such as source apportionment, to identify sources in the context of examining the relationship between source exposures and daily mortality. As detailed in the Preface, the evaluation of associations between health effects and sources is limited to those studies that use mathematical approaches and do not identify sources a priori.

Within the NPACT study Lippmann et al. (2013a) conducted a factor analysis to identify $PM_{2.5}$ sources. The factor analysis was conducted at the national level using both $PM_{2.5}$ components along with gaseous pollutant data from all 64 U.S. cities to identify source categories: traffic (EC, OC, and NO_2), soil (Al, Si, and Ti), coal combustion (As, Se, and SO_2), residual oil combustion (Ni and V), salt (Na and Cl), and metals (Fe, Mn, and Zn). These source categories were then applied to each of the 64 U.S. cities to see which sources were found in each city. Because the source categories were based on a mathematical model they may not be representative of the sources in each city, and the interpretation of a source category on a city-to-city basis may be different (Lippmann et al., 2013a).

When examining source categories in each city, the number of cities that were found to encompass each of the source categories varied. Across cities, the sources identified in each varied with 63 cities having a traffic and soil source, 46 cities having a coal combustion source, 42 cities having a salt

source, 29 cities having a residual oil combustion source, and 16 cities having a metals source. The results of the source analysis using the individual city results and the national results were found to be relatively similar. As depicted in Figure 11-16, in all-year and seasonal analyses multiple sources were found to be associated with mortality at a number of lags.



Source: Permission pending, Lippmann et al. (2013a).

Figure 11-16 Percent increase in total (nonaccidental) mortality for individual cities within the 64 U.S. cities examined in the National Particle Component Toxicity (NPACT) study for a median interquartile range (IQR) increase in factor scores for the cities combined.

In addition to Lippmann et al. (2013a) where specific sources where defined using statistical approaches, Kollanus et al. (2016) examined whether there was evidence of differential effects on days impacted by vegetative fires (i.e., smoke days) compared to regular (i.e., nonsmoke) days in Helsinki, Finland. The authors predicted surface smoke concentrations at 1°×1° grid cells, and defined smoke days using three approaches: (1) 24-hour average $PM_{2.5}$ concentrations at urban background site ≥25 μg/m^3; (2) 24-hour average $PM_{2.5}$ or PM_{10} concentration at regional background site ≥20 μg/m^3; or (3) the smoke prediction model indicated abundant or some smoke due to long-range transport from vegetative fires. On smoke days, mean $PM_{2.5}$ concentrations were more than three times higher than nonsmoke says (i.e., 30 μg/m^3 vs. 8.6 μg/m^3); however, only 72 days during the 10-year study period were classified as smoke days. When comparing smoke to nonsmoke days, the percent increase in nonaccidental mortality was almost double on smoke days (i.e., lag 2: 2.5−2.7% for all ages and ≥65 years, respectively), but dramatically larger when examining cardiovascular mortality where there was no evidence of an association for nonsmoke days (i.e., 8.0−13.8% across individual lags of 0 and 3 day for all ages and ≥65 years).

In summary, when examining sources of $PM_{2.5}$, the results of the limited number of recent studies further support studies evaluated in the 2004 PM AQCD and 2009 PM ISA, demonstrating that combustion-related sources are often found to be associated with mortality. Collectively, the results of recent studies that examined the association between $PM_{2.5}$ sources and mortality are consistent with the conclusions of the 2009 PM ISA.

11.1.12 Summary and Causality Determination

Recent multicity studies evaluated since the completion of the 2009 PM ISA continue to provide evidence of primarily positive associations between short-term $PM_{2.5}$ exposures and total (nonaccidental) mortality from studies conducted mostly in urban areas using traditional exposure assignment approaches (i.e., average of all available monitors) as well as studies with a larger spatial coverage (i.e., urban and rural areas) employing new methods using all available $PM_{2.5}$ data (i.e., combination of monitoring, satellite and LUR). Additionally, the evidence from recent studies further substantiates the relationship between short-term $PM_{2.5}$ exposure and mortality by providing additional information on potential copollutant confounding; effect modification (e.g., stressors, pollutants, season); geographic heterogeneity in associations; and the shape of the C-R relationship, which collectively reaffirms that a causal relationship exists between short-term $PM_{2.5}$ exposure and mortality. The body of evidence for total mortality is supported by generally consistent positive associations with cardiovascular and respiratory mortality. Although there is coherence of effects across the scientific disciplines (i.e., animal toxicological, controlled human exposure studies, and epidemiologic) and biological plausibility for $PM_{2.5}$-related cardiovascular (Chapter 6) and respiratory (Chapter 5) morbidity, there is strong evidence indicating biological plausibility for $PM_{2.5}$-related cardiovascular mortality with more limited evidence for respiratory mortality. This section describes the evaluation of evidence for total (nonaccidental)

mortality, with respect to the causality determination for short-term exposures to $PM_{2.5}$ using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015b). The key evidence, as it relates to the causal framework, is summarized in Table 11-4.

Table 11-4 Summary of evidence for a causal relationship between short-term $PM_{2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{2.5}$ concentrations	Increases in mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia. Total mortality associations, further supported by increases in cardiovascular and respiratory mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia.	Section 11.1.2 Figure 11-1 Figure 11-2 Section 5.1.9 Section 6.1.9	Mean 24-h avg: U.S. and Canada: 4.37–17.97 Europe: 13–27.7[d] Asia: 11.8–69.9 Table 11-1
Epidemiologic evidence from copollutant models provides some support for an independent $PM_{2.5}$ association	The magnitude of $PM_{2.5}$ associations remain positive, but in some cases are reduced with larger confidence intervals in copollutant models with gaseous pollutants and $PM_{10-2.5}$, supporting the limited evidence from the 2009 PM ISA. Further support from copollutant analyses indicating positive associations for cardiovascular and respiratory mortality. Recent studies that examined potential copollutant confounding are limited to studies conducted in Europe and Asia. When reported, correlations with gaseous copollutants were primarily in the low ($r < 0.4$) to moderate ($r \geq 0.4$ or <0.8) range.	Section 11.1.4 Figure 11-3 Section 5.1.10.1 Section 6.1.14.1	
Epidemiologic evidence supports a linear, no-threshold concentration-response (C-R) relationship	Recent multicity studies conducted in the U.S. and Europe provide direct evidence of a linear, no-threshold C-R relationship at lower $PM_{2.5}$ concentrations with initial evidence of a steeper slope, but extensive systematic evaluations of alternatives to linearity have not been conducted.	Section 11.1.10 Shi et al. (2015) Lee et al. (2015c) Di et al. (2017a)	

Table 11-4 (Continued): Summary of evidence indicating that a causal relationship exists between short-term $PM_{2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Biological plausibility from cardiovascular morbidity evidence	Strong evidence for coherence of effects across scientific disciplines and biological plausibility for a range of cardiovascular effects in response to short-term $PM_{2.5}$ exposure, specifically for ischemic events and heart failure, which is supported by experimental evidence and epidemiologic studies examining hospital admissions and ED visits. The collective body of cardiovascular morbidity evidence provides biological plausibility for a relationship between short-term $PM_{2.5}$ exposure and cardiovascular mortality, which comprises ~33% of total mortality.[e]	Section 6.1.16 Table 6-33	
Limited biological plausibility from respiratory morbidity evidence	Limited evidence for coherence of effects across scientific disciplines and biological plausibility, with the strongest evidence for exacerbations of COPD and asthma. The collective body of respiratory morbidity evidence provides limited biological plausibility for a relationship between short-term $PM_{2.5}$ exposure and respiratory mortality, which comprises ~9% of total mortality.[e]	Section 5.1.12 Table 5-18	
Uncertainty regarding geographic heterogeneity in $PM_{2.5}$ associations	Multicity U.S. studies demonstrate city-to-city and regional heterogeneity in $PM_{2.5}$-mortality associations. Evidence supports that a combination of factors including composition and exposure factors may contribute to the observed heterogeneity.	Section 11.1.6.3	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015b).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to the causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

[d]Median concentration from Samoli et al. (2013).

[e]Statistics taken from NHLBI (2017).

Collectively, the evidence from recent multicity studies of short-term $PM_{2.5}$ exposures and mortality primarily demonstrates positive associations with total (nonaccidental) mortality, with increases ranging from 0.19% (Lippmann et al., 2013a) to 2.80% (Kloog et al., 2013) at lags of 0 to 1 days in single-pollutant models. These results are further supported by initial studies employing causal inference and quasi-experimental statistical approaches (Section 11.1.2.1). Whereas most studies rely on assigning exposure using data from ambient monitors, some recent studies have also employed approaches that use

all available $PM_{2.5}$ data (i.e., monitor, satellite, and LUR) allowing for the inclusion of less urban and rural locations in analyses (Lee et al., 2015c; Shi et al., 2015; Kloog et al., 2013). Recent studies expand the assessment of potential copollutant confounding on the $PM_{2.5}$-mortality relationship, and provide additional evidence supporting that $PM_{2.5}$ associations remain positive and relatively unchanged in copollutant models with both gaseous pollutants and $PM_{10-2.5}$, but this assessment is limited to multicity studies conducted in Europe and Asia where mean 24-hour average $PM_{2.5}$ concentrations are higher (Table 11-4). However, the low ($r < 0.4$) to moderate correlations ($r = 0.4 < 0.7$ between $PM_{2.5}$ and gaseous pollutants and $PM_{10-2.5}$ increase the confidence in $PM_{2.5}$ having an independent effect on mortality.

The positive associations for total (nonaccidental) mortality reported across the majority of studies evaluated is further supported by analyses focusing on cause-specific mortality that continue to provide evidence of generally consistent positive associations with both cardiovascular and respiratory mortality, except in the case of a multicity study conducted in Europe (Lanzinger et al., 2016). Risk estimates for cardiovascular mortality ranged from 0.09% (Lippmann et al., 2013a) to 2.32% (Lee et al., 2015c) while those for respiratory mortality ranged from 0.09% (Lee et al., 2015c) to 2.30% (Janssen et al., 2013), but overall associations tend to be larger in magnitude for respiratory mortality. For both cardiovascular and respiratory mortality there was a limited assessment of potential copollutant confounding, but for both outcomes initial evidence indicates that associations remain positive and relatively unchanged in models with gaseous pollutants and $PM_{10-2.5}$, further supporting the copollutant analyses conducted for total (nonaccidental) mortality. The strong evidence for ischemic events and heart failure as detailed in the assessment of cardiovascular morbidity (Chapter 6), provide strong biological plausibility for $PM_{2.5}$-related cardiovascular mortality, which comprises the largest percent of total mortality (i.e., ~33%) (NHLBI, 2017). Although there is evidence for exacerbations of COPD and asthma, the collective body of respiratory morbidity evidence provides limited biological plausibility for $PM_{2.5}$-related respiratory mortality (Chapter 5).

In addition to examining potential copollutant confounding, a number of studies also assessed whether statistical models adequately account for temporal trends and weather covariates. Across studies that evaluated model specification, $PM_{2.5}$-mortality associations remained positive, although in some cases were attenuated, when using different approaches to account for temporal trends or weather covariates (Section 11.1.5). Seasonal analyses continue to provide evidence that associations are larger in magnitude during warmer months, but it remains unclear if copollutants confound the associations observed. In addition to seasonal analyses, some studies also examined whether temperature modifies the $PM_{2.5}$-mortality relationship. Initial evidence indicates that the $PM_{2.5}$-mortality association may be larger in magnitude at lower and higher temperatures, but this observation has not been substantiated by studies conducted in the U.S. (Section 11.1.6.2).

At the completion of the 2009 PM ISA, one of the main uncertainties identified was the regional and city-to-city heterogeneity in $PM_{2.5}$-mortality associations observed in multicity studies. Recent studies

examined both city specific as well as regional characteristics to identify the underlying factors that contribute to this heterogeneity (Section 11.1.6.3). Analyses focusing on effect modification of the $PM_{2.5}$-mortality relationship by $PM_{2.5}$ components, regional patterns in $PM_{2.5}$ components and city-specific differences in composition and sources indicate some differences in the $PM_{2.5}$ composition and sources across cities and regions, but these differences do not fully explain the heterogeneity observed. Additional studies examined whether exposure factors play a role in explaining the heterogeneity in $PM_{2.5}$-mortality associations and found that some factors related to housing stock and commuting as well as city-specific factors (e.g., land-use, port volume, and traffic information) also explain some of the observed heterogeneity. Collectively, recent studies indicate that the heterogeneity in $PM_{2.5}$-mortality risk estimates cannot be attributed to one factor, but instead a combination of factors including, but not limited to, compositional and source differences as well as exposure differences.

A number of recent studies conducted systematic evaluations of the lag structure of associations for the $PM_{2.5}$-mortality relationship by examining either a series of single-day or multiday lags and these studies continue to support an immediate effect (i.e., lag 0 to 1 days) of short-term $PM_{2.5}$ exposures on mortality (Section 11.1.8.1). Recent studies also conducted analyses comparing the traditional 24-hour average exposure metric with a subdaily metric (i.e., 1-hour max). These initial studies provide evidence of a similar pattern of associations for both the 24-hour average and 1-hour max metric, with the association larger in magnitude for the 24-hour average metric. Additionally, some studies examined alternative exposure metrics representing size fractions smaller than $PM_{2.5}$ and reflecting NC and SC. The generally positive associations reported with mortality for these smaller PM size fractions support the larger body of $PM_{2.5}$-mortality evidence, but it is difficult to compare NC and SC metrics with the traditional mass-based metric.

Building off the initial analysis of the C-R relationship between short-term PM exposure and mortality that focused on PM_{10}, recent multicity studies conducted in the U.S. and Europe examined the shape of the C-R relationship and whether a threshold exists specifically for $PM_{2.5}$ (Section 11.1.10). These studies have used different statistical approaches and consistently demonstrated a linear relationship with no evidence of a threshold. Additionally, recent analyses conducted at lower $PM_{2.5}$ concentrations (i.e., 24-hour average $PM_{2.5}$ concentrations <30 $\mu g/m^3$) provide initial evidence indicating that $PM_{2.5}$-mortality associations persist and may be stronger (i.e., a steeper slope) at lower concentrations. However, to date, studies have not conducted extensive analyses exploring alternatives to linearity when examining the shape of the $PM_{2.5}$-mortality C-R relationship.

Overall, recent epidemiologic studies build upon and further reaffirm the conclusions of the 2009 PM ISA for total mortality. The evidence particularly from the assessment of $PM_{2.5}$-related cardiovascular morbidity, with more limited evidence from respiratory morbidity, provides biological plausibility for mortality due to short-term $PM_{2.5}$ exposures. In conclusion, the primarily positive associations observed across studies conducted in various locations is further supported by the results from copollutant analyses indicating robust associations, along with evidence from analyses of the C-R relationship. **Collectively,**

this body of evidence is sufficient to conclude that a causal relationship exists between short-term $PM_{2.5}$ exposure and total mortality.

11.2 Long-Term $PM_{2.5}$ Exposure and Total Mortality

The 2009 PM ISA reported that the evidence was "sufficient to conclude that the relationship between long-term $PM_{2.5}$ exposures and mortality is causal" (U.S. EPA, 2009).[79] Two seminal cohort studies, the American Cancer Society (ACS) and the Harvard Six Cities studies provided the strongest evidence for this conclusion (i.e., consistency across studies and among replication and reanalysis of the same cohort; study designs appropriate for causal inference), and were supported by evidence from other cohort studies conducted in North America and Europe. Evidence presented in the 2009 PM ISA was largely consistent with past studies reporting associations between long-term $PM_{2.5}$ exposure and increased risk of human mortality. Additional analyses of the Harvard Six Cities cohort demonstrated a reduction in mortality risk associated with decreases in $PM_{2.5}$ concentrations (Laden et al., 2006). Similarly, Pope et al. (2009) reported that decreases in $PM_{2.5}$ concentrations were associated with increases in life expectancy. Another new line of evidence supporting the causality determination in the 2009 PM ISA was the increased risk in death from cardiovascular disease among a cohort of post-menopausal women with no previous history of cardiovascular disease (Miller et al., 2007).

The following section provides a brief, integrated evaluation of evidence for long-term $PM_{2.5}$ exposure and mortality presented in the previous NAAQS review with evidence that is newly available for this review (see Table 11-5 for study descriptions). This section focuses on assessing the degree to which newly available studies further characterize the relationship between long-term $PM_{2.5}$ exposure and mortality, focusing on studies where long-term average $PM_{2.5}$ concentrations are less than 20 $\mu g/m^3$ across all cities or where at least half of the cities have long-term average $PM_{2.5}$ concentrations less than 20 $\mu g/m^3$ (see Preface). For example, areas of research that inform differences in the exposure window used to evaluate long-term exposures and mortality or comparisons of statistical techniques will be highlighted. Studies that address the variability in the associations observed across $PM_{2.5}$ epidemiologic studies due to exposure error and the use of different exposure assessment techniques will be emphasized. Another important consideration will be characterizing the shape of the concentration-response (C-R) relationship across the full concentration range observed in epidemiologic studies. The evidence in this section will focus on epidemiologic studies because experimental studies of long-term exposure and mortality are generally not conducted. However, this section will draw from the morbidity evidence presented for different health endpoints across the scientific disciplines (i.e., animal toxicological, epidemiologic and controlled human exposure studies) to support the associations observed for cause-specific mortality.

[79] As detailed in the Preface, risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations, unless otherwise noted.

Table 11-5 North American epidemiologic studies of long-term exposure to $PM_{2.5}$ and mortality.

Study	Study Population	Exposure Assessment	Mean (μg/m³)	Copollutant Examination
Laden et al. (2006) Multicity; U.S. $PM_{2.5}$: 1979−1998 Follow-up: 1979−1998 Cohort Study	Harvard Six Cities Study n = 8,096 white participants enrolled between 1974 and 1977	City-specific averages from monitors (1979−1987); City-specific regression equations based on extinction coefficient and PM_{10} fixed-site monitoring data (1985−1998); r = 0.93	Mean: 10.2−22.0	Correlation (r): NA Copollutant models with: NA
Pope et al. (2009) Multicity, U.S. $PM_{2.5}$: 1979−1983; 1999−2000 Follow-up: 1978−1982; 1997−2001 Cohort Study	American Cancer Society Cancer Prevention Study II n = 383,000 population in study area (1980) n = 482,000 population in study area (2000)	City-specific averages from fixed-site monitors	1979−1983 Mean: 20.61 1999−2000 Mean: 14.10	Correlation (r): NA Copollutant models with: NA
Miller et al. (2007) Multicity, U.S. $PM_{2.5}$: 2000 Follow-up: 1994−2003 Cohort Study	Women's Health Initiative n = 58,610 post-menopausal women; 349,643 person-years of follow-up	City-specific averages from fixed-site monitors within 30 km	Mean: 13.5 90th: 18.3 Range: 3.4−28.3	Correlation (r): NA Copollutant models with: NA
Pope et al. (1995) Multicity, U.S. $PM_{2.5}$: 1979−1983 Follow-up: 1982−1989 Cohort Study	American Cancer Society Cancer Prevention Study II n = 552,138 participants	City-specific averages from fixed-site monitors	Median: 18.2 Range: 9.0−33.5	Correlation (r): NA Copollutant models with: NA
†Pope et al. (2014) Multicity, U.S. $PM_{2.5}$: 1999−2008 Follow-up: 1982−2004 Cohort Study	American Cancer Society Cancer Prevention Study II n = 669,046 participants; 237,201 deaths during 12,662,562 person-years of follow-up	City-specific averages from LUR-BME; cross-validated with 10% of data (R^2 = 0.79); see Beckerman et al. (2013) for details	Mean: 12.6 Range: 1−28	Correlation (r): NA Copollutant models with: NA

Table 11-5 (Continued): North American epidemiologic studies of long-term exposure to $PM_{2.5}$ and mortality.

Study	Study Population	Exposure Assessment	Mean (μg/m³)	Copollutant Examination
†Turner et al. (2016) Multicity, U.S. $PM_{2.5}$: 1999–2004 Follow-up: 1982–2004 Cohort Study	American Cancer Society Cancer Prevention Study II: n = 669,046 participants; 237,201 deaths during 12,662,562 person-years of follow-up	City-specific averages from LUR-BME; cross-validated with 10% of data (R^2 = 0.79); see Beckerman et al. (2013) for details	Mean: 12.6 Range: 1.4–27.9	Correlation (*r*): O_3: 0.43 NO_2: 0.40 Copollutant models with: O_3
†Jerrett et al. (2009) Multicity, U.S. $PM_{2.5}$: 1999–2000 Follow-up: 1982–2000 Cohort Study	American Cancer Society Cancer Prevention Study II: n = 448,850 subjects and 118,777 deaths during 18-year follow-up period	City-specific averages from fixed-site monitors	NR	Correlation (*r*): O_3: 0.64 Copollutant models with: O_3
†Jerrett et al. (2013) Multicity, California $PM_{2.5}$: 1998–2002 Follow-up: 1982–2000 Cohort Study	American Cancer Society Cancer Prevention Study II: n = 73,711 cohort members; 19,755 deaths	Land use regression; $PM_{2.5}$ concentration predicted at residence	Mean: 14.09 90th: 18.42 95th: 19.36 Range: 4.25–25.09	Correlation (*r*): O_3: 0.56 NO_2: 0.55 Copollutant models with: O_3, NO_2
†Lepeule et al. (2012) Multicity; U.S. $PM_{2.5}$: 1979–2009 Follow-up: 1979–2009 Cohort Study	Harvard Six Cities Study: n = 8,096 cohort members, 212,067 person-years of follow-up; 4,496 deaths	City-specific averages from fixed-site monitors (1979–1987); City-specific regression equations based on extinction coefficient and PM_{10} fixed-site monitoring data (1985–1998); U.S. EPA fixed-site monitoring system (1999–2009)	11.4–23.6	Correlation (*r*): NA Copollutant models with: NA
†Kloog et al. (2013) Massachusetts $PM_{2.5}$: 2000–2008 Follow-up: 2000–2008 Cohort Study	n = 468,570 deaths	Satellite-based methods and land use regression; 10 km × 10 km grid cells; $PM_{2.5}$ concentration predicted at residence; see Kloog et al. (2011) for details	Mean: 9.9 Range: 7.05–16.11	Correlation (*r*): NA Copollutant models with: NA
†Di et al. (2017c) Multicity, U.S. EPA $PM_{2.5}$: 2000–2012 Follow-up: 2000–2012 Cohort Study	Medicare Cohort n = 60,925,443 460,310,521 person-years of follow-up n = 22,567,924 deaths	Three-stage exposure model: (1) satellite-based methods, (2) land use regression, (3) fixed-site monitor data, good validation (r > 0.85); 1 km × 1 km grid cells; $PM_{2.5}$ concentration predicted at zip code; see Kloog et al. (2011) and Kloog et al. (2014) for details	Mean: 11.5 Range: 6.21–15.64 (5th–95th)	Correlation (*r*): O_3: 0.239 Copollutant models with: O_3

Table 11-5 (Continued): North American epidemiologic studies of long-term exposure to $PM_{2.5}$ and mortality.

Study	Study Population	Exposure Assessment	Mean ($\mu g/m^3$)	Copollutant Examination
†Shi et al. (2015) Multicity, U.S. $PM_{2.5}$: 2003−2008 Follow-up: 2003−2008 Time-Series Study	Medicare Cohort–New England n = 268,050 deaths; 10,938,852 person-years of follow-up	Three-stage exposure model: (1) satellite-based methods (2) land use regression, (3) fixed-site monitor data, good validation (r > 0.85); 1 km × 1 km grid cells; $PM_{2.5}$ concentration predicted at residence; see Kloog et al. (2011) and Kloog et al. (2014) for details	Mean: 8.12 Range: 0.8−20.22	Correlation (r): NA Copollutant models with: NA
†Kioumourtzoglou et al. (2016) Multicity, U.S. $PM_{2.5}$: 2000−2010 Follow-up: 2000−2010 Cohort Study	Medicare Cohort n = 35,295,005 cohort members; 11,411,282 deaths	City-specific average from fixed-site monitors	Mean: 12.0	Correlation (r): NA Copollutant models with: NA
†Wang et al. (2017b) Multicity, US $PM_{2.5}$: 2000−2013 Follow-up: 2000−2013 Cohort Study	Medicare cohort: N = 13.1 million older adults from seven southeastern states; 95.1 million person-years of follow-up; 4.7 million deaths	Three-stage exposure model: (1) satellite-based methods, (2) land use regression, (3) fixed-site monitor data, good validation (r = 0.70−0.81); 1 km × 1 km grid cells; $PM_{2.5}$ concentration predicted at zip code level; see Kloog et al. (2014) and Lee et al. (2015b) for details	Median: 10.7 75th: 12.9 95th: 15.1 Max: 20.6	Correlation (r): NA Copollutant models with: NA
†Thurston et al. (2015) Multicity, U.S. $PM_{2.5}$: 2000−2008 Follow-up: 2000−2009 Cohort Study	NIH-AARP Cohort: n = 517,041 cohort members; 84,404 deaths	Two-stage exposure model: (1) fixed-site monitor data and (2) LUR-BME; $PM_{2.5}$ concentration predicted to census tract centroid; see Beckerman et al. (2013) for details	Mean: 10.2−13.6	Correlation (r): NA Copollutant models with: O_3; $PM_{2.5}$
†Crouse et al. (2012) Multicity, Canada $PM_{2.5}$: 2001−2006 Follow-up:1991−2006 Cohort Study	CanCHEC Cohort: n = 2,145,400 (census population); 192,300 deaths	Satellite-based methods, r = 0.77 with fixed-site measurements; 10 km × 10 km grid cells; $PM_{2.5}$ concentration predicted at residence	Mean: 8.9 Range: 1.9−19.2	Correlation (r): NA Copollutant models with: NA
†Brook et al. (2013) Multicity, Canada $PM_{2.5}$: 2001−2006 Follow-up:1991−2001 Cohort Study	CanCHEC Cohort: n = 2,145,400 (census population); 5,200 diabetes deaths	Satellite-based methods, r = 0.89 with fixed-site measurements; 10 km × 10 km grid cells; $PM_{2.5}$ concentration predicted at residence	Mean: 8.7	Correlation (r): NA Copollutant models with: NA
†Chen et al. (2016) Ontario, Canada $PM_{2.5}$: 2001−2010 Follow-up:1999−2011 Cohort Study	EFFECT Cohort: n = 8,873 acute myocardial infarction patients from 86 hospitals	Satellite-based methods, r = 0.89 with fixed-site measurements; 10 km × 10 km grid cells; $PM_{2.5}$ concentration predicted at residence; see van Donkelaar et al. (2010) for details	Mean: 10.7	Correlation (r): NA Copollutant models with: NA

Table 11-5 (Continued): North American epidemiologic studies of long-term exposure to $PM_{2.5}$ and mortality.

Study	Study Population	Exposure Assessment	Mean ($\mu g/m^3$)	Copollutant Examination
†Crouse et al. (2015) Multicity, Canada $PM_{2.5}$: 1984–2006 Follow-up:1991–2006 Cohort Study	CanCHEC Cohort: n = 2,521,525 (census population); 36,377,506 person-years of follow-up; 301,115 deaths	Satellite-based methods; $PM_{2.5}$ concentrations predicted at postal code, r = 0.90 with fixed-site measurements; see van Donkelaar et al. (2015) for details	Mean: 8.9 Range: 0.9–17.6	Correlation (r): NA O_3 (r = 0.73) NO_2 (r = 0.40) Copollutant models with: NA
†Weichenthal et al. (2016) Ontario, Canada $PM_{2.5}$: 1998–2009 Follow-up: 2001–2008 Cohort Study	CanCHEC Cohort: n = 193,300 (census population); 40,300 deaths	Residence within 5 km of a fixed-site monitor (n = 30)	Mean: 9.81 Range: 4.74–13.62	Correlation (r): NA Copollutant models with: NA
†Pinault et al. (2016) Multicity, Canada $PM_{2.5}$: 1998–2011 Follow-up: 2000–2011 Cohort Study	CCHS: n = 299,500; 26,300 deaths	Three-stage exposure model: (1) Satellite-based methods, (2) land use regression, (3) fixed-site monitor data, R^2 with fixed-site measurements = 0.82; 1 km × 1 km grid cells; $PM_{2.5}$ concentration predicted at residence; see van Donkelaar et al. (2015) for details	Mean: 6.3 Range: 1.0–13.0	Correlation (r): NA Copollutant models with: NA
†Villeneuve et al. (2015) Multicity, Canada $PM_{2.5}$: 1998–2006 Follow-up: 1993–2009 Cohort Study	CNBSS: n = 89,835 women between 40 and 59 yr of age	Satellite-based methods adjusting for temporal variation using GEOS-Chem chemical transport model, correlation with fixed-site monitors, r = 0.79; 10 km × 10 km grid cells; see van Donkelaar et al. (2010) for details	Mean: 9.1 Range: 1.3–17.6	Correlation (r): NA Copollutant models with: NA
†Garcia et al. (2015) Multicity, U.S. $PM_{2.5}$: 2000–2006 Follow-up: 2006 Cohort Study	California Cohort n = 33,292,571 individuals 65+ years old; 162,124 deaths	Nearest fixed-site monitor, Inverse distance weighting with fixed-site monitors	Mean: 10.2-15.4	Correlation (r): NA Copollutant models with: NA
†Lipsett et al. (2011) Multicity, California $PM_{2.5}$: 1999–2005 Follow-up: 2000–2005 Cohort Study	CA Teachers Study: n = 7,888 (within 8 km of monitor) or 44,847 (within 30 km of monitor) women enrolled in State Teachers' Retirement System	Inverse distance weighting with fixed-site monitors located within 20 km of participant's residence	Mean: 15.6 Range: 3.11–28.35	Correlation (r): O_3: 0.54 NO_X: 0.52 NO_2: 0.81 CO: 0.53 SO_2: 0.02 Copollutant models with: O_3

Table 11-5 (Continued): North American epidemiologic studies of long-term exposure to $PM_{2.5}$ and mortality.

Study	Study Population	Exposure Assessment	Mean ($\mu g/m^3$)	Copollutant Examination
†Ostro et al. (2010) Multicity, California $PM_{2.5}$: 2002–2007 Follow-up: 2002–2007 Cohort Study	California Teachers Study: n = 73,489 women enrolled in State Teachers' Retirement System	Nearest fixed-site monitor within 8 or 30 km of residence	Mean: 17.0 (8 km) Mean: 17.5 (30 km)	Correlation (*r*): NA Copollutant models with: NA
†Ostro et al. (2015) Multicity, California $PM_{2.5}$: 2002–2007 Follow-up: 2001–2007 Cohort Study	California Teachers Study: n = 101,884 women enrolled in State Teachers' Retirement System; 642,269 person-years of follow-up; 6,285 deaths	UCD/CIT chemical transport model; predicted to 4 × 4 km grid cells; correlations between predictions and measurements were >0.8; see Hu et al. (2014b) and Hu et al. (2014a) for details	Mean: 17.9	Correlation (*r*): NA Copollutant models with: NA
†Puett et al. (2009) Multicity, U.S. $PM_{2.5}$: 1988–2002 Follow-up: 1992–2002 Cohort Study	Nurses' Health Study: n = 66,250 women in northeastern and Midwestern U.S.; 3,785 deaths	Separate spatio-temporal models for 1988–1998 and 1999–2002; models performed well using cross-validation; see Paciorek et al. (2009) and Yanosky et al. (2009) for details	Mean: 13.9 Range: 5.8–27.6	Correlation (*r*): NA Copollutant models with: $PM_{10-2.5}$ (estimated by subtracting modeled $PM_{2.5}$ from modeled PM_{10} estimates)
†Hart et al. (2015) Multicity, U.S. $PM_{2.5}$: 2000–2006 Follow-up: 2000–2006 Cohort Study	Nurses' Health Study: n = 108,767 women in northeastern and Midwestern U.S.; 628,186 person-years of follow-up; 8,617 deaths	Nearest fixed-site monitor or spatio-temporal models; models performed well using cross-validation; see Yanosky et al. (2014) for details	Mean: 12.7 (nearest monitor) Mean: 12.0 (spatio-temporal model)	Correlation (*r*): NA Copollutant models with: NA
†Puett et al. (2011) Multicity, U.S.: $PM_{2.5}$: 1988–2003 Follow-up: 1989–2003 Cohort Study	Health Professionals Follow-Up Study: n = 17,545 male dentists, pharmacists, optometrists, podiatrists, osteopaths, and veterinarians in northeastern and midwestern U.S.; 2,813 deaths	Separate spatio-temporal models for 1988–1998 and 1999–2002; models performed well using cross-validation; see Paciorek et al. (2009) and Yanosky et al. (2009) for details	Mean: 17.8 (1988 annual average); concentrations declined over study period	Correlation (*r*): NA Copollutant models with: NA

Table 11-5 (Continued): North American epidemiologic studies of long-term exposure to $PM_{2.5}$ and mortality.

Study	Study Population	Exposure Assessment	Mean (μg/m^3)	Copollutant Examination
†Hart et al. (2011) Multicity, U.S. $PM_{2.5}$: 2000 Follow-up: 1985−2000 Cohort Study	TrIPS: n = 39,948 men employed in four trucking companies	Nearest fixed-site monitor (annual average in 2000)	Mean: 14.1	Correlation (*r*): NA Copollutant models with: NA
†Weichenthal et al. (2014) Multicity, U.S. $PM_{2.5}$: 2001–2006 Follow-up: 1993–2009 Cohort Study	Agricultural Health Study N = 83,378 farmers in North Carolina and Iowa; 5,929 deaths	Satellite-based methods adjusting for temporal variation using GEOS-Chem chemical transport model	Mean: 8.8	Correlation (*r*): NA Copollutant models with: NA
†Cox and Popken (2015) Multicity, U.S. $PM_{2.5}$: 2000−2010 Follow-up: 1999−2010 Ecologic Study	n = 21,613 counties (unit of analysis) in 15 states	County-level averages from fixed-site monitors	Mean: 9.16	Correlation (*r*): O_3: 0.28 Copollutant models with: NA
†Wang et al. (2016) Multicity, NJ $PM_{2.5}$: 2004−2009 Follow-up: 2004−2009 Ecological Study	n = 1,938 census tracts (unit of analysis) in New Jersey	Three-stage exposure model: (1) satellite-based methods, (2) land use regression, (3) fixed-site monitor data, good validation ($r > 0.85$); 1 × 1 km grid cells; $PM_{2.5}$ concentration predicted at residence; See Kloog et al. (2014) for details	Mean: 11.3 95th: 12.9	Correlation (*r*): NA Copollutant models with: NA

NA = not available; km = kilometer; LUR-BME = land use regression—Bayesian maximum entropy; CVD = cardiovascular disease; IHD = ischemic heart disease; NIH-AARP = National Institutes of Health American Association of Retired Persons; CanCHEC = Canadian Census Health and Environment Cohort; EFFECT = Enhanced Feedback For Effective Cardiac Treatment; CCHS = Canadian Community Health Survey; CNBSS = Canadian National Breast Screening Survey; TrIPS = Trucking Industry Particle Study.

†Studies published since the 2009 PM ISA.

11.2.1 Biological Plausibility for Long-Term $PM_{2.5}$ Exposure and Total Mortality

The preceding chapters characterized evidence related to evaluating the biological plausibility by which long-term $PM_{2.5}$ exposure may lead to the morbidity effects that are the largest contributors to total (nonaccidental) mortality, specifically cardiovascular and respiratory morbidity and metabolic disease (Section 6.2.1, Section 5.2.1, and Section 7.2.1, respectively). This evidence is derived from animal toxicological, controlled human exposure, and epidemiologic studies. Section 6.2.1 outlines the available evidence for plausible mechanisms by which inhalation exposure to $PM_{2.5}$ could progress from initial events to endpoints relevant to the cardiovascular system and to population outcomes such as IHD, stroke and atherosclerosis. Similarly, Section 5.2.1 characterizes the available evidence by which inhalation exposure to $PM_{2.5}$ could progress from initial events to endpoints relevant to the respiratory system and to population outcomes such as exacerbation of COPD. Section 7.2.1 outlines the available evidence for plausible mechanisms by which inhalation exposure to $PM_{2.5}$ could progress from initial events (e.g., pulmonary inflammation, autonomic nervous system activation) to intermediate endpoints (e.g., insulin resistance, increased blood glucose and lipids) and result in population outcomes such as metabolic disease and diabetes. Collectively, the progression demonstrated in the available evidence for cardiovascular and respiratory morbidity and metabolic disease supports potential biological pathways by which long-term $PM_{2.5}$ exposures could result in mortality.

11.2.2 Associations between Long-Term $PM_{2.5}$ Exposure and Mortality

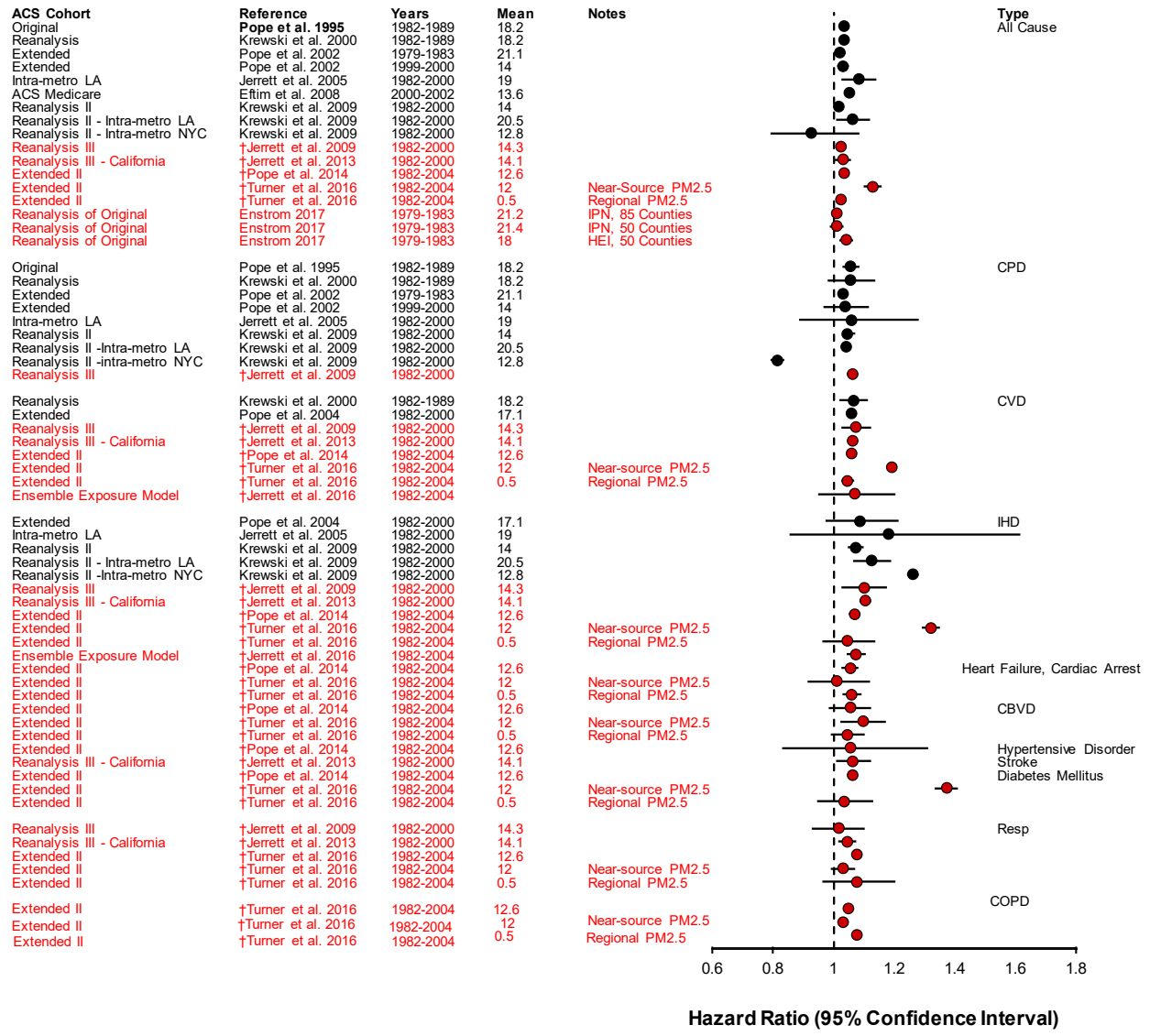
11.2.2.1 Results of American Cancer Society (ACS) and Harvard Six Cities Cohort Studies

Results from the ACS and Harvard Six Cities cohorts have provided evidence on the associations between long-term $PM_{2.5}$ exposure and mortality in the 1996 PM AQCD (U.S. EPA, 1996), the 2004 PM AQCD (U.S. EPA, 2004) and the 2009 PM ISA (U.S. EPA, 2009). Each of these cohort studies are broadly representative of the U.S. population and have undergone extensive independent replication and extended reanalysis. Numerous results from replication and reanalysis of the ACS study are summarized in Figure 11-17.

Many new analyses further evaluated the associations of long-term $PM_{2.5}$ exposures with risk of mortality based on the original ACS study (Pope et al., 1995), adding new details about deaths due to cardiovascular disease (including IHD) and respiratory disease (including COPD), and extending the follow-up period of the ACS to 22 years (1982−2004). In particular, Pope et al. (2014) and Turner et al. (2016) used the extended follow-up period of the ACS to examine the associations between long-term

$PM_{2.5}$ exposure and total (nonaccidental), cardiovascular, ischemic heart disease, heart failure and cardiac arrest, cerebrovascular disease, hypertensive disease, diabetes mellitus, respiratory disease, COPD and lung cancer. In these extended analyses, they applied a new method to assign exposure, specifically a national-level land use regression (LUR) and Bayesian Maximum Entropy (BME) prediction model (LUR-BME; see Section 3.4.5.2 for details). The results of these extended analyses were consistent with previous results from the ACS cohort for total (nonaccidental), cardiovascular, and ischemic heart disease (Figure 11-17). In addition, these extended analyses provide evidence of positive associations for causes of death that had previously not been evaluated among the ACS cohort. Positive associations were observed with heart failure and cardiac arrest, cerebrovascular disease, hypertensive disorder, diabetes mellitus, respiratory disease and COPD. A recent reanalysis of early ACS results observed a null association between county-level averages of $PM_{2.5}$ measured by the Inhalable Particle Network between 1979 and 1983 and deaths between 1982 and 1988 (HR: 1.01; 95% CI: 1.00, 1.02) (Enstrom, 2017). Inconsistencies in the results could be due to the use of 85 counties in the ACS analysis by Enstrom (2017) and 50 Metropolitan Statistical Areas in the original ACS analysis (Pope et al., 1995).

Another benefit of the multiple reanalysis and extended analyses of the ACS cohort is the ability to compare the results of using different techniques to assign long-term $PM_{2.5}$ exposures (e.g., monitors, models, satellite-based methods, or combinations of multiple techniques). The original analysis of the ACS cohort (Pope et al., 1995) and several extended analyses [e.g., (Jerrett et al., 2009)] used area-wide averages of $PM_{2.5}$ concentrations measured by fixed-site monitors to assign exposure. As previously mentioned, the most recent extended analyses relied on LUR-BME models (Turner et al., 2016; Pope et al., 2014). In addition, Jerrett et al. (2013) used a LUR model to assign exposure to the subset of the ACS cohort residing in California while evaluating the association between long-term $PM_{2.5}$ exposure and total (nonaccidental) and cause-specific mortality. Turner et al. (2017) evaluated the interaction between ambient $PM_{2.5}$ exposure and smoking in the entire ACS cohort. As demonstrated in Figure 11-17, the results of all of these studies are consistent in the direction and magnitude of effect, providing evidence that these associations are not artifacts related to the type of exposure assessment used, and that they are robust to different kinds of exposure measurement error that may be associated with different exposure assessment techniques (Section 3.4.5.2).



CPD = cardiopulmonary disease; CVD = cardiovascular disease; IHD = ischemic heart disease; CBVD = cerebrovascular disease; Resp = respiratory disease; COPD = chronic obstructive pulmonary disease; IPN = inhalable particle network; HEI = $PM_{2.5}$ data from Health Effects Institute reanalysis.

Note: †Studies published since the 2009 PM ISA. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Mean concentrations in $\mu g/m^3$. Hazard Ratios are standardized to a 5-$\mu g/m^3$ increase in $PM_{2.5}$ concentrations. Studies are nationwide unless otherwise noted.

Corresponding quantitative results are reported in Supplemental Table S11-4 (U.S. EPA, 2018b).

Figure 11-17 Associations between long-term exposure to PM2.5 and total (nonaccidental) mortality in the American Cancer Society (ACS) cohort.

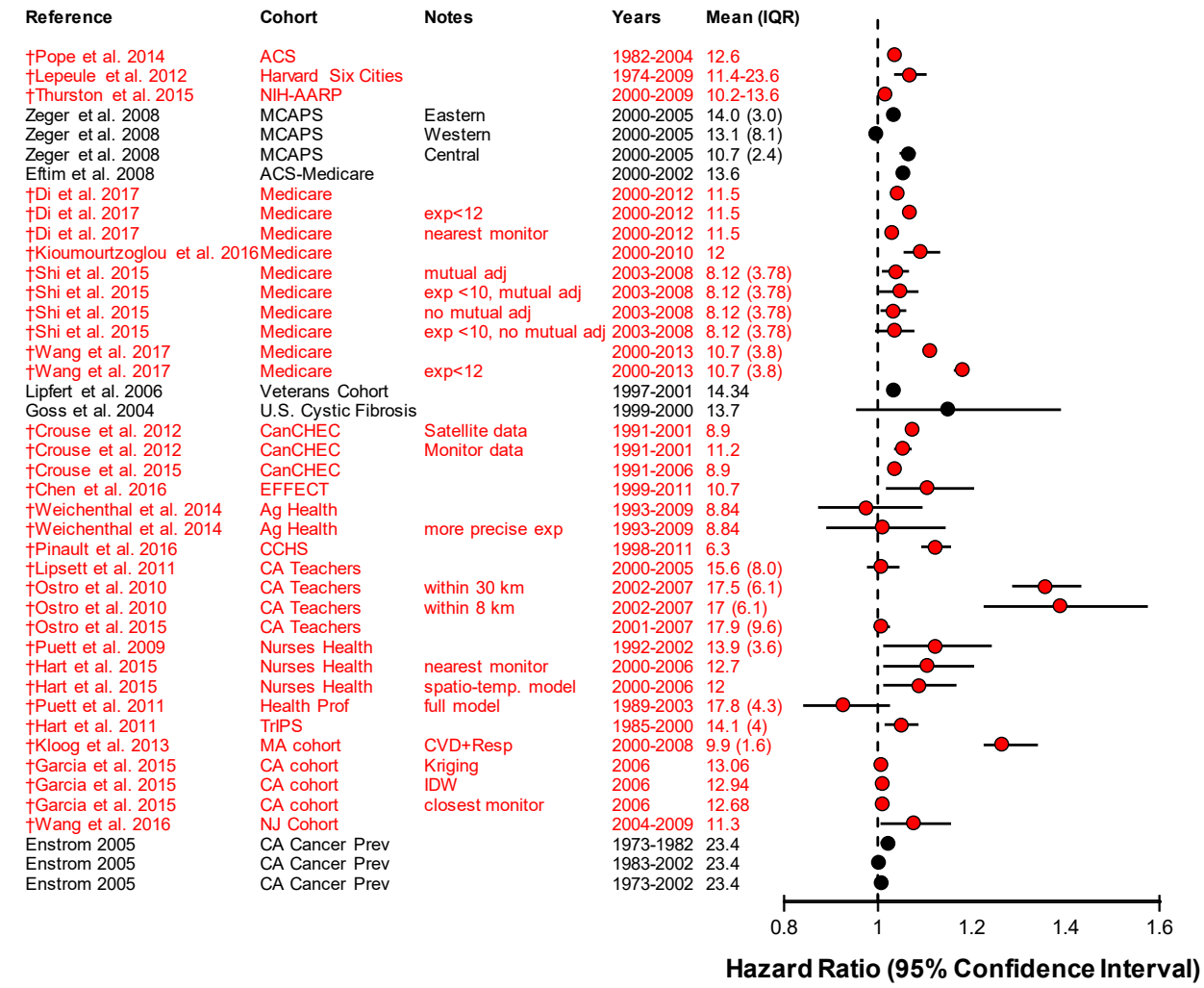
In addition to the reanalysis of the ACS cohort, Lepeule et al. (2012) reported the results of an extended analysis of the Harvard Six Cities cohort, extending the follow-up period to include deaths between 1974 and 2009. The authors included results for the association between long-term $PM_{2.5}$

exposure and total (nonaccidental), cardiovascular, COPD and lung cancer mortality. The results for total (nonaccidental), cardiovascular, and lung cancer mortality were consistent with previous analyses of the Harvard Six Cities cohort. This was the first time that COPD mortality was evaluated among the Harvard Six Cities cohort; the relative risk was positive with wide confidence intervals due to the smaller number of COPD deaths compared to deaths from other causes.

Overall, analyses of the ACS and the Harvard Six Cities cohorts continue to provide strong support for the causal relationship between long-term $PM_{2.5}$ exposure and mortality. Results from recent reanalysis and extended analyses of data from the ACS cohort are consistent with the previous results from this cohort, and have also added more information about some causes of mortality that was not available in the 2009 PM ISA. These studies also contribute to the improved characterization of the relationship between $PM_{2.5}$ and mortality, informing the shape of the C-R relationship (Section 11.2.4), role of copollutants evaluated in copollutant models (Section 11.2.3), impact of different exposure assessment techniques (Section 11.2.5.1), and evaluation of different windows of exposure (Section 11.2.5.3). Results from the ACS and Harvard Six Cities Cohorts that inform these aspects of the relationship will be integrated and synthesized with the results from other cohort studies in the following sections.

11.2.2.2 Results of other North American Cohort Studies

A number of cohort studies have recently been conducted in the U.S. and Canada and are consistent with the results observed in the ACS and Harvard Six Cities cohort studies, while providing additional information about the relationship between long-term $PM_{2.5}$ exposure and mortality among different subpopulations (e.g., women, teachers, nurses, truck drivers), in locations with generally low annual $PM_{2.5}$ concentrations, and using different methods for assigning exposure to $PM_{2.5}$. Results from studies of total (nonaccidental) mortality are summarized in Figure 11-18, while the results for all cardiovascular and all respiratory mortality are summarized in Figure 11-19. More specific results on cause-specific mortality can be found in Section 6.3.9 and Section 5.2.10.

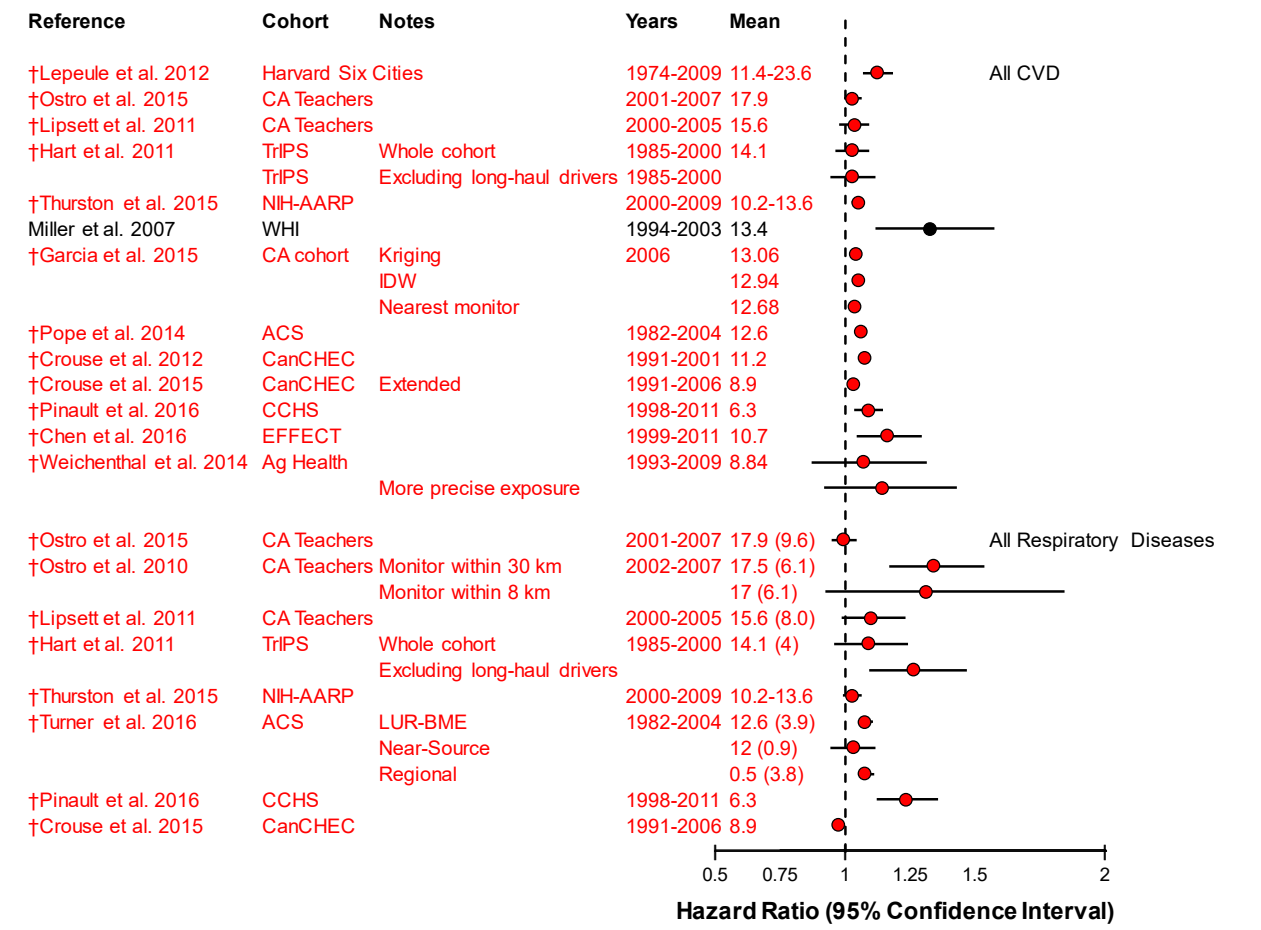


ACS = American Cancer Society; NIH-AARP = National Institutes of Health American Association of Retired Persons; MCAPS = Medicare Cohort Air Pollution Study; CanCHEC = Canadian Census Health and Environment Cohort; Ag Health = Agricultural Health Study; CCHS = Canadian Community Health Survey; Health Prof = Health Professionals; TrIPS = Trucking Industry Particle Study; Cancer Prev = Cancer Prevention; adj = Adjustment; exp = exposure; km = kilometer; CVD = cardiovascular; Resp = Respiratory; IDW = Inverse Distance Weighting; IQR = Interquartile Range.

Note: †Studies published since the 2009 PM ISA. Associations are presented per 5 μg/m^3 increase in pollutant concentration. Circles represent point estimates, horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Study results from Pope et al. (2014) are representative of the results from the American Cancer Society Cohort. For complete results from this cohort, see Figure 11-17.

Corresponding quantitative results are reported in Supplemental Table S11-5 (U.S. EPA, 2018b).

Figure 11-18 Associations between long-term exposure to $PM_{2.5}$ and total (nonaccidental) mortality in recent North American cohorts.



ACS = American Cancer Society; NIH-AARP = National Institutes of Health American Association of Retired Persons; CanCHEC = Canadian Census Health and Environment Cohort; Ag Health = Agricultural Health Study; TrIPS = Trucking Industry Particle Study; EFFECT = Enhanced Feedback For Effective Cardiac Treatment; CCHS = Canadian Community Health Survey; LUR-BME = land use regression Bayesian maximum entropy; km = kilometer; CVD = cardiovascular disease; IDW = Inverse Distance Weighting.

Note: †Studies published since the 2009 PM ISA. Associations are presented per 5 μg/m^3 increase in pollutant concentration. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Corresponding quantitative results are reported in Supplemental Table S11-6 (U.S. EPA, 2018b).

Figure 11-19 Associations between long-term exposure to $PM_{2.5}$ and all cardiovascular disease (CVD) and all respiratory mortality in recent North American cohorts.

A number of recent cohort studies conducted in the U.S. and Canada have examined the relationship between long-term $PM_{2.5}$ exposure and mortality using innovative and novel exposure assessment and statistical techniques in areas where annual average $PM_{2.5}$ concentrations are relatively low (i.e., less than 12 μg/m^3). In the U.S., Kloog et al. (2013) described a novel method of estimating temporally and spatially resolved $PM_{2.5}$ concentrations by combining results of a LUR model with daily satellite-based observations of aerosol optical depth (AOD) (see Section 3.3.3 for details). The authors

then assigned exposure based on residence at time of death for all deaths in Massachusetts, and the association between long-term $PM_{2.5}$ exposure and cardiovascular and respiratory mortality (combined) was estimated using a relative incidence analysis with a 365-day moving average of estimated $PM_{2.5}$ concentration, similar to statistical analyses of short-term exposure often used in time-series studies. Kloog et al. (2013) observed a positive association in the 365-day moving average of $PM_{2.5}$ and cardiovascular and respiratory mortality (RR: 1.26, 95% CI: 1.22, 1.34). Building on the innovative exposure assessment and statistical techniques introduced by Kloog et al. (2013), Shi et al. (2015) expanded the exposure assessment to include all of New England and used a model output that refined the spatial resolution to 1 × 1 km grid cells (see Section 3.4.5.2 for discussion of effect of spatial resolution risk estimates). These exposure data were linked to a population-based Medicare cohort and the authors observed a relative risk of 1.04 (95% CI: 1.01, 1.06) for the 365-day moving average of $PM_{2.5}$ and total (nonaccidental) mortality. This association persisted when the analysis was restricted to those with annual exposures <10 $\mu g/m^3$ (RR: 1.05, 95% CI: 1.00, 1.09 for the 365-day moving average of $PM_{2.5}$). Finally, these authors applied the refined spatial resolution (i.e., 1 × 1 km grid cells) to all Medicare beneficiaries in the continental U.S. between 2000 and 2012 (Di et al., 2017c). In an open cohort of over 60 million people, 460 million person-years of follow-up, and 22 million deaths, (Di et al., 2017c) observed an HR of 1.041 (95% CI: 1.039, 1.042) for the relationship between $PM_{2.5}$ and all-cause mortality. This association was robust in copollutant models with O_3 and when the nearest monitor was used to assign exposure. When restricting the analysis to locations for which the annual $PM_{2.5}$ concentration was <12 $\mu g/m^3$, the authors observed a stronger relationship (HR: 1.066; 95% CI: 1.063, 1.068).

Additional cohort studies looked at the relationship between long-term $PM_{2.5}$ exposure and mortality among older adults across a larger spatial extent, using more traditional exposure assessment and statistical techniques. Kioumourtzoglou et al. (2016) also used the Medicare cohort, but expanded from New England to include Medicare deaths in 207 cities across the U.S. from 2000–2010. These authors used fixed-site monitor data to calculate city-specific annual and two-year average $PM_{2.5}$ concentrations. Using a Cox proportional hazard statistical model, Kioumourtzoglou et al. (2016) observed a 9% increase in the risk of total (nonaccidental) mortality (HR: 1.09, 95% CI: 1.05, 1.13). Wang et al. (2017b) used a similar exposure assessment protocol to examine mortality in seven southeastern states. These exposure data were linked to a population-based Medicare cohort and the authors observed a hazard ratio of 1.11 (95% CI: 1.10, 1.11) for the annual average of $PM_{2.5}$ and total (nonaccidental) mortality. This association was stronger when the analyses were restricted to those with annual exposures <12 $\mu g/m^3$ (RR: 1.18, 95% CI: 1.16, 1.19). In another nationwide cohort of older Americans, Thurston et al. (2015) used census-tract estimates of monthly $PM_{2.5}$ concentration from a LUR model to assign annual mean concentrations to participants in the NIH-AARP cohort study that died between 2000 and 2009. The authors observed positive associations with total (nonaccidental), CVD and respiratory mortality, with the largest magnitude of effect observed with CVD mortality.

A recent series of studies conducted in Canada linked census data with data from the Canadian Mortality Database to create the Canadian Census Health Environment Cohort (CanCHEC). The

CanCHEC cohort included adults (≥25 years) who died between 1991 and 2001. Mean annual concentrations of $PM_{2.5}$ were calculated from fixed-site monitors in 11 cities and assigned to 43% of the cohort. In addition to using fixed-site monitors to assign exposure, exposure was also assigned using $PM_{2.5}$ predictions from satellite-based observations (with a spatial resolution of 10 × 10 km). Crouse et al. (2012) developed Cox proportional hazards models to evaluate the relationship between long-term $PM_{2.5}$ exposure and total (nonaccidental) and CVD (including IHD, CBVD, and circulatory) mortality. The authors observed positive associations between total (nonaccidental) and CVD mortality and long-term $PM_{2.5}$ exposure, with similar estimates for satellite-based observations of AOD and fixed-site monitor concentrations. The strongest association was for IHD mortality (HR: 1.31, 95% CI: 1.27, 1.35) and the weakest was for cerebrovascular mortality (HR: 1.04; 95% CI: 0.99, 1.10) (see Figure 6-19).

Using the same CanCHEC cohort and methods, Brook et al. (2013) evaluated the association between long-term exposure to $PM_{2.5}$ and mortality due to diabetes, and observed a positive association similar in magnitude to the one observed for IHD mortality in the previous study (HR: 1.23; 95% CI: 1.18, 1.28). Similarly, Chen et al. (2016) limited their analyses to cohort participants residing in Ontario who had experienced an acute myocardial infarction, and observed positive associations with total (nonaccidental), CVD, and IHD deaths, as well as deaths due to subsequent acute myocardial infarctions (range of HRs: 1.10−1.28). Crouse et al. (2015) extended the follow-up period to include five additional years (1991−2006) and evaluated several additional mortality causes, but otherwise used the same methods as those in Crouse et al. (2012). Positive associations were observed for total (nonaccidental) and cardiovascular mortality, with the strongest association observed between long-term exposure to $PM_{2.5}$ and mortality due to diabetes (HR: 1.15, 95% CI; 1.11, 1.19), followed by IHD (HR: 1.09; 95% CI: 1.07, 1.10). The associations for cerebrovascular, respiratory and COPD mortality were just below the null. The general pattern and magnitude of these associations were generally unchanged in cumulative risk models that include O_3 and/or NO_2. Weichenthal et al. (2016) evaluated the subset of the CanCHEC cohort living within 5 km of a fixed-site monitor (n = 193,300) for associations between long-term $PM_{2.5}$ exposure and mortality. They assigned the average (1998−2009) $PM_{2.5}$ concentration to each of the participants living within 5 km of each of 30 fixed-site monitors. In additional analyses, these authors observed positive associations between $PM_{2.5}$ exposure and total (nonaccidental) (HR: 1.05, 95% CI: 1.03, 1.09) and respiratory mortality (HR: 1.08, 95% CI: 0.96, 1.21), but the results for cardio-metabolic and IHD mortality were closer to the null value.

Pinault et al. (2016) linked a subset of participants from the CanCHEC cohort to the Canadian Community Health Survey, which allowed them to include an expanded set of individual-level covariates in their analyses. Among the nearly 300,000 participants included the study, the authors observed positive associations with total (nonaccidental), circulatory, and respiratory mortality similar in magnitude to those observed in the larger cohort (Crouse et al., 2012). In addition, Pinault et al. (2016) was able to make use of the individual-level covariate data to examine effect measure modification by age, sex, smoking, alcohol consumption, obesity, and fruit/vegetable consumption. In an attempt to validate the results observed in the CanCHEC cohort, Villeneuve et al. (2015) examined the association of long-term $PM_{2.5}$

exposure and mortality in a cohort of Canadian women originally enrolled in the Canadian National Breast Screening Study (CNBSS). Using similar exposure methods that relied on satellite-based estimates linked with the centroid of each six-digit postal code, Villeneuve et al. (2015) observed positive associations, similar in magnitude to those observed in previous Canadian cohorts, for total (HR: 1.06; 95% CI: 1.02, 1.10) and cardiovascular mortality (HR: 1.16; 95% CI: 1.07, 1.26), though they did not observe a positive association with respiratory mortality.

Several recent U.S. cohort studies examined the association between long-term $PM_{2.5}$ exposure and mortality in occupational cohorts. The California Teachers Study (Lipsett et al., 2011; Ostro et al., 2010) examined the association between $PM_{2.5}$ measures at fixed-site monitors and mortality among current and former female public school teachers. The authors observed positive associations between long-term $PM_{2.5}$ exposure and IHD, cerebrovascular, cardiopulmonary, and respiratory mortality, with the strongest association observed with IHD (HR: 1.70; 95% CI: 1.51, 1.91). Analyses restricted to post-menopausal women yielded results similar to those for all subjects. In a reanalysis of the cohort with refined exposure assessment, Ostro et al. (2015) used a chemical transport model to predict $PM_{2.5}$ concentrations with a 4 km spatial resolution, observing a pattern of results similar to those in the original analyses, although the magnitude of the risk estimates was smaller. Puett et al. (2009) examined the association between long-term $PM_{2.5}$ exposure and total (nonaccidental) mortality among a cohort of female nurses in the Nurses' Health Study from 13 states in the northeast and Midwest from 1992 through 2002. The authors observed positive associations with total (nonaccidental) and CHD mortality, with the strongest association observed for fatal CHD events (HR: 1.42, 95% CI: 1.03-1.94). Hart et al. (2015) expanded the Nurses' Health Study to the full nationwide cohort and extended the years of follow-up through 2006. In the updated cohort, the average $PM_{2.5}$ exposure over the previous 12 months was 12.0 $\mu g/m^3$. The results for total (nonaccidental) mortality were similar in the nationwide cohort for the extended follow-up period compared to the original results from the earlier follow-up period and more limited (i.e., smaller) spatial extent. The magnitude of the associations for long-term $PM_{2.5}$ exposure and cardiovascular mortality among women (Hart et al., 2015; Lipsett et al., 2011; Ostro et al., 2010; Puett et al., 2009) was higher than those observed in many of the other North American cohorts of men or men and women combined, but similar to that observed by Miller et al. (2007), who also evaluated fatal CHD events among a cohort of women. Using a design similar to that of the Nurses' Health Study, Puett et al. (2011) investigated the effect of long-term $PM_{2.5}$ exposure and mortality among men enrolled in the Health Professionals Follow-up Study cohort. Near null associations were observed for both total (nonaccidental) (HR: 0.94, 95% CI: 0.87, 1.02) and CHD mortality (HR: 0.97, 95% CI: 0.83, 1.13) in this cohort. In another occupational cohort, Hart et al. (2011) examined the association between residential exposure to $PM_{2.5}$ estimated from a single year of monitoring data (2000) and mortality among men in the U.S. trucking industry in the Trucking Industry Particle Study (TrIPS). Elevated risks of total (nonaccidental), lung cancer, and respiratory mortality were observed, with generally higher effects observed in subset analyses that excluded long-haul drivers.

The results of these recent U.S. and Canadian cohort studies demonstrate a consistent, positive association between long-term $PM_{2.5}$ exposure and mortality across various spatial extents, exposure assessment metrics, statistical techniques, and locations, including those where mean annual average concentrations are below ≤12 µg/m^3. Recent cohort studies in the U.S. observed increases in total mortality and mortality due to cardiovascular disease in separate cohorts of men and women. Additional cohort studies conducted in Europe observed similarly consistent, positive associations between long-term $PM_{2.5}$ exposure and mortality (see Table 11-6), and support the evidence from the U.S. and Canada. Particularly noteworthy is a study conducted in Europe that combined data from 22 existing cohort studies and evaluated the association between long-term $PM_{2.5}$ exposure and total (nonaccidental) (Beelen et al., 2014a), cardiovascular (Beelen et al., 2014b), and respiratory (Dimakopoulou et al., 2014) mortality. Including participants from 13 European countries, the authors applied a common statistical protocol to data from each of the 22 cohorts in the first stage of the analysis and combined the cohort-specific effects in a second stage. The authors observed a positive association between long-term $PM_{2.5}$ exposure and total (nonaccidental) mortality (HR: 1.07, 95% CI 1.02, 1.13) (Beelen et al., 2014a), but the associations for cardiovascular and respiratory mortality were near the null value, except for the subset of cardiovascular deaths attributable to cerebrovascular disease (HR: 1.21, 95% CI: 0.87, 1.69) (Beelen et al., 2014b).

Table 11-6 European epidemiologic studies of long-term exposure to $PM_{2.5}$ and mortality.

Study	Study Population	Exposure Assessment	Mean SD in µg/m^3	Copollutant Examination
†Beelen et al. (2014a) Multicity; Europe $PM_{2.5}$: 2008−2011 Follow-up: 1985−2007 (variable, depending on cohort) Pooled Cohort Study	ESCAPE: 367,251 participants; 5,118,039 person-years of follow-up; 29,076 deaths	LUR; model validation R^2 = 0.57−0.89	Mean: 6.6−31.0	Correlation (*r*): $PM_{10-2.5}$: 0.11−0.90 NO_2: 0.17−0.88 Copollutant models with: copollutant models limited to cohorts for which pollutant correlation was <0.7
†Beelen et al. (2014b) Multicity; Europe $PM_{2.5}$: 2008−2011 Follow-up: 1985−2007 (variable, depending on cohort) Pooled Cohort Study	ESCAPE: 22 cohorts from 13 European countries 367,383 participants; 5,119,317 person-years of follow-up; 9,994 deaths due to CVD	LUR; model validation R^2 = 0.57−0.89	Mean: 6.6−31.0	Correlation (*r*): NA Copollutant models with: NA
†Beelen et al. (2009) Multicity; Netherlands $PM_{2.5}$: 1987−1996 Follow-up: 1987−1996	NLCS: 1,117,528 participants; 6,137 CVD deaths	Interpolation of measurements from national fixed-site monitoring network	NA	Correlation (*r*): NA Copollutant models with: NA

Table 11-6 (Continued): European epidemiologic studies of long term exposure to $PM_{2.5}$ and mortality.

Study	Study Population	Exposure Assessment	Mean SD in µg/m³	Copollutant Examination
†Bentayeb et al. (2015) Multicity, France $PM_{2.5}$: 1989−2008 Follow-up: 1989−2013 Cohort Study	Gazel cohort: 20,327 participants 1,967 deaths	CHIMERE chemical transport model (2 km resolution)	Mean: 15.0	Correlation (*r*): NA Copollutant models with Copollutant models conducted with correlation between pollutants was <0.7 (O_3, benzene).
†Carey et al. (2013) Multicity; England $PM_{2.5}$: 2002 Follow-up: 2003−2007 Cohort Study	National English Cohort: 835,607 patients ages 40−89; 83,103 deaths	Dispersion model, 1 km grid cells; model validation R^2 = 0.23−0.71	Mean: 12.9	Correlation (*r*): PM_{10}: 0.99 SO_2: 0.46 NO_2: 0.85 O_3: −0.39 Copollutant models with: SO_2, O_3
†de Keijzer et al. (2016) Multicity; Spain $PM_{2.5}$: 2009−2013 Follow-up: 2009−2013 Ecologic Study	Mortality data from 2,148 small areas covering Spain	CALIOPE Air Quality Forecasting System (combines meteorological, emissions, chemical transport and atmospheric mineral dust models)	Mean: 8.22	Correlation (*r*): PM_{10}: 0.91 NO_2: 0.55 O_3: 0.33 Copollutant models with: NA
†Dehbi et al. (2016) Multicity: UK $PM_{2.5}$: 2010−2011 Follow-up: 1989−2015 Pooled Cohort Study	Combines data from two British cohorts: Medical Research Council National Survey of Health and Development (4,400 participants born in March 1946) and Southall and Brent Revisited study (3,129 tri-ethnic men and women recruited 1989−1991)	Exposure data same as used in ESCAPE Cohort; see Beelen et al. (2014a)	Median: 9.90	Correlation (*r*): NO_2: 0.83 NO_X: 0.82 PM_{10}: 0.60 $PM_{10-2.5}$: 0.35 Copollutant models with: NA
†Dimakopoulou et al. (2014) Multicity; Europe $PM_{2.5}$: 2008−2011 Follow-up: 1985−2007 (variable, depending on cohort) Pooled Cohort Study	ESCAPE: 16 cohorts from 11 European countries 307,553 participants; 1,559 deaths due to nonmalignant respiratory disease	LUR; model validation R^2 = 0.57−0.89	Mean: 7.1−31.0	Correlation (*r*): NA Copollutant models with: NA
Naess et al. (2007) Oslo, Norway $PM_{2.5}$: 1992−1995 Follow-up: 1992−1998 Cohort Study	Oslo Cohort: 143,842 individuals ages 51−90	AirQUIS dispersion model; model validation (*r* = 0.57 [summer)], –0.79 [winter]) reported in Oftedal et al. (2009)	Mean: 15	Correlation (*r*): NO_2: *r* > 0.88 PM_{10}: *r* > 0.88 Copollutant models with: NA

Table 11-6 (Continued): European epidemiologic studies of long term exposure to $PM_{2.5}$ and mortality.

Study	Study Population	Exposure Assessment	Mean SD in µg/m³	Copollutant Examination
†Tonne et al. (2015) London; U.K. $PM_{2.5}$: 2003−2010 Follow-up: 2003−2010 Cohort Study	MINAP: 18,138 participants with hospital admissions between 2003–2007; 5,129 deaths	KCLurban dispersion model; see Beevers et al. (2013) for details	Mean: 14.6	Correlation (*r*): NO_2: 0.71 NO_X: 0.73 O_3: −0.82 PM_{10}: 0.96 $PM_{10-2.5}$: 0.70 Copollutant models with: NA

NR = not available; km = kilometer; LUR = land use regression; CVD = cardiovascular disease; ESCAPE = European Study of Cohorts for Air Pollution Effects; NLCS = Netherlands Cohort Study on Diet and Cancer; MINAP = Myocardial Ischaemia National Audit Project.

†Studies published since the 2009 PM ISA.

11.2.2.3 Cardiovascular Mortality

Overall, the results of the recent U.S. and Canadian cohort studies demonstrate a consistent, positive association between long-term $PM_{2.5}$ exposure and cardiovascular mortality across various spatial extents, exposure assessment techniques, and statistical techniques, and locations, including those where mean annual average concentrations are ≤12 µg/m³. Additional cohort studies conducted in Europe observed similarly consistent, positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality (see Table 11-6), and support the evidence from the U.S. and Canada. However, a study conducted in Europe that combined data from 22 existing cohort studies and evaluated the association between long-term $PM_{2.5}$ exposure and cardiovascular mortality (Beelen et al., 2014b) reported associations near the null value, except for the subset of cardiovascular deaths attributable to cerebrovascular disease (HR: 1.21, 95% CI: 0.87, 1.69). More detailed results of long-term $PM_{2.5}$ exposure and cardiovascular mortality are included in Section 6.3.9.

11.2.2.4 Respiratory Mortality

Overall, the results of these recent U.S. cohort studies demonstrate a generally consistent, positive association between long-term $PM_{2.5}$ exposure and respiratory mortality, though the results from the two Canadian studies are inconsistent. In addition, a study conducted in Europe that pooled data from 22 existing cohort studies and evaluated the association between long-term $PM_{2.5}$ exposure and respiratory mortality observed an association for respiratory mortality near the null value (Dimakopoulou et al., 2014). Overall, the associations for respiratory mortality were generally positive, though some inconsistencies among the results from different analyses of the same cohort provide some uncertainty in the stability of these results [Ostro et al. (2010) and Ostro et al. (2015); Crouse et al. (2015) and Pinault et al. (2016)]. Recent studies have evaluated the association between long-term $PM_{2.5}$ exposure and COPD mortality, a cause of death for which there has previously been little examination. These studies report

modest positive associations with COPD mortality and the hazard ratios are generally less precise (i.e., wider 95% confidence intervals) than those for respiratory mortality. More detailed results of long-term $PM_{2.5}$ exposure and cardiovascular mortality are included in Section 5.2.10.

11.2.2.5 Causal Inference Studies

Recently, several studies have explored the use of causal inference methods (i.e., quantitative methods and/or study design attributes) to specifically inform the causal nature of the relationship between long-term $PM_{2.5}$ exposure and mortality. A recent study employed a difference-in-difference approach as a quantitative causal inference method to examine the relationship between long-term $PM_{2.5}$ exposure and mortality in New Jersey (Wang et al., 2016). $PM_{2.5}$ concentrations were estimated at the census tract level using similar exposure assessment techniques as those used by Shi et al. (2015), discussed previously. The difference-in-difference method controls for geographical differences using dummy variables for each tract, long-term temporal trends using dummy variables for each year, and temperature, which is both correlated with $PM_{2.5}$ and can vary differentially over space and time. Wang et al. (2016) observed a positive relationship between long-term exposure to $PM_{2.5}$ and total (nonaccidental) mortality (RR: 1.08; 95% CI: 1.01, 1.15). Cox and Popken (2015) conducted an ecologic, county-level, repeated-measures analysis to evaluate the changes in $PM_{2.5}$ concentrations from 2000 to 2010 in 15 large U.S. states, and the association with age-specific mortality rates for older adults (65+ years) over the same period. The authors observed positive correlations between county-level $PM_{2.5}$ concentrations and county-level mortality rates for total (nonaccidental) and cardiovascular mortality, but not for external-cause mortality (e.g., accidents), a negative control. The authors applied several quantitative methods to inform causal inference (e.g., Granger tests), and observed effects in 6−7% of counties studied (Cox and Popken, 2015). Inference from this study is limited by a lack of individual-level data; it is an ecologic study relying on county-level mortality rates, with no control for potential confounders other than age, making it difficult to adequately interpret the results. Overall, the results of these causal inference studies contribute to the body of epidemiologic evidence that informs the causal relationship between long-term $PM_{2.5}$ exposure and total mortality. Observing consistent results for this relationship across studies using different analytic techniques (i.e., difference-in-difference approach) increases our confidence in the relationship.

11.2.2.6 Studies of Temporal Trends and Life Expectancy

A recent series of studies has added to the body of evidence on the relationship between long-term exposure to $PM_{2.5}$ and mortality by examining the temporal trends in $PM_{2.5}$ concentrations and changes in life expectancy, testing the hypothesis that decreases in $PM_{2.5}$ concentrations would be associated with increases in life expectancy. Pope et al. (2009) used air quality data in a cross-sectional analysis from 51 metropolitan areas across the U.S., beginning in the 1970s through the early 2000s, to

demonstrate that a 10 µg/m^3 decrease in long-term $PM_{2.5}$ concentration was associated with a 0.61-year increase in life expectancy. In a subsequent analysis, these authors extended the period of analysis to include 2000 to 2007 (Correia et al., 2013). While the decline in concentrations of $PM_{2.5}$ was slower for the 2000 to 2007 period, compared to the period from 1980 to 2000, a decrease in long-term $PM_{2.5}$ concentration continued to be associated with an increase in life expectancy, though the magnitude of the increase was smaller than in the previous analysis and the earlier time period (10 µg/m^3 decrease in long-term $PM_{2.5}$ concentration was associated with a 0.35-year increase in life expectancy). It is noteworthy that, by 2007, 48 of the 545 counties included in the study were not in compliance with the NAAQS (at that time, the annual standard was 15 µg/m^3). The mean concentration across all counties was 13.2 µg/m^3 in 2000, and decreased to 11.6 µg/m^3 by 2007. Using a doubly robust additive hazards model, Wang et al. (2017a) calculated that a 1 µg/m^3 decrease in the annual concentration of $PM_{2.5}$ would prevent about 5,400 premature deaths among the 13.1 million Medicare beneficiaries in seven southeastern states analyzed in Wang et al. (2017b). In an analysis conducted in Spain, de Keijzer et al. (2016) focused on the years of life lost associated with an increase in $PM_{2.5}$ rather than the life expectancy gain associated with a decrease in $PM_{2.5}$. They observed 0.64 (95% CI 0.59, 0.70) years of life lost for every 2 µg/m^3 increase in $PM_{2.5}$. Evaluating life expectancy in a different manner, Baccarelli et al. (2016) conducted an ecologic study to investigate whether or not there was an association between county-level $PM_{2.5}$ concentrations and the proportion of 55−64 and 70- to 74-year-olds that survived for an additional 30 years. They started with the numbers of 55−64 and 70- to 74-year-olds in 3,034 U.S. counties in 1980 and compared it with the numbers of 85−94 and 100- to 104-year-olds in 2010 in each county, using county-level $PM_{2.5}$ estimated from a hybrid of LUR and BME and averaged from 1999−2008. They observed that counties with higher estimated $PM_{2.5}$ concentrations were associated with a lower proportion of adults reaching age 85 years or more.

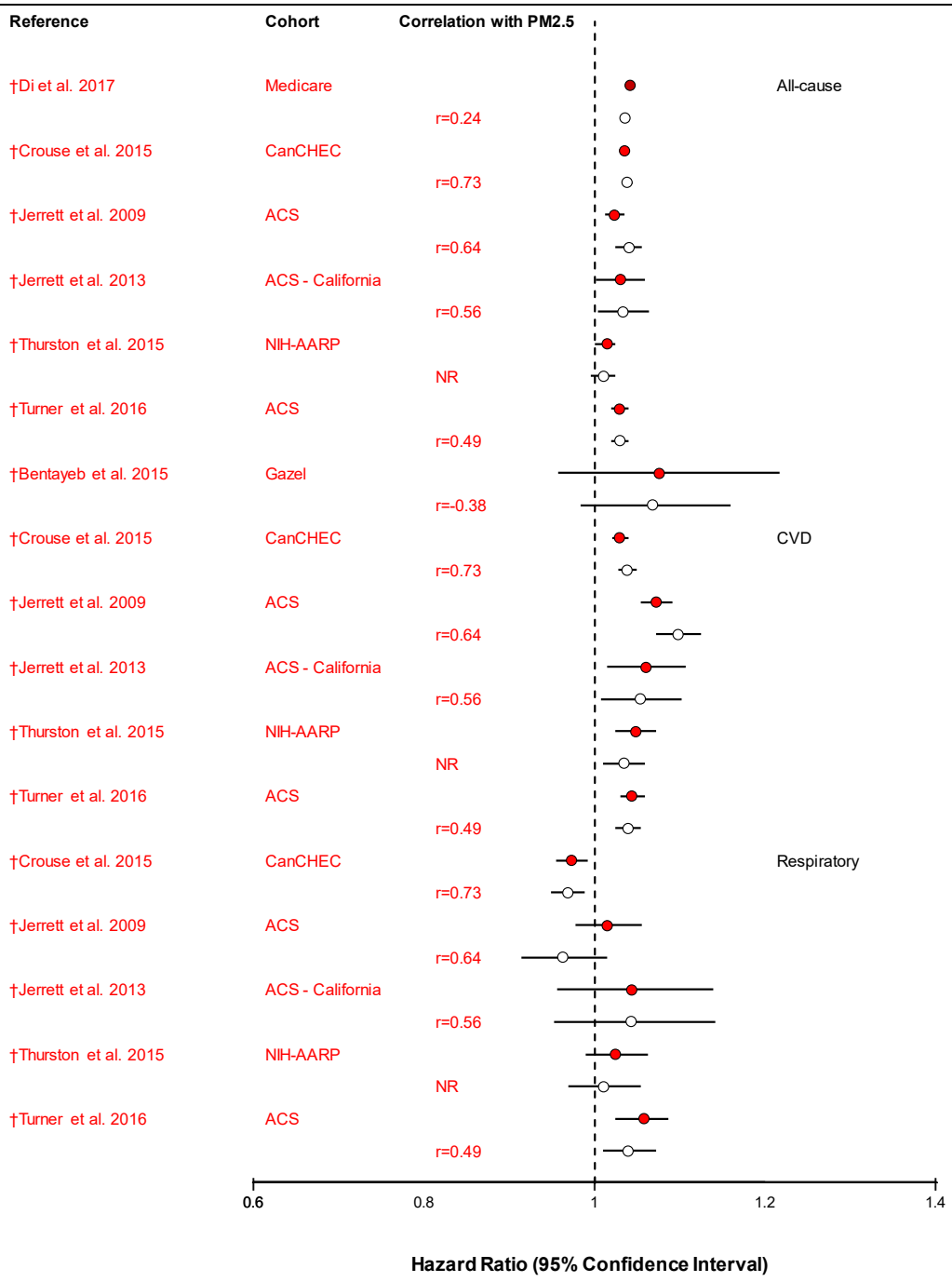
11.2.3 Potential Copollutant Confounding of the $PM_{2.5}$-Mortality Relationship

In the examination of potential confounding effects of copollutants on the relationship between long-term $PM_{2.5}$ exposure and mortality, it is informative to evaluate whether $PM_{2.5}$ risk estimates are changed in copollutant models. Recent studies have examined the potential for copollutant confounding by evaluating copollutant models that include O_3 (Figure 11-20), NO_2, $PM_{10-2.5}$, SO_2, and benzene (Figure 11-21). These recent studies address a previously identified data gap by informing the extent to which effects associated with exposure to $PM_{2.5}$ are independent of co-exposure to correlated copollutants in long-term analyses.

The results for associations between long-term $PM_{2.5}$ exposure and mortality in single pollutant models and copollutant models adjusted for O_3 are shown in Figure 11-20. The correlations between $PM_{2.5}$ and O_3 exposures in the studies that conducted copollutant analyses were generally positive and moderate to strong, ranging from r = 0.49 to 0.73, except for two studies which reported a weak-to-

moderate negative correlation [$r = -0.38$; (Bentayeb et al., 2015) and $r = -0.24$; (Di et al., 2017c)]. Generally, the $PM_{2.5}$ effect estimates remained relatively unchanged in copollutant models adjusted for O_3. The trend persisted for total (nonaccidental) mortality, as well as mortality due to cardiovascular or respiratory disease. There were several exceptions to the trend. The effect of long-term $PM_{2.5}$ exposure on CHD mortality among women in the AHSMOG cohort (Chen et al., 2005) increased after adjusting for O_3 in the model. Conversely, the effect of long-term $PM_{2.5}$ exposure on respiratory mortality in the ACS cohort (Jerrett et al., 2009) decreased (and changed from positive to negative) after adjusting for O_3 in the model.

The results for associations between long-term $PM_{2.5}$ exposure and mortality in single pollutant models and copollutant models adjusted for NO_2, $PM_{10-2.5}$, SO_2, or benzene are shown in Figure 11-21. The correlations between $PM_{2.5}$ and NO_2 exposures in studies that conducted copollutant analyses were positive and weak ($r = 0.25$) or moderate ($r = 0.40$; $r = 0.55$). The correlations between $PM_{2.5}$ and $PM_{10-2.5}$ were not reported in one study (Puett et al., 2009), and in another meta-analysis, the copollutant analyses were limited to cohorts that reported a correlation of $r < 0.7$. One study evaluated SO_2 (Chen et al., 2005) and another benzene (Bentayeb et al., 2015) in copollutant models, and reported correlations of $r = 0.30$ and $r = 0.66$, respectively. Generally, the $PM_{2.5}$ effect estimates remained relatively unchanged in copollutant models adjusted for NO_2, $PM_{10-2.5}$, SO_2, or benzene.

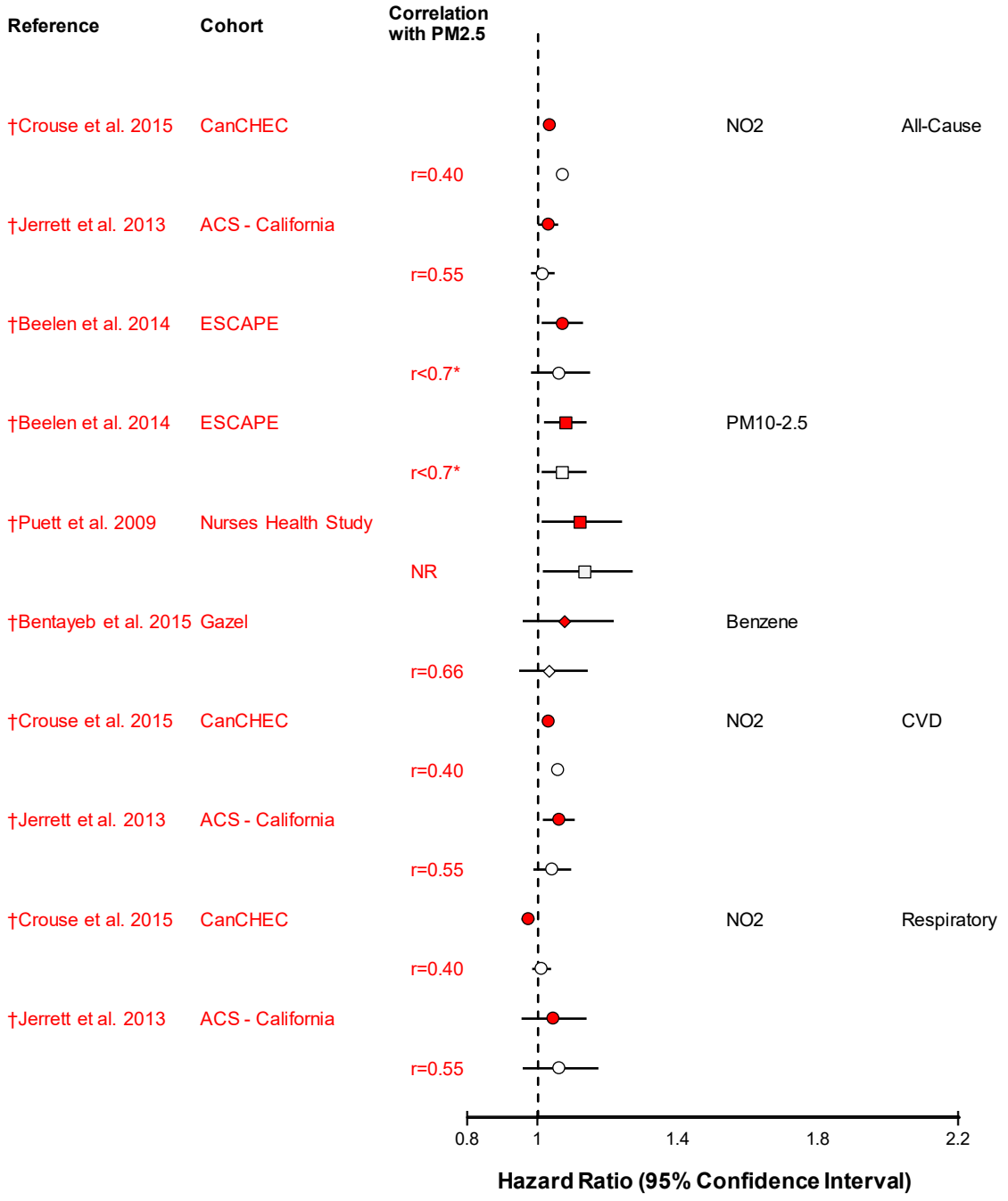


ACS = American Cancer Society Cohort; CanCHEC = Canadian Census Health and Environment Cohort; CVD = cardiovascular disease; NIH-AARP = National Institutes of Health American Association of Retired Persons Diet & Health Cohort; NR = not reported.

Note: †Studies published since the 2009 PM ISA. Associations are presented per 5 μg/m^3 increase in pollutant concentration. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Closed circles represent effect of $PM_{2.5}$ in single pollutant models, open circles represent effect of $PM_{2.5}$ adjusted for O_3.

Corresponding quantitative results reported in Supplemental Table S11-7 (U.S. EPA, 2018b).

Figure 11-20 Associations between long-term exposure to $PM_{2.5}$ and mortality in single pollutant models and models adjusted for O_3.



Note: †Studies published since the 2009 PM ISA. Associations are presented per 5 μg/m^3 increase in pollutant concentration. Circles, squares, triangles and diamonds represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Filled symbols represent effect of $PM_{2.5}$ in single pollutant models, open circles represent effect of $PM_{2.5}$ adjusted for NO_2; open squares represent effect of $PM_{2.5}$ adjusted for $PM_{10-2.5}$; open triangles represent effect of $PM_{2.5}$ adjusted for SO_2; open diamonds represent effect of $PM_{2.5}$ adjusted for benzene. *includes cohorts from meta-analysis where the correlation was less than 0.7.

ACS = American Cancer Society Cohort; CanCHEC = Canadian Census Health and Environment Cohort; CVD = cardiovascular disease; NR = not reported.

Corresponding quantitative results reported in Supplemental Table S11-8 (U.S. EPA, 2018b).

Figure 11-21 Long-term exposure to $PM_{2.5}$ and mortality in single pollutant models and models adjusted for other pollutants.

11.2.4 Evaluation of the $PM_{2.5}$-Mortality Concentration-Response Relationship

An important consideration in characterizing the association between long-term $PM_{2.5}$ exposure and mortality is whether the concentration-response relationship is linear across the full concentration range that is encountered, or if there are concentration ranges where there are departures from linearity. The 2009 PM ISA characterized the results of an analysis by Schwartz et al. (2008) that demonstrated that the shape of the concentration-response curve was generally linear.

A number of recent studies have conducted analyses to inform the shape of the concentration-response relationship for the association between long-term exposure to $PM_{2.5}$ and mortality, and are summarized in Table 11-7. Generally, the results of these analyses continue to support a linear, no-threshold relationship for total (nonaccidental) mortality, especially at lower ambient concentrations of $PM_{2.5}$ (i.e., ≤12 μg/m^3). Lepeule et al. (2012), Di et al. (2017c) and Shi et al. (2015) observed linear, no-threshold concentration-response relationships for total (nonaccidental) mortality, with confidence in the relationship down to a concentration of 8, 5, and 6 μg/m^3, respectively (Figure 11-22). Similar linear, no-threshold concentration-response curves were observed for total (nonaccidental) mortality in other studies (Chen et al., 2016; Hart et al., 2015; Thurston et al., 2015; Cesaroni et al., 2013). Pinault et al. (2016) demonstrated that though the relationship was not statistically different than linear across the range of $PM_{2.5}$ concentrations observed in the study, the slope of the line tended to be steeper at lower concentrations (Figure 11-23), and Crouse et al. (2015) reported a supralinear model was a better fit to the data than the linear model (Figure 11-23). In contrast, Villeneuve et al. (2015) observed that the best fit for the long-term $PM_{2.5}$ exposure—total (nonaccidental) mortality relationship was in a threshold model with a threshold at 11 μg/m^3 (Figure 11-23). In addition, there is emerging evidence for a nonlinear concentration-response function for some causes of death (Section 6.3.9.2).

Table 11-7 Summary of studies examining the concentration-response relationship or conduction threshold analyses for long-term exposure to $PM_{2.5}$ and total (nonaccidental) mortality.

Study Location—Cohort Table/Figure from Reference	Exposure $PM_{2.5}$ Mean; Range in $\mu g/m^3$	Statistical Analysis Summary
†Beelen et al. (2014a) Europe–ESCAPE (Table 5; Figure on appendix pg. 51)	LUR NR; (6.6−31.0)	Cut-point Analysis—include only participants with exposure estimates below prespecified thresholds (25, 20, 15, 10 $\mu g/m^3$). Studied shape of association for each cohort by inputting exposure term as natural cubic spline. HRs remained positive and statistically significant when only participants with exposure concentrations below 25 and 20 $\mu g/m^3$ were included. Below 15 $\mu g/m^3$, HRs were elevated but less precise (i.e., wider 95% confidence intervals). Results of spline model show no deviation from linear relationship.
†Cesaroni et al. (2013) Italy–RoLS (Figure 2B)	Eulerian Dispersion Model (1 × 1 km) 23.0; (7.2−32.1)	Natural splines with 2, 3, or 4 df; compared goodness of fit using BIC and likelihood ratio test No evidence of deviation from linearity. Results similar for 2, 3 or 4 degrees of freedom
†Chen et al. (2016) Canada–EFFECT (Figure 2)	Satellite-based methods (10 × 10 km) 10.7; (1.2-18.0)	Natural splines with 2, 3, or 4 df, compared goodness of fit using AIC. Comparisons made with 2.2 $\mu g/m^3$ No evidence for departure from linearity
†Crouse et al. (2012) Canada–CanCHEC (Figure 2A-D)	Fixed-site monitors in 11 cities; Satellite-based methods (10 × 10 km) 11.2; (1.9−19.2)	Natural splines with 2, 3, or 4 df, compared goodness of fit using BIC. Log function of $PM_{2.5}$ ($\ln[PM_{2.5} + 1]$) yielded lower BIC than each of the spline models No evidence for departure from linearity. Natural spline model with 4 df had best model fit based on BIC
†Crouse et al. (2015) Canada–CanCHEC (Figures S3a)	Satellite-based methods (at postal code) 8.9; (1−18)	Restricted cubic spline functions with 2 df Natural spline fit was superior to linear model. Natural spline fit is supralinear (i.e., larger changes in risk for low concentrations compared to higher values)
†Di et al. (2017c) U.S.−Medicare (Figure 3, panel A)	Hybrid satellite-based methods, LUR, monitor; 1 × 1 km 11.5; (6.2−15.64 [5th−95th percentiles])	Examined potential of non-linear effects using a series of thin-plate splines and meta-smoothing Nearly linear with no signal of threshold down to 5 $\mu g/m^3$

Table 11-7(Continued): Summary of studies examining the concentration-response relationship or conduction threshold analyses for long-term exposure to $PM_{2.5}$ and total (nonaccidental) mortality.

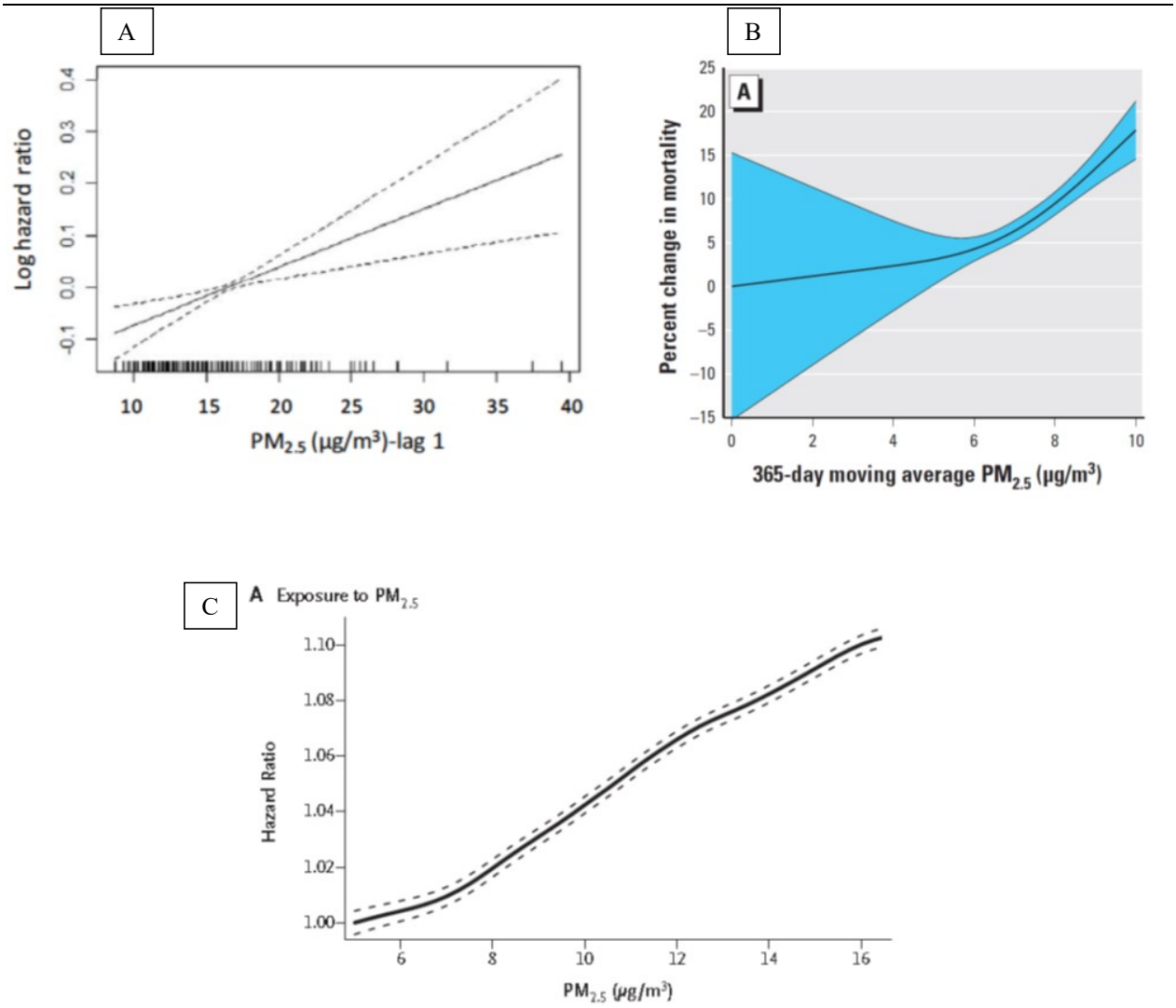
Study Location—Cohort Table/Figure from Reference	Exposure $PM_{2.5}$ Mean; Range in $\mu g/m^3$	Statistical Analysis Summary
†Hart et al. (2015) U.S.−Nurses' Health Study (Figures 1 and 2)	Spatio-temporal model; nearest monitor 12.0; (NR)	Comparison of mortality rates for a given $PM_{2.5}$ concentration (based on prediction from spatio-temporal model [Figure 1] or nearest monitor [Figure 2])
		Linear relationship for both spatio-temporal model and nearest monitor; Linear relationship for both uncorrected and measurement error-corrected mortality rates, slope steeper for measurement error-corrected exposure compared to uncorrected
†Lepeule et al. (2012) U.S.–HSC (Suppl. Figure 1)	Fixed-site monitor 15.9; (11.4−23.6)	Penalized spline models
		Linear relationship with exposures down to 8 $\mu g/m^3$. No evidence of a threshold. Highest confidence from 10−20 $\mu g/m^3$ based on greatest data density
†Pinault et al. (2016) Canada–CCHS (Figure 2)	Hybrid satellite-based methods, LUR, monitor 1 × 1 km 6.3; (0−13)	C-R: *R* package—"SmoothHR"; combination of AIC and BIC to determine optimal df; Threshold Analysis: newly defined exposure variables based on concentration corresponding to the largest log-likelihood value from the Cox model
		Linear relationship from 1.0–7.0 $\mu g/m^3$; slope is attenuated between 7.0 and 13.0 $\mu g/m^3$; Threshold concentration: 0 $\mu g/m^3$ (upper 95% CI 4.5 $\mu g/m^3$)
†Shi et al. (2015) U.S.–Medicare (Figure 3a)	Hybrid satellite-based methods, LUR, monitor; 1 × 1 km 8.12; (0.08, 20.22)	Penalized spline model (1.7 df) restricted to annual exposures <10 $\mu g/m^3$
		Linear relationship with evidence of an attenuated slope at concentrations <6 $\mu g/m^3$
†Thurston et al. (2015) U.S.–NIH–AARP (Figure 2)	Hybrid LUR geo-statistical model 12.2 (2.9–28.0)	Natural spline plots with 4 df (Referent HR = 1.0 at mean exposure level)
		Observed linear relationship
†Villeneuve et al. (2015) Canada–CNBSS (Figure 3)	Satellite-based methods (10 × 10 km) 9.1; (0.1–20.0)	C-R: Natural cubic spline functions with 3 df; Threshold analysis: newly defined exposure variables based on concentration corresponding to the largest log-likelihood value from the Cox model
		Non-linear V-shaped curve; Threshold analysis: best fitting model for a threshold at 11 $\mu g/m^3$

Table 11-7(Continued): Summary of studies examining the concentration-response relationship or conduction threshold analyses for long-term exposure to $PM_{2.5}$ and total (nonaccidental) mortality.

Study Location—Cohort Table/Figure from Reference	Exposure $PM_{2.5}$ Mean; Range in $\mu g/m^3$	Statistical Analysis Summary
†Wong et al. (2015) Hong Kong–Elderly Health Center (Figure 3)	Satellite-based methods (10 × 10 km) 35; (27–49)	Natural spline model (df not reported).
		Observed linear relationship, greatest certainty between 32 and 35 $\mu g/m^3$

AIC = Akaike Information Criterion; BIC = Bayesian information criterion; CanCHEC = Canadian Census Health and Environment Cohort; CCHS = Canadian Community Health Survey; CNBSS = Canadian National Breast Screening Study; df = degrees of freedom; EFFECT = Enhanced Feedback For Effective Cardiac Treatment; ESCAPE = European Study of Cohorts for Air Pollution Effects; HSC = Harvard Six Cities study; km = kilometer; LUR = land use regression; NIH-AARP = National Institutes of Health American Association of Retired Persons Diet & Health Cohort; NR = not reported; RoLS = Rome Longitudinal Study.

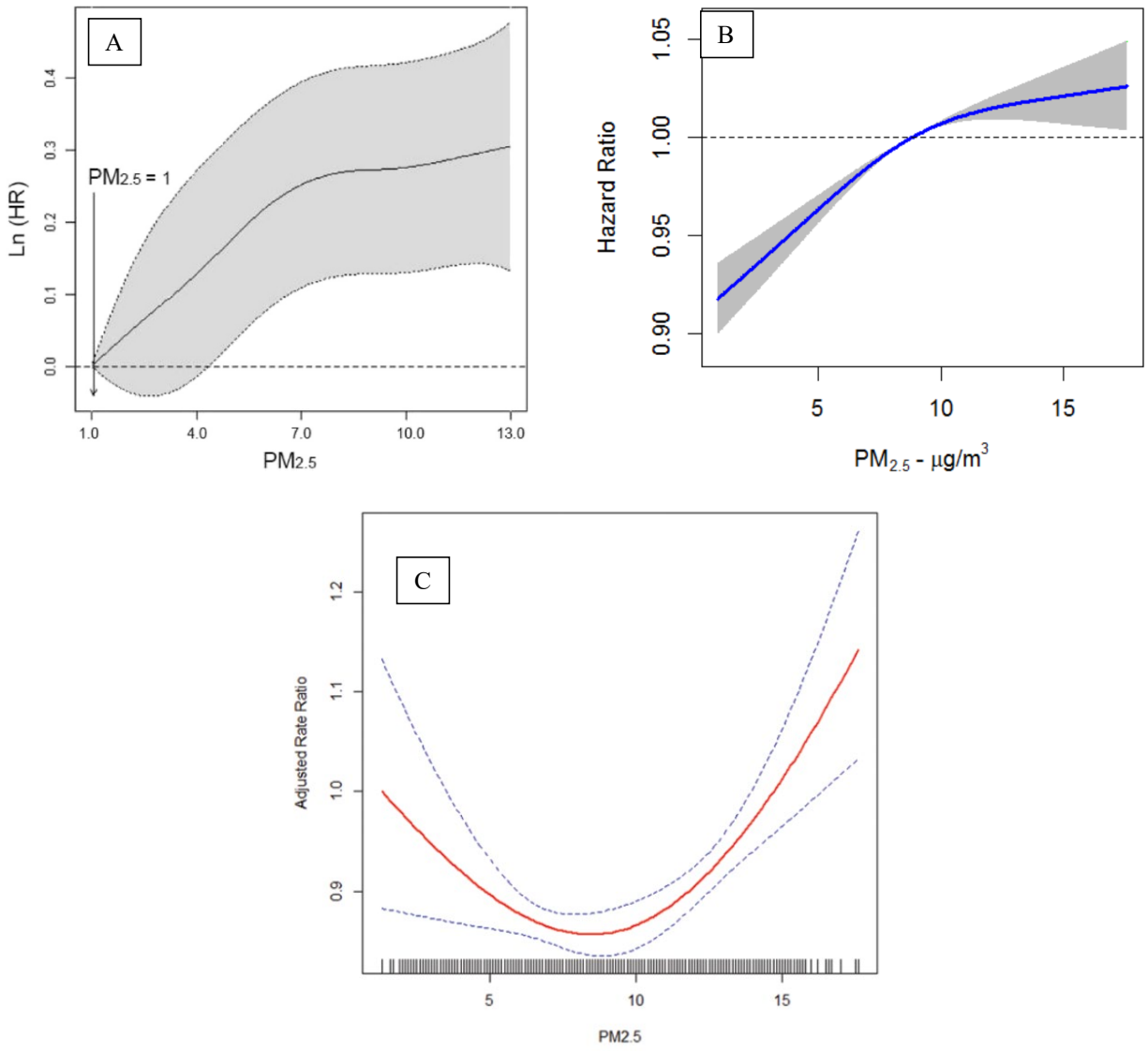
†Studies published since the 2009 PM ISA.



Note: Shaded areas or dotted lines indicate 95% confidence intervals. The tick marks on the *x*-axis identify the distribution of observations according to $PM_{2.5}$ concentrations.

Source: Permission pending, Panel A Lepeule et al. (2012); Panel B Shi et al. (2015); Panel C Di et al. (2017c)

Figure 11-22 Examples of concentration-response relationships between long-term $PM_{2.5}$ exposure and total (nonaccidental) or all-cause mortality in (A) the Harvard Six Cities Study using penalized splines (1974−2009); (B) long-term time-series study; (C) the Medicare Cohort using thin-plate spines.



Note: Shaded areas or dotted lines indicate 95% confidence intervals. The tick marks on the *x*-axis identify the distribution of observations according to $PM_{2.5}$ concentrations.

Source: Permission pending, Panel A Pinault et al. (2016); Panel B Crouse et al. (2015); Panel C Villeneuve et al. (2015).

Figure 11-23 Examples of concentration-response relationships between long-term $PM_{2.5}$ exposure and total (nonaccidental) mortality in (A) nonparametric estimates; (B) in the CanCHEC cohort study; (C) the Canadian National Breast Screening Study.

Rather than using splines to model the concentration-response relationship across a continuous range of $PM_{2.5}$ concentrations, Beelen et al. (2014a) conducted a cut-point analysis estimating the risk of long-term $PM_{2.5}$ exposure on total (nonaccidental) mortality when only participants with assigned $PM_{2.5}$ concentrations below 25, 20, 15, and 10 $\mu g/m^3$ were included in the model. The effect estimate was relatively unchanged when only participants with concentrations below 25 and 20 $\mu g/m^3$ were included in the model. Below 20 $\mu g/m^3$ the effect estimates remained positive but became less precise (i.e., wider 95% confidence intervals) as fewer observations were included in the model. The results of this cut-point analysis support the results of a spline model that evaluated the concentration-response relationship across the entire range of concentrations observed in the study area and found a generally linear association.

Overall, the majority of evidence continues to indicate a linear, no-threshold concentration-response relationship for long-term exposure to $PM_{2.5}$ and total (nonaccidental) mortality, though some recent evidence indicates the possibility of a nonlinear concentration-response function. There is less certainty in the shape of the concentration-response curve at mean annual $PM_{2.5}$ concentrations generally below 8 $\mu g/m^3$, though some studies characterize the concentration-response relationship with certainty down to 4 $\mu g/m^3$.

11.2.5 Evaluation of Factors That May Influence $PM_{2.5}$ Associations

11.2.5.1 Comparison of Exposure Assessment Techniques

Recent studies have used a variety of both fixed-site (i.e., monitors), model (e.g., CMAQ, dispersion models) and satellite-based (e.g., aerosol optical depth [AOD] observations from satellites) methods, including hybrid methods that combine two or more fixed-site, model and/or satellite-based techniques to measure, estimate or predict $PM_{2.5}$ concentrations for use in assigning long-term $PM_{2.5}$ exposure in epidemiologic studies (see Section 3.3.2.4.3).

In a systematic comparison of fixed-site and satellite-based methods, Lee et al. (2011) concluded that, though observations were generally highly correlated, fixed-site measurements of $PM_{2.5}$ were more accurate than satellite-based observations of AOD when predicting concentrations within 98 km of the monitor, but that at distances greater than 98 km, satellite-based observations of AOD were better predictors of $PM_{2.5}$ concentrations (see Section 3.3.3 for details). In order to compare the use of fixed-site measurements and satellite-based observations of AOD, Jerrett et al. (2016) applied both methods to a common data set, the ACS cohort, and calculated effect estimates for circulatory and IHD mortality associated with $PM_{2.5}$ using both methods. They observed consistently positive associations between long-term $PM_{2.5}$ exposure and circulatory and IHD mortality, regardless of the exposure assessment technique used to assign exposure. However, they did note that when exposure assessment relied on satellite-based techniques, hazard ratios tended to be lower than when fixed-site measurements were used, or when fixed-site and satellite-based techniques were combined. Additionally, Jerrett et al. (2016)

combined all of the models into an ensemble model, weighted by model fit (i.e., AIC), and observed a 7.0% increase in circulatory mortality and a 7.5% increase in IHD mortality per 5 $\mu g/m^3$ increase in $PM_{2.5}$.

Hart et al. (2015) assigned exposure from the nearest fixed-site monitor as well as from a spatio-temporal model that included monitor observations, land use regression, and point-source emission density [see Yanosky et al. (2014) for details]. Effect estimates resulting from each exposure methods were nearly identical.

Alternately, Garcia et al. (2015) compared different exposure assessment techniques that all relied on observations from fixed-site monitors. Specifically, they evaluated assigning exposure based on the $PM_{2.5}$ concentration measured at the closest monitor, using inverse distance weighting (IDW) from multiple monitors, and by using a kriging model based on fixed-site monitor measurements. Exposure was assigned to ZIP code centroids by each exposure assessment technique. The results were consistent across exposure assessment techniques, with RRs ranging from 1.07 to 1.13 for CVD mortality, 1.20 to 1.28 for IHD mortality, and 1.01 to 1.03 for total (nonaccidental) mortality when considering the entire study area. Substantially more variability was observed for rural areas when analyses were stratified by urban and rural areas, with greater, though less precise (i.e., wider 95% confidence intervals), associations generally observed in rural areas.

A single study, Hart et al. (2015), used risk set regression calibration to correct for bias due to exposure measurement error resulting from differences in ambient concentrations and personal exposures to $PM_{2.5}$ in effect estimates for total (nonaccidental) mortality (see Section 3.4.5.2 for more detail on bias correction). They assumed that the "true" exposure was equal to the 12-month moving average for personal $PM_{2.5}$ exposure, and used percent difference in HRs ([("personal"—"ambient")/"personal"] × 100) to estimate the impact of exposure measurement error. They observed moderately higher HRs after adjusting for measurement error (1.18 vs. 1.13 from spatio-temporal exposure model; 1.22 vs. 1.12 from nearest monitor exposure model).

Overall, a number of studies demonstrate that the positive associations observed between long-term $PM_{2.5}$ exposure and mortality are robust to different methods of assigning exposure. In addition, a single study provides modest evidence that failing to correct for bias due to exposure measurement error could result in attenuated risk estimates.

11.2.5.2 Comparison of Statistical Techniques

Several recent studies have evaluated and compared the results of multiple statistical models in order to examine the robustness of the long-term $PM_{2.5}$ exposure-mortality relationship and to address concerns related to the sensitivity of results to model specification. In a reanalysis of the Harvard Six Cities study, Lepeule et al. (2012) evaluated a Cox proportional hazards model and a Poisson survival

analysis. The authors observed no substantial changes in results for the Cox models compared to the results from the Poisson survival analysis. Similarly, Thurston et al. (2016) evaluated both a traditional Cox proportional hazards model and a multilevel random-effects Cox proportional hazards model in analyses of the ACS cohort. The fully adjusted models included spatial random effects as well as contextual socio-economic variables. In addition, they examined models with random effects but not contextual variables, models with contextual variables but not random effects, and fixed effect models adjusted only for individual-level variables. The association between long-term exposure to $PM_{2.5}$ mass and IHD mortality was consistent across all of the models (HR ranged from 1.02 to 1.05). Estimates based on models without random effects and/or adjustment for contextual variables had more power and tended to be more precise. Similarities were observed in a different cohort, the NIH-AARP cohort (Thurston et al., 2015). Specifically, associations were more precise when contextual variables were not included, and the inclusion of random effects terms in the time independent Cox proportional hazards model resulted in associations similar to those observed from models without random effect terms. In an analysis of CVD mortality, Dehbi et al. (2016) used competing risk hazards regression models to allow for the influence of death from causes other than CVD. In addition, they used Cox modelling to verify that the observed results were not an artefact of using competing risk hazards regression models and observed similar results. Overall, these results from well-studied, highly regarded cohorts help to reduce uncertainties that the observed associations between long-term $PM_{2.5}$ exposure and mortality could be due to the statistical techniques employed or model specification, rather than a causal relationship.

11.2.5.3 Effects of Different Long-Term Exposure Windows

The delay between changes in exposure and changes in health has important policy implications. The 2009 PM ISA concluded that there was developing coherence in the evidence base that indicated that the health benefits from reducing air pollution could be expected within a few years of intervention (U.S. EPA, 2009). Several recent studies provide additional evidence to support this conclusion. Bentayeb et al. (2015) examined long-term exposure for four different averaging times: (1) annual mean exposure at baseline, (2) annual mean exposure 1 year before death, (3) yearly mean exposure during follow-up, and (4) average cumulative exposure from baseline through death or censure. Results for long-term $PM_{2.5}$ exposure and total (nonaccidental), cardiovascular and respiratory mortality were consistent for all four exposure windows examined. Lepeule et al. (2012) evaluated two exposure periods, 1 or 5 years before death or censure, and evaluated model fit using Akaike's Information Criterion (AIC). They observed the best fit for the 5-year exposure period. In additional sensitivity analyses, they allowed the exposure window to vary from 1 to 5 years before death or censure, and observed similar effect estimates to those in the main analysis. Using a different strategy, Wong et al. (2015) stratified the follow-up period to examine deaths occurring 2−4, 5−8, or ≥9 years after the baseline date. They observed greater risks for the period closest to the baseline date, though it is unclear if this is a result of a difference in the exposure window, or if it could be due to the age of the cohort. The cohort included participants aged 65 years or

older, and there is evidence indicating that risk decreases for individuals over 70 or 75 years of age. Thus, it is unclear if the greater risk observed for the early exposure window is due to the exposure window itself, or the age of participants during that exposure window. Overall, new evidence from recent studies continues to support the previous conclusion that health benefits from reducing air pollution could be expected with a few years of intervention.

11.2.6 Associations between $PM_{2.5}$ Sources and Components and Mortality

The 2009 PM ISA (U.S. EPA, 2009) included one study that examined the association between long-term exposure to $PM_{2.5}$ components and mortality (Lipfert et al., 2006). Integrating across health endpoints, the 2009 PM ISA concluded that there is not sufficient evidence to differentiate the components or sources more closely related to health outcomes when compared with $PM_{2.5}$ mass. A number of recent studies have examined the relationship between long-term exposure to PM components and mortality. A number of these studies estimate the risk associated with individual components of $PM_{2.5}$ (Figure 11-24), while others evaluate the potential for $PM_{2.5}$ composition to explain some of the regional/geographic heterogeneity observed in the risk estimates from studies of long-term $PM_{2.5}$ exposure.

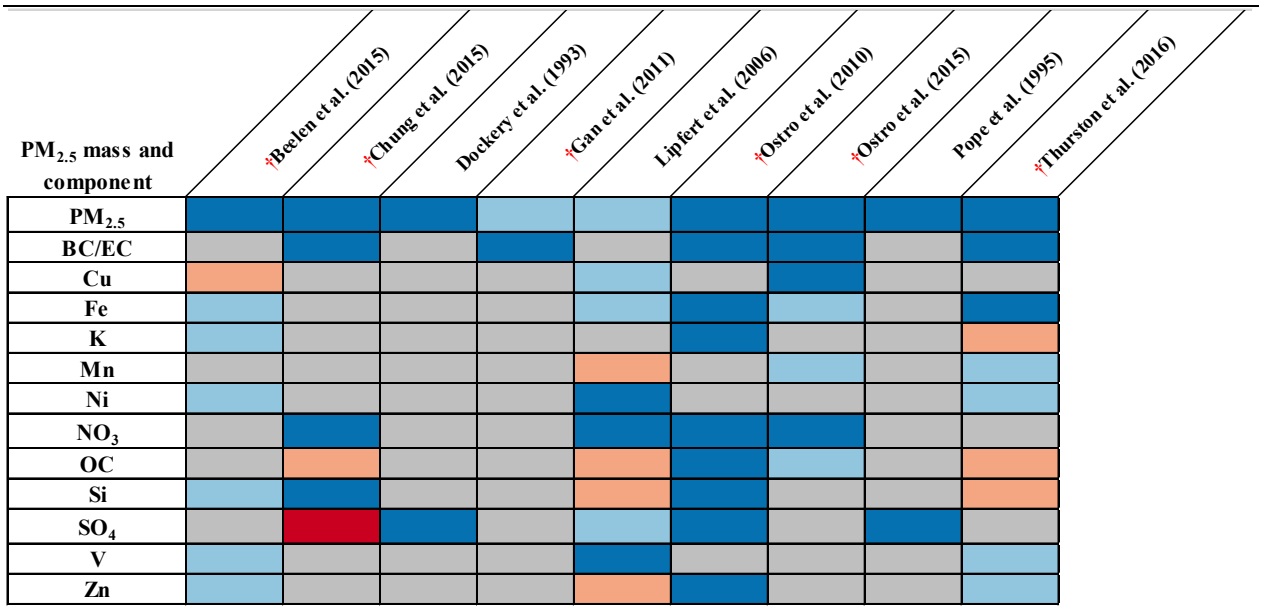
In an additional analysis of the CanCHEC cohort (described previously in Section 11.2.2.2), Crouse et al. (2016) used a novel method to calculate the risk of total (nonaccidental) and cardio-metabolic mortality associated with long-term exposure to $PM_{2.5}$ adjusted for the proportion of six individual $PM_{2.5}$ components (i.e., sulfate, nitrate, ammonium, OC, BC, dust). They observed that models of $PM_{2.5}$ mass alone were a better predictor of mortality than models of the combination of $PM_{2.5}$ mass and the proportion of any one of the six components they evaluated, but that models including the combination of $PM_{2.5}$ mass and the proportion of all six of the components were better predictors of mortality than models of $PM_{2.5}$ mass alone. In separate analyses of the CanCHEC cohort, authors collected $PM_{2.5}$ filters from 30 fixed-site monitors between 2012 and 2013 and evaluated the oxidative potential of the nonvolatile portion of $PM_{2.5}$ mass on the filter via antioxidant (glutathione and ascorbate) depletion tests (Weichenthal et al., 2016). When the $PM_{2.5}$ glutathione-related oxidative burden was estimated, the results were similar to those for $PM_{2.5}$ mass, though generally higher in magnitude. Generally null or negative hazard ratios were observed for all-cause and cause-specific mortality when $PM_{2.5}$ ascorbate-related oxidative burden was analyzed. Although not entirely consistent, these oxidative burden results may help to explain the potential for low concentrations of $PM_{2.5}$ to cause disease or to help explain geographic heterogeneity observed with $PM_{2.5}$-mortality associations.

A meta-analysis of European cohorts (i.e., the ESCAPE study, described previously in Table 11-6), evaluated mortality due to incident IHD events and eight different $PM_{2.5}$ components: S, K, Cu, Fe, Ni, V, Zn, and Si (Wolf et al., 2015). These authors used LUR to estimate $PM_{2.5}$ and component

concentrations, and cross validation of the models revealed variable performance, with some models performing poorly (i.e., $R^2 < 0.30$) and others performing moderately (i.e., $R^2 = 0.30–0.50$). The authors calculated single-component hazard ratios, as well as $PM_{2.5}$-adjusted hazard ratios, by regressing total PM on each component separately and then including the residual for each component in a model with total $PM_{2.5}$, using the estimate of the residual component to represent the independent component effect. Previous analyses of the ESCAPE cohort observed associations between long-term $PM_{2.5}$ exposure and CVD mortality. The results presented by Wolf et al. (2015) are consistent with these associations, and provide additional evidence for associations with K, Si and Fe, which could represent the resuspended road dust portion of $PM_{2.5}$. In sensitivity analyses where only cohorts for which the cross validation of the LUR model was ≥0.50, the results were relatively unchanged.

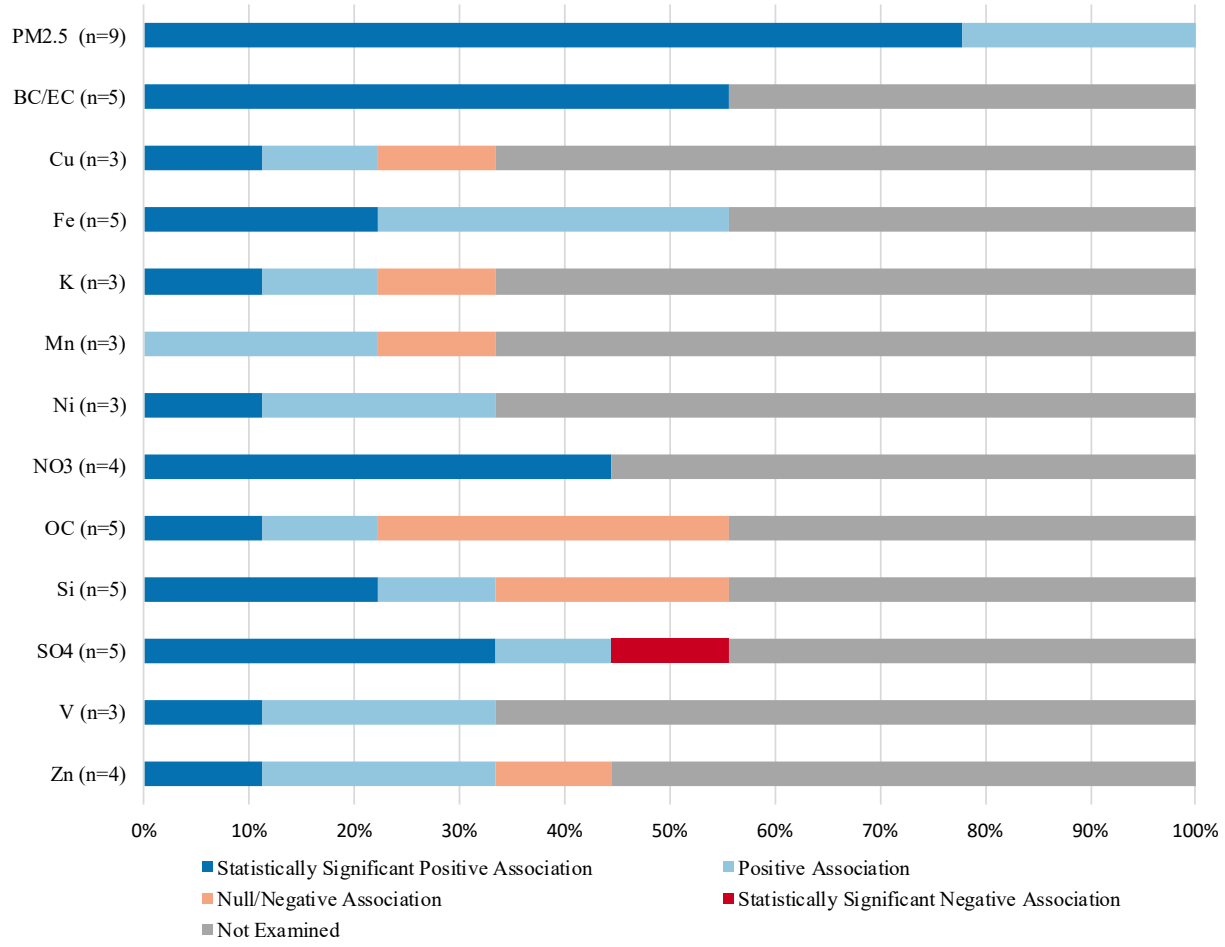
The evaluation of the association between $PM_{2.5}$ components and mortality is complicated by the different methods applied across studies. As a result, the systematic standardization of results across studies (i.e., per 5 $\mu g/m^3$ increase), as is the convention throughout this ISA, is not possible when evaluating results for $PM_{2.5}$ components. Overall, the results for individual $PM_{2.5}$ components across studies are generally more imprecise than the results for $PM_{2.5}$ (i.e., much wider confidence intervals, often including the null value), which make the individual results, as well as results across studies, more difficult to interpret. As such, for the purposes of characterizing results with respect to $PM_{2.5}$ components a different convention is employed to evaluate the pattern of associations across studies. Specifically, risk estimates from studies are classified into four categories in Figure 11-24 and Figure 11-25: (1) statistically significant positive associations; (2) positive associations, regardless of width of the confidence interval; (3) null or negative association; and (4) statistically significant negative association. Figure 11-24 and Figure 11-25 demonstrate consistent positive associations for total (nonaccidental) mortality and exposure to $PM_{2.5}$, BC/EC, Fe, Ni, NO_3^-, and V, with more studies evaluating $PM_{2.5}$, BC/EC and NO_3^-, and fewer studies examining the metals Fe, Ni, and V. Based on the pattern of results across this limited number of studies, it is difficult to disentangle the independent effect of any of these components from the effect of $PM_{2.5}$ mass.

Thurston et al. (2016) used source apportionment to evaluate the relationship between air pollution sources and IHD mortality in the ACS cohort. Sources were categorized based on source-identifier elemental tracers. They observed the strongest associations coal burning (HR: 1.05, 95% CI: 1.02, 1.08) and other combustion sources, and diesel traffic (HR: 1.03, 95% CI: 1.00, 1.06). Generally null associations were observed for other sources (i.e., wind-blown soil and biomass combustion). These results are generally consistent with previous studies of short-term exposure and mortality that have used source apportionment methods; previous studies have not considered long-term exposure and IHD mortality.



Note: †$PM_{2.5}$ component studies published since the 2009 PM ISA. Results are for total (nonaccidental) mortality except for Gan et al. (2011), who examine CVD mortality. Dark blue = study reported statistically significant positive association; Light blue = study reported a positive association regardless of width of confidence intervals; Light orange = study reported null or negative association; Red = study reported statistically significant negative association; Gray = study did not examine individual component. Only those $PM_{2.5}$ components that were examined in at least three studies are included in this figure.

Figure 11-24 Heat map of associations observed between $PM_{2.5}$ and $PM_{2.5}$ components and mortality.



n = number of studies that provided an estimate for $PM_{2.5}$ mass and individual $PM_{2.5}$ components.

Note: Bars represent the percent of associations across studies for $PM_{2.5}$ mass or $PM_{2.5}$ components detailed in Figure 11-24 that are statistically significant positive (dark blue), positive (light blue), null/negative (light orange), statistically significant negative (red), or not examined (gray).

Figure 11-25 Distribution of mortality associations for $PM_{2.5}$ and $PM_{2.5}$ components examined in studies detailed in Figure 11-24.

11.2.7 Summary and Causality Determination

Recent cohort studies evaluated since the completion of the 2009 PM ISA continue to provide consistent evidence of positive associations between long-term $PM_{2.5}$ exposures and total (nonaccidental) mortality from studies conducted mainly in North America and Europe. Many recent analyses further evaluated the association between long-term $PM_{2.5}$ exposures and the risk of mortality based on the original ACS study (Pope et al., 1995), adding new details about deaths due to cardiovascular disease (including IHD) and respiratory disease (including COPD), and extending the follow-up period of the ACS to 22 years (1982−2004). Adding to this evidence, recent U.S. and Canadian cohort studies

demonstrate consistent, positive associations between long-term $PM_{2.5}$ exposure and mortality across various spatial extents, exposure assessment metrics, and statistical techniques, and locations, where mean annual average concentrations are ≤12 μg/m^3 (Section 11.2.2.2). Additionally, the evidence from recent studies reduce uncertainties related to potential copollutant confounding (Section 11.2.3) and continues to provide strong support for a linear, no-threshold C-R relationship (Section 11.2.4). The body of evidence for total mortality is supported by generally consistent positive associations with cardiovascular and respiratory mortality. There is coherence of effects across the scientific disciplines (i.e., animal toxicological, controlled human exposure studies, and epidemiologic) and biological plausibility for $PM_{2.5}$-related cardiovascular (Chapter 6) respiratory (Chapter 5) and metabolic (Chapter 7) disease, which supports the $PM_{2.5}$-mortality relationship. This section describes the evaluation of evidence for total (nonaccidental) mortality, with respect to the causality determination for long-term exposures to $PM_{2.5}$ using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015b). The key evidence, as it relates to the causal framework, is summarized in Table 6-89.

The strongest evidence supporting the conclusion of a causal relationship between long-term $PM_{2.5}$ exposure and total mortality in the 2009 PM ISA was derived from analyses of the ACS and HSC cohorts. Recent extended analyses and reanalysis of these cohorts continues to support this relationship, demonstrating consistent positive associations for total (nonaccidental mortality) and across different cause-specific mortality outcomes. A recent series of analyses of the Medicare cohort of U.S. individuals provides additional support, culminating with the largest cohort study of nearly 61 million U.S. Medicare enrollees that reports positive associations with increases in $PM_{2.5}$ concentrations and stronger associations in areas where the mean annual $PM_{2.5}$ concentrations are ≤12 μg/m^3 (Di et al., 2017c). Another recent series of studies conducted in Canada provides results consistent with those of the Medicare cohort (i.e., positive associations between long-term $PM_{2.5}$ exposure and total mortality in areas where mean annual $PM_{2.5}$ concentrations are ≤12 μg/m^3. One difference between these studies is that the Canadian cohorts include all adults (aged 25+ years) and the Medicare cohort only includes adults aged 65+ years, demonstrating that these effects are not specific to one lifestage, but affect all adults. Also, an additional line of evidence is available that includes results from a number of cohorts that recruited subjects based on their place of employment, including female nurses, female teachers, male health professionals, and male truck drivers, which observe consistent, positive associations between long-term $PM_{2.5}$ exposure and total mortality.

Table 11-8 Summary of evidence for a causal relationship between long-term $PM_{2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Consistent epidemiologic evidence from multiple, high-quality studies at relevant $PM_{2.5}$ concentrations	Positive associations between long-term $PM_{2.5}$ exposure and mortality in the multiple analyses of the ACS and HSC cohorts, with effect estimates similar in magnitude, even after adjustment for common potential confounders.	Section 11.2.2.1	Mean concentrations across studies: 11.4−23.6 μg/m^3
	Positive associations between long-term $PM_{2.5}$ exposure and mortality in the multiple analyses of the Medicare cohort, with effect estimates similar in magnitude, even after adjustment for common potential confounders.	Section 11.2.2.2	Mean concentrations across studies: 8.12−12.0 μg/m^3
	Positive associations between long-term $PM_{2.5}$ exposure and mortality in the multiple analyses of Canadian cohorts, with effect estimates similar in magnitude, even after adjustment for common potential confounders.	Section 11.2.2.2	Mean concentrations across studies: 8.7−9.1 μg/m^3
	Positive associations between long-term $PM_{2.5}$ exposure and mortality in the multiple North American occupational cohorts, even after adjustment for common potential confounders.	Section 11.2.2.2	Mean concentrations across studies: 12.7−17.0 μg/m^3
	Positive associations with cardiovascular, respiratory, and lung cancer mortality.	Section 6.3.10.1	Mean (across studies): 4.1−17.9 μg/m^3
		Section 5.2.10	Mean (across studies): 4.1−17.9 μg/m^3
		Section 10.2.5.1	Mean (across studies): 6.1−33.7 μg/m^3

Table 11-8 (Continued): Summary of evidence indicating that a causal relationship exists between long-term $PM_{2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Epidemiologic evidence from copollutant models provides some support for an independent $PM_{2.5}$ association	Positive associations observed between long-term $PM_{2.5}$ exposure and total mortality remain relatively unchanged after adjustment for O_3, NO_2 and $PM_{10-2.5}$ When reported, correlations with copollutants were highly variable (low to high).	Section 1.1.1.1; Figure 11-20; Figure 11-21	
Consistent positive epidemiologic evidence for associations between $PM_{2.5}$ exposure and total mortality across exposure measurement metrics	Positive associations consistently observed across studies that used fixed-site (i.e., monitors), model (e.g., CMAQ, dispersion models) and satellite-based (e.g., AOD observations from satellites) methods, including hybrid methods that combine two or more of these methods.	Section 11.2.2.6; Jerrett et al. (2016)	
Epidemiologic evidence supports a linear, no-threshold concentration-response (C-R) relationship	No evidence for deviation from linearity in several U.S. and Canadian cohorts	Section 11.2.2.4	

Table 11-8 (Continued): Summary of evidence indicating that a causal relationship exists between long-term $PM_{2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Biological plausibility from studies of cardiovascular and respiratory morbidity and lung cancer incidence and mortality	Cardiovascular morbidity studies provide expanded body of evidence for associations between long-term $PM_{2.5}$ exposure and CHD, stroke and atherosclerosis, providing biological plausibility for a relationship between long-term $PM_{2.5}$ exposure and cardiovascular mortality.	Section 6.3 Miller et al. (2007) Chi et al. (2016)	Mean (across studies): 10.7−13.4 μg/m^3
	Respiratory morbidity studies provide some evidence for an association between long-term $PM_{2.5}$ exposure and development of COPD, providing limited biological plausibility for a relationship between long-term $PM_{2.5}$ exposure and respiratory mortality	Section 5.2.5	
	Consistent epidemiologic evidence for associations between $PM_{2.5}$ exposure and lung cancer incidence and mortality in cohort studies conducted in the U.S., Canada, Europe and Asia	Section 10.2.5.1 Figure 10-3	Mean (across U.S. and Canadian studies): 6.3−23.6 μg/m^3

ACS = American Cancer Society; AHSMOG = Adventist Health Study of Smog; AOD = aerosol optical depth; CO = carbon monoxide; EC = elemental carbon; HSC = Harvard Six Cities; MI = myocardial infarction; NLCS = Netherlands Cohort Study on Diet and Cancer; NO_2 = nitrogen dioxide; ppb = parts per billion; $PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm and greater than a nominal diameter of 2.5 μm; SO_2 = sulfur dioxide.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to the causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

Recent evidence helps to reduce uncertainties related to potential copollutant confounding of the relationship between long-term $PM_{2.5}$ exposure and mortality. Multiple studies evaluated ozone (Figure 11-20) and NO_2 (Figure 11-21) in copollutant models and observed similar hazard ratios for $PM_{2.5}$ regardless of whether ozone or NO_2 were included in the model. This supports an independent effect of long-term $PM_{2.5}$ exposure on mortality. Evidence for other potential copollutants (e.g., SO_2, CO) is limited.

Recent studies have used a variety of both fixed-site (i.e., monitors), model (e.g., CMAQ, dispersion models) and satellite-based [e.g., aerosol optical depth (AOD) measurements from satellites] methods, including hybrid methods that combine two or more fixed-site, model and/or satellite-based techniques to measure, estimate or predict $PM_{2.5}$ concentrations for use in assigning long-term $PM_{2.5}$ exposure in epidemiologic studies. Overall, the exposure assessment technique has had little influence on study results, with consistently positive associations of similar magnitude observed across studies using a variety of exposure assessment techniques. Notably, Jerrett et al. (2016) applied fixed-site measurements and satellite-based observations of AOD to a common data set, the ACS cohort, and calculated effect estimates for circulatory and IHD mortality associated with $PM_{2.5}$ using both methods. They observed consistently positive associations between long-term $PM_{2.5}$ exposure and mortality, regardless of the exposure assessment technique used to assign exposure. Additionally, Jerrett et al. (2016) combined multiple exposure assessment techniques into an ensemble model, weighted by model fit, and continued to observe similar positive associations with mortality. These results support an independent effect of long-term $PM_{2.5}$ exposure on mortality that is not overtly influenced by or a residual of the exposure assessment technique used in the study.

The number of studies examining the shape of the C-R function for long-term $PM_{2.5}$ exposure and mortality has substantially increased since the 2009 PM ISA. These studies used a number of different statistical techniques to evaluate the shape of the C-R function, including natural cubic splines, restricted cubic splines, penalized splines, thin-plate splines, and cut-point analyses (Table 11-7), and generally observe linear, no-threshold relationships down to 4−8 $\mu g/m^3$. Few studies have conducted extensive analyses exploring alternatives to linearity when examining the shape of the $PM_{2.5}$-mortality C-R relationship. Among these studies, there is some emerging evidence for a supra-linear C-R function, with steeper slopes observed at lower $PM_{2.5}$ concentrations. Though few, such supra-linear C-R functions are most commonly observed for cardiovascular mortality compared to total (nonaccidental) or respiratory mortality.

The 2009 PM ISA concluded that there is not sufficient evidence to differentiate the components or sources more closely related to health outcomes when compared with $PM_{2.5}$ mass, though the evidence for long-term exposure and mortality was limited. More recently, a number of studies examined the relationship between long-term exposure to PM components and mortality (Figure 11-24). Collectively, recent studies continue to demonstrate that no individual $PM_{2.5}$ component or source is a better predictor of mortality than $PM_{2.5}$ mass.

Overall, recent epidemiologic studies build upon and further reaffirm the conclusions of the 2009 PM ISA for total mortality. The evidence particularly from the assessment of $PM_{2.5}$-related cardiovascular and metabolic diseases, with more limited evidence from respiratory morbidity, provides biological plausibility for mortality due to long-term $PM_{2.5}$ exposures. In conclusion, the consistent positive associations observed across cohort studies conducted in various locations across North America are further supported by the results from copollutant analyses indicating robust associations independent of

O_3 and NO_2. **Collectively, this body of evidence is sufficient to conclude that a causal relationship exists between long-term $PM_{2.5}$ exposure and total mortality.**

11.3 Short-Term $PM_{10–2.5}$ Exposure and Total Mortality

The 2009 PM ISA concluded that the evidence is "suggestive of a causal relationship between short-term exposure to $PM_{10–2.5}$ and mortality" (U.S. EPA, 2009).[80] This evidence was based on generally consistent, positive associations across mortality outcomes from primarily single-city studies, with some additional evidence from a few multicity studies, conducted in the U.S. and Canada. However, there was uncertainty with respect to the associations observed across epidemiologic studies due to the different methods used to measure $PM_{10–2.5}$ concentrations, which included direct measurements of $PM_{10–2.5}$ using dichotomous samplers and calculating the difference between PM_{10} and $PM_{2.5}$ concentrations (e.g., at collocated monitors, taking the difference between area-wide averages of PM_{10} and $PM_{2.5}$). Compared to studies of $PM_{2.5}$, there were relatively few studies that conducted additional analyses to further examine the $PM_{10–2.5}$-mortality relationship, resulting in the inability to adequately assess potential copollutant confounding, as well as the influence of model specification, seasonal associations, and effect measure modification. Additionally, there was a lack of information on the chemical and biological components that comprise $PM_{10–2.5}$.

Since the completion of the 2009 PM ISA a number of new studies, with the majority being multicity, conducted in diverse geographic locations (e.g., U.S., Asia, and Europe) have examined the relationship between short-term $PM_{10–2.5}$ exposure and mortality. However, the relative number of studies focusing on short-term $PM_{10–2.5}$ exposure and mortality has remained small, with many of the studies still using rather crude approaches to estimating exposures to $PM_{10–2.5}$. As detailed in Section 11.2.1 on short-term $PM_{2.5}$ exposure and mortality, this section on $PM_{10–2.5}$ and mortality focuses primarily on multicity studies because they examine the association between short-term $PM_{2.5}$ exposure and a health effect over a large geographic area that consists of diverse atmospheric conditions and population demographics, using a consistent statistical methodology, which avoids the potential publication bias often associated with single-city studies (U.S. EPA, 2008). Other recent studies (i.e., single and multicity) that do not further inform uncertainties or limitations in the short-term $PM_{10–2.5}$ exposure and mortality evidence are not the focus of this section, and are available at: https://hero.epa.gov/hero/particulate-matter.

The following section provides a brief overview of the associations observed in recent studies of mortality and short-term $PM_{10–2.5}$ exposures, with the main focus on evaluating whether recent studies address the uncertainties and limitations identified in the 2009 PM ISA (U.S. EPA, 2009), specifically: copollutant confounding; model specification; effect modification (e.g., temperature, season); exposure

[80] As detailed in the Preface, risk estimates are for a 10 $\mu g/m^3$ increase in 24-hour average $PM_{10–2.5}$ concentrations, unless otherwise noted.

assessment; and the concentration-response relationship and related issues (e.g., lag structure of associations). The multicity studies discussed throughout this section, along with study-specific details, air quality characteristics, and the approach used to estimate $PM_{10-2.5}$ concentrations are highlighted in Table 11-9.

Table 11-9 Study-specific details and $PM_{10-2.5}$ concentrations from multicity studies in the 2009 PM ISA and 2004 PM air quality criteria document (AQCD), and recent multicity studies and meta-analyses.

Study	Mortality Outcome(s)	Mean Concentration µg/m^3	Upper Percentile Concentrations µg/m^3	Measurement of $PM_{10-2.5}$ Concentrations	Copollutant Examination
Klemm and Mason (2003)[a] Six U.S. cities (1979–1988)	Total	9.0[b]	75th: 15.5 Max: 30.1	$PM_{10-2.5}$ directly measured using dichotomous samplers[c]	Correlation (*r*): NA Copollutant models with: NA
Burnett and Goldberg (2003)[a] Eight Canadian cities (1986–1996)	Total	12.6	95th: 30.0 Max: 99.0	$PM_{10-2.5}$ directly measured using dichotomous samplers	Correlation (*r*): NA Copollutant models with: NA
Burnett et al. (2004) 12 Canadian cities (1981–1999)	Total	11.4	Max: 151.0	$PM_{10-2.5}$ directly measured using dichotomous samplers	Correlation (*r*): 0.27 NO_2 Copollutant models with: NO_2
Zanobetti and Schwartz (2009) 47 U.S. cities (1999–2005)	Total Cardiovascular Respiratory	11.8	98th: 40.2 99th: 47.2 Max: 88.3	$PM_{10-2.5}$ estimated by calculating difference between county-wide average PM_{10} and $PM_{2.5}$ concentrations	Correlation (*r*): NA Copollutant models with: $PM_{2.5}$
†Malig and BD (2009) 15 California counties, U.S. (1999–2005)	Total Cardiovascular	12.3	75th: 13.7–52.8	$PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors	Correlation (*r*): −0.03–0.35 $PM_{2.5}$ Copollutant models with: $PM_{2.5}$
†Janssen et al. (2013) Netherlands (2008–2009)	Total	7.7	75th: 9.5 Max: 53.9	$PM_{10-2.5}$ estimated by calculating difference between nationwide average of PM_{10} and $PM_{2.5}$ using 10 locations were both monitored	Correlation (*r*): 0.57 PM_{10}; 0.29 $PM_{2.5}$ Copollutant models with: $PM_{2.5}$

Table 11-9 (Continued): Study-specific details and $PM_{10-2.5}$ concentrations from multicity studies in the 2009 PM ISA and 2004 PM AQCD, and recent multicity studies and meta-analyses.

Study	Mortality Outcome(s)	Mean Concentration μg/m³	Upper Percentile Concentrations μg/m³	Measurement of $PM_{10-2.5}$ Concentrations	Copollutant Examination
†Pascal et al. (2014) Nine French cities (2001–2006)	Total Cardiovascular Respiratory	7–9	Max: 25–83	$PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors	Correlation (*r*): <0.40 $PM_{2.5}$ Copollutant models with: $PM_{2.5}$, O_3
†Samoli et al. (2013) Eight European Mediterranean cities (2001–2010)	Total Cardiovascular Respiratory	8.0–15.8[b]	75th: 12.0–20.3	$PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors	Correlation (*r*): 0.19–0.68 $PM_{2.5}$ Copollutant models with: $PM_{2.5}$, NO_2, SO_2, O_3
†Lanzinger et al. (2016)[d] Five Central European cities (UFIREG) (2011–2014)	Total Cardiovascular Respiratory	4.7–9.8	Max: 21.6–44.6	$PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors	Correlation (*r*): 0.37–0.44 NO_2; 0.58–0.78 PM_{10}; 0.40–0.61 $PM_{2.5}$; 0.40–0.51 UFP; 0.50–0.58 PNC Copollutant models with: NA
†Stafoggia et al. (2017)[e] Eight European cities (1999–2013)	Total Cardiovascular Respiratory	5.0–16.0	NA	$PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at the same monitors	Correlation (*r*): 0.09–0.36 UFP Copollutant models with: NA
†Lee et al. (2015a) 11 East Asian cities (2001–2009)	Total Cardiovascular Respiratory	10.7–50.4[b]	75th: 15.4–82.5	$PM_{10-2.5}$ estimated by calculating difference between city-wide average of PM_{10} and $PM_{2.5}$ for each city	Correlation (*r*): NA Copollutant models with: $PM_{2.5}$, O_3, SO_2, NO_2
†Chen et al. (2011) Three Chinese cities (CAPES) (2004–2008)	Total	49–101	---	$PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors	Correlation (*r*): 0.74–0.86 PM_{10}; 0.28–0.53 $PM_{2.5}$ Copollutant models with: $PM_{2.5}$

CAPES = China Air Pollution and Health Effects Study; UFIREG = Ultrafine Particles—an evidence based contribution to the development of regional and European environmental and health policy.

[a]Multicity studies included in the 2004 PM AQCD.

[b]Median concentration.

[c]Until 1984 consisted of particles with aerodynamic diameter greater than 2.5 μm and less than 15 μm, and after first quarter 1984 upper end was less than 10 μm (Klemm et al., 2000).

[d]PM only measured in 4 of the 5 cities.

[e]Stafoggia et al. (2017) did not report quantitative estimates for cardiovascular and respiratory mortality.

†Studies published since the 2009 PM ISA.

11.3.1 Biological Plausibility for Short-Term $PM_{10-2.5}$ Exposure and Total Mortality

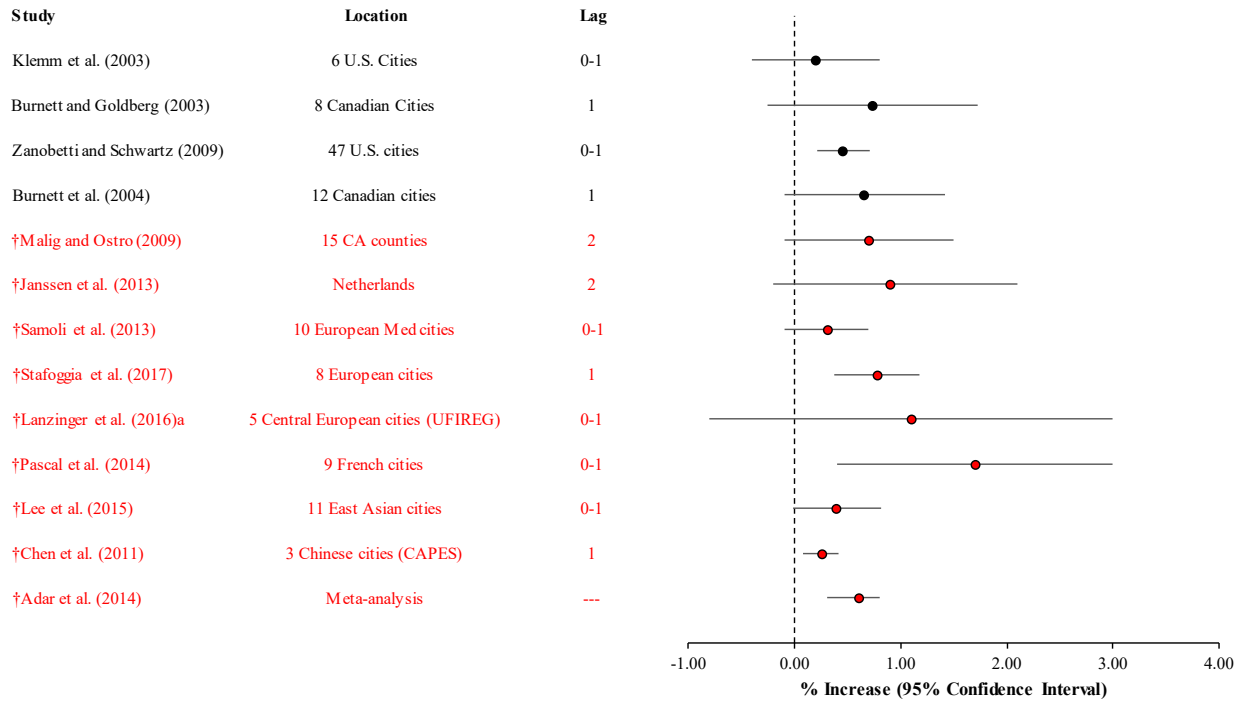
The preceding chapters characterized evidence related to evaluating the biological plausibility by which short-term $PM_{10-2.5}$ exposure may lead to the morbidity effects that are the largest contributors to total (nonaccidental) mortality, specifically cardiovascular and respiratory morbidity (Section 6.3.1 and Section 5.3.1, respectively). This evidence is derived from animal toxicological, controlled human exposure, and epidemiologic studies. Section 6.3.1 outlines the available evidence for plausible mechanisms by which inhalation exposure to $PM_{10-2.5}$ could result in initial events, such as an inflammatory response in the lungs, as well as systemic inflammation and altered hemostasis. Currently, evidence is lacking for progression to intermediate endpoints (e.g., endothelial dysfunction) and population outcomes (e.g., IHD, emergency department [ED] visits, and hospital admissions) that are observed in experimental and observational health studies. Similarly, Section 5.3.1 characterizes the available evidence by which inhalation exposure to $PM_{10-2.5}$ could progress from initial events to endpoints relevant to the respiratory system. There is some evidence for an initial event characterized by inflammatory responses that could support progression along an inflammation-mediated pathway. However, the evidence for how the initial events and subsequent endpoints could lead to increases in respiratory ED visits and hospital admissions is limited. Collectively, the progression demonstrated in the available evidence for cardiovascular and respiratory morbidity supports potential biological pathways by which short-term $PM_{10-2.5}$ exposures could result in cardiovascular and respiratory morbidity, but there is still uncertainty related to how these initial events could progress to more severe endpoints, including mortality.

11.3.2 Associations between Short-Term $PM_{10-2.5}$ Exposure and Total (Nonaccidental) Mortality in All-Year Analyses

Recent multicity studies that examined the relationship between short-term $PM_{10-2.5}$ exposure and total (nonaccidental) mortality have primarily been limited to Europe and Asia. The results from these studies, along with a meta-analysis, build on the relatively consistent, positive associations observed in multicity studies evaluated in the 2009 PM ISA and 2004 PM AQCD (Figure 11-26). It is worth noting that in the meta-analysis by Adar et al. (2014) an examination of publication bias indicated that estimates for $PM_{10-2.5}$ showed possible evidence of publication bias, which was not observed for $PM_{2.5}$ and may contribute to the small literature base for $PM_{10-2.5}$.

Consistent with the 2009 PM ISA, across studies different methods were used to measure $PM_{10-2.5}$ concentrations with most studies relying on some form of the difference method (i.e., subtracting PM_{10} concentrations from $PM_{2.5}$ concentrations) (Table 11-9). Although some studies have attempted to examine the relationship between different $PM_{10-2.5}$ monitoring methods as detailed in Section 2.4.2, these

analyses are limited to a few locations and it remains unclear how similar the absolute magnitude of $PM_{10-2.5}$ concentrations are across each method and whether the $PM_{10-2.5}$ concentrations estimated from each method are temporally correlated.



CAPES = China Air Pollution and Health Effects Study; UFIREG = Ultrafine Particles—an evidence based contribution to the development of regional and European environmental and health policy.

[a]Only four of the five cities measured $PM_{2.5}$.

Note: †Studies published since the 2009 PM ISA. Black circles = U.S. and Canadian multicity studies evaluated in the 2004 PM AQCD and 2009 PM ISA. Red circles = Multicity studies and meta-analyses published since the completion of the 2009 PM ISA. Corresponding quantitative results are reported in Supplemental Table S11-9 (U.S. EPA, 2018b).

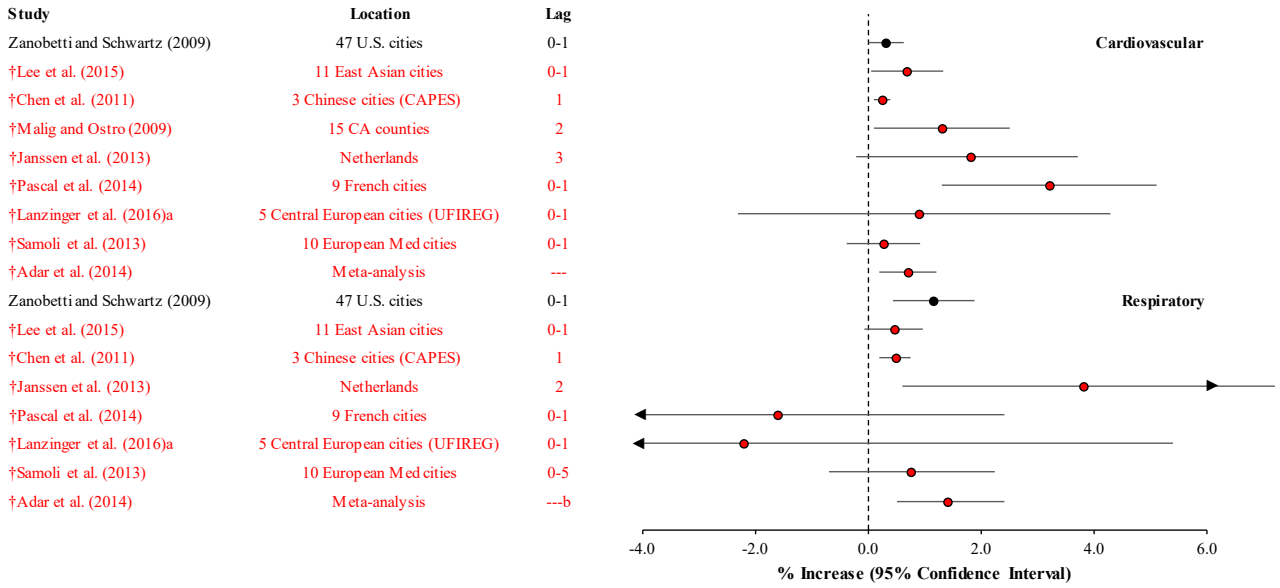
Figure 11-26 Summary of associations between short-term $PM_{10-2.5}$ exposure and total (nonaccidental) mortality in multicity studies for a 10 μg/m³ increase in 24-hour average concentrations.

11.3.3 Associations between Short-Term $PM_{10-2.5}$ Exposure and Cause-Specific Mortality in All-Year Analyses

In addition to evaluating the relationship between short-term $PM_{10-2.5}$ exposure and total (nonaccidental) mortality a number of studies also evaluated cause-specific mortality (i.e., cardiovascular and respiratory mortality) (U.S. EPA, 2009). Studies that examined cardiovascular mortality reported

evidence of consistent positive associations. Fewer studies examined the association between short-term $PM_{10–2.5}$ exposure and respiratory mortality, with most, but not all studies reporting positive associations. Across both cardiovascular and respiratory mortality studies confidence intervals were larger than those observed for total (nonaccidental) mortality, which is a reflection of a majority of studies consisting of single-city studies.

Recent multicity studies add to the body of evidence detailed in the 2009 PM ISA (Figure 11-27). An examination of cardiovascular mortality finds evidence of consistent positive associations, but both the magnitude of the association along with the width of the 95% confidence intervals vary across studies. For respiratory mortality, most, but not all studies, reported evidence of positive associations. However, similar to the examination of cardiovascular mortality and short-term $PM_{10–2.5}$ exposures, the confidence intervals were large for some studies, particularly Janssen et al. (2013) and Lanzinger et al. (2016), which could be attributed to the rather short time-series for both studies.



CAPES = China Air Pollution and Health Effects Study; UFIREG = Ultrafine Particles—an evidence based contribution to the development of regional and European environmental and health policy.

[a]Only four of the five cities measured $PM_{2.5}$, study included ages >1.

[b]Adar et al. (2014) focused on single-day lag results, specifically lag 0, 1, or 2.

Note: †Studies published since the 2009 PM ISA. Black circles = U.S. and Canadian multicity studies evaluated in the 2004 PM AQCD and 2009 PM ISA. Red circles = Multicity studies and meta-analyses published since the completion of the 2009 PM ISA. Corresponding quantitative results are reported in Supplemental Table S11-10 (U.S. EPA, 2018b).

Figure 11-27 Summary of associations between short-term $PM_{10-2.5}$ exposure and cardiovascular and respiratory mortality in multicity studies for a 10 μg/m^3 increase in 24-hour average concentrations.

11.3.4 Potential Confounding of the $PM_{10-2.5}$-Mortality Relationship

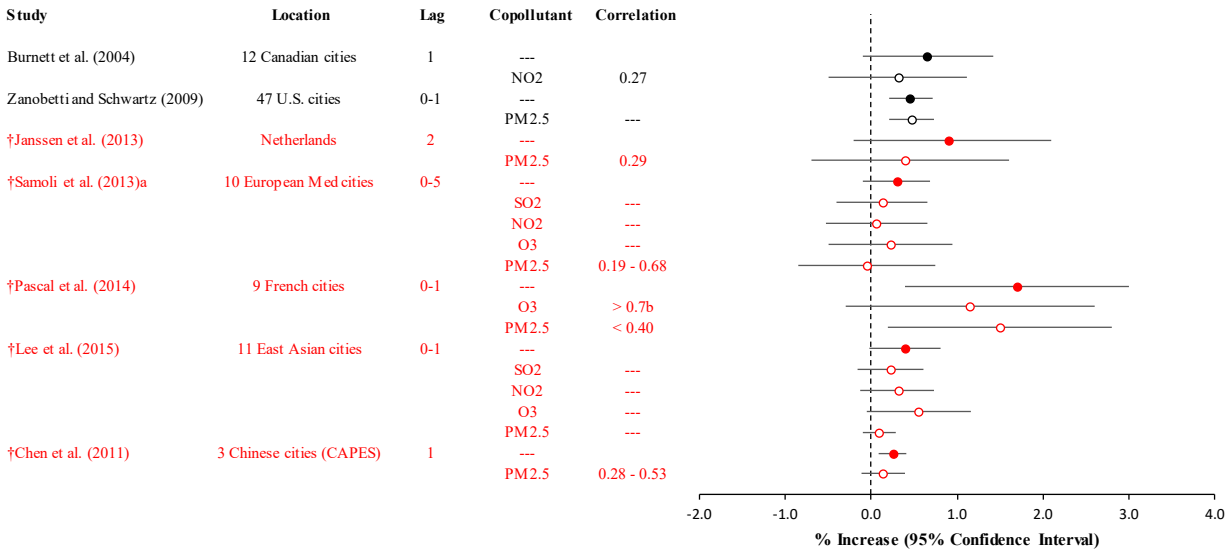
At the completion of the 2009 PM ISA, there was relatively little information on the potential confounding effects of other pollutants (i.e., both gaseous as well as $PM_{2.5}$) along with weather covariates on the $PM_{10-2.5}$-mortality relationship. As often detailed in air pollution epidemiology, a thorough evaluation of potential confounding by both copollutants and weather variables is important in understanding the relationship between an air pollutant exposure and health outcome.

11.3.4.1 Copollutants

Multicity studies that evaluated potential copollutant confounding in the 2009 PM ISA were limited to studies conducted by Zanobetti and Schwartz (2009) in 47 U.S. cities and Burnett et al. (2004)

in 12 Canadian cities, which examined copollutant models with $PM_{2.5}$ and NO_2, respectively. These studies provided initial evidence that $PM_{10–2.5}$-mortality associations remained positive in copollutant models with particles and gaseous pollutants although the $PM_{10–2.5}$ measurement methods varied between the studies (Figure 11-28). Recent multicity studies expand upon the limited number of studies evaluating the potential copollutant confounding of the $PM_{10–2.5}$-mortality relationship.

As summarized in Figure 11-28, copollutant models that included $PM_{2.5}$ resulted in $PM_{10–2.5}$-mortality associations that were often attenuated and generally remained positive in analyses conducted specifically in the U.S. and Canada, but in some cases became null (Samoli et al., 2013). This observation is supported by a study conducted in California that observed $PM_{10–2.5}$ mortality associations were similar in magnitude in copollutant models with $PM_{2.5}$ (quantitative results not presented) (Malig and BD, 2009). The indication that $PM_{10–2.5}$ results generally remain positive in copollutant models with $PM_{2.5}$, as presented in Figure 11-28, is supported by analyses that examined potential copollutant confounding in the context of a meta-analysis. When examining studies that conducted copollutant models with $PM_{2.5}$, Adar et al. (2014) observed that the $PM_{10–2.5}$-mortality association was similar in magnitude to that observed in single-pollutant models (quantitative results not provided). The results from copollutant models were further supported when stratifying $PM_{10–2.5}$-mortality estimates by the correlation with $PM_{2.5}$ (low, $r < 0.35$; medium, $r = 0.35$ to < 0.5; high, $r > 0.5$). The authors observed evidence of positive associations across each stratification, although the magnitude varied, with the association being largest in magnitude for correlations <0.35. Adar et al. (2014) further examined potential copollutant confounding by $PM_{2.5}$ through an analysis focusing on whether $PM_{10–2.5}$-mortality associations were present when the correlation between $PM_{2.5}$ and $PM_{10–2.5}$ increased and when $PM_{2.5}$ was also associated with mortality. As highlighted in Figure 11-29, there was not a consistent pattern of $PM_{10–2.5}$-mortality associations when there was also evidence of a $PM_{2.5}$-mortality association.



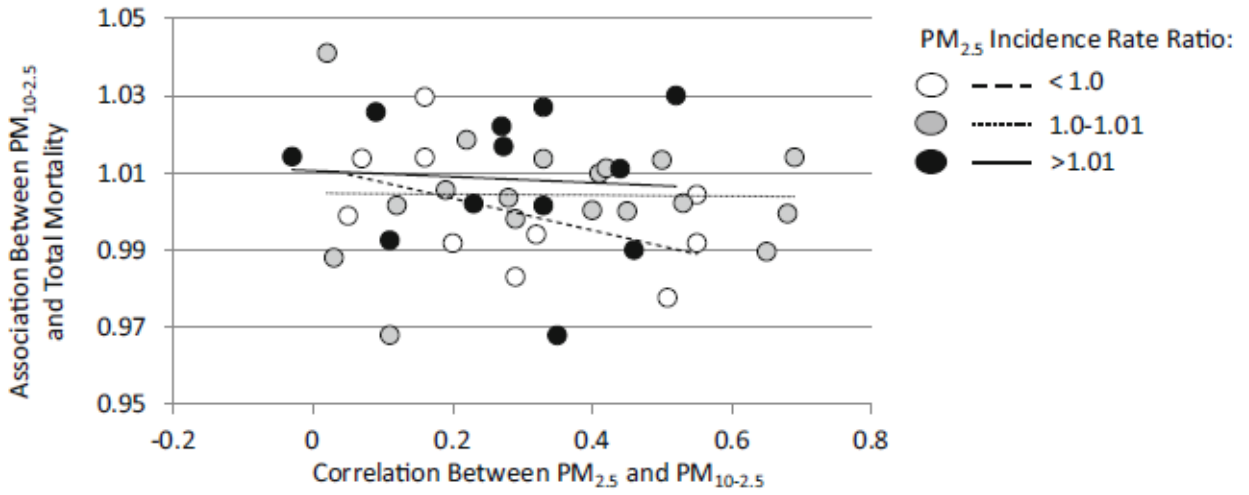
CAPES = China Air Pollution and Health Effects Study.

[a]Copollutant results only presented for a lag of 0−5 days.

[b]Correlation is for the summer across cities, no correlation was observed in all-year analyses.

Note: †Studies published since the 2009 PM ISA. Black circles = single-pollutant model. White circles = copollutant models. Corresponding quantitative results are reported in Supplemental Table S11-11 (U.S. EPA, 2018b).

Figure 11-28 Summary of associations between short-term $PM_{10-2.5}$ exposure and total (nonaccidental) mortality for a 10 μg/m^3 increase in 24-hour average concentrations in single and copollutant models from multicity studies.



Source: Permission pending, Adar et al. (2014).

Figure 11-29 Incidence rate ratios as a function of the correlation between short-term $PM_{10-2.5}$ and $PM_{2.5}$ concentrations stratified by $PM_{2.5}$ associations.

An evaluation of copollutant models including gaseous pollutants finds that in many instances the $PM_{10-2.5}$-mortality association is robust or slightly attenuated, but remains positive across studies (Figure 11-28). However, the interpretation of results across these studies is complicated by the relative lack of information on the correlation between $PM_{10-2.5}$ and gaseous pollutants.

Collectively, recent multicity studies provide additional information on whether the $PM_{10-2.5}$-mortality association is confounded by copollutants. However, uncertainty still remains, particularly with respect to the correlation between $PM_{10-2.5}$ and gaseous pollutants, which could further inform the copollutant model results observed across studies. Overall, there is some evidence that the $PM_{10-2.5}$-mortality association remains positive in copollutant models with $PM_{2.5}$ and O_3, with a more limited number of studies examining NO_2 and SO_2.

11.3.4.2 Long-Term Temporal Trends and Weather

The studies evaluated in the 2009 PM ISA that focused on the relationship between short-term $PM_{10-2.5}$ exposure and mortality did not conduct systematic evaluations or sensitivity analyses to examine the potential influence of model specification, specifically pertaining to the control for weather and temporal trends, on the $PM_{10-2.5}$-mortality association. Although a limited evaluation of model specification for the $PM_{10-2.5}$-mortality relationship has been conducted in a few recent multicity studies, compared to $PM_{2.5}$ (see Section 11.1.5.1) the overall evaluation remains rather limited.

Of the multicity studies that examined the influence of model specification, the focus has tended to be on adequate control for temporal trends. Lee et al. (2015a) in a study consisting of 11 East Asian countries examined the influence of altering the df per year to control for temporal trends from 6 to 12. The authors observed that as the df per year increased above 8 there was evidence that the $PM_{10–2.5}$ risk estimate was attenuated, but remained positive. The results of the systematic analysis of control for temporal trends in Lee et al. (2015a) may explain those observed in Samoli et al. (2013) where risk estimates were compared across models that selected 8 df/year to control for temporal trends a priori, used the absolute sum of the residuals of the partial autocorrelation function (PACF) to control for temporal trends, or conducted a case-crossover analysis, which inherently removes the need to control for temporal trends. The authors observed that the a priori method of selecting 8 df/yr resulted in the most conservative estimate of the $PM_{10–2.5}$-mortality association, which indicates that the results of Samoli et al. (2013) are comparable to those of Lee et al. (2015a). However, without knowing the df/yr selected through the PACF method it is unclear if the results between the two studies are consistent.

Only Pascal et al. (2014) in the study of nine French cities examined the influence of alternative weather covariates on the $PM_{10–2.5}$-mortality association. The authors used two distinct approaches: (1) a traditional analysis where daily mean temperature at lag 0 and lag 1−7 days was used instead of daily maximum and minimum temperature and (2) an alternative approach using a case crossover design where referent days were matched on days with the same temperature within the same month and year as the case day. Including a covariate for mean temperature instead of daily maximum and minimum temperature resulted in a dramatic reduction in the mortality risk estimate; whereas, when controlling for temperature using the case-crossover approach, the mortality risk estimate was almost identical to that obtained using the main generalized additive Poisson model.

Collectively, the studies that examined model specification indicate some potential sensitivity in $PM_{10–2.5}$-mortality risk estimates depending the number of df/yr included to control for temporal trends and the weather covariates included in the model. To date, however, the limited number of studies that examined the influence of model specification on the $PM_{10–2.5}$-mortality relationship do not allow for a full assessment of model specification and the potential sensitivity of risk estimates.

11.3.5 Effect Modification of the $PM_{10-2.5}$-Mortality Relationship

Relatively few studies have examined effect modification of the $PM_{10–2.5}$-mortality relationship. However, consistent with studies focusing on $PM_{2.5}$ and mortality, some studies examine whether specific individual- or population-level characteristics modify the $PM_{10–2.5}$-mortality association while other studies focus more broadly on examining those factors that potentially modify that $PM_{10–2.5}$-mortality association. The evaluation of individual- or population-level characteristics that may contribute to a population being at increased risk of PM-related health effects is detailed in Chapter 12. The following

section focuses exclusively on exploring those factors that may modify and further inform the relationship between short-term $PM_{10–2.5}$ exposure and mortality.

11.3.5.1 Season and Temperature

To date, few studies have conducted seasonal analyses to examine whether there is evidence that a specific season modifies the $PM_{10–2.5}$-mortality-relationship. Lee et al. (2015a) and Samoli et al. (2013) in studies of 11 East Asian cities and 10 European Mediterranean cities, respectively, focused on warm (April−September) and cold (October−March) season analyses. In Lee et al. (2015a), the authors observed a larger association during the cold season (0.71% [95% CI: 0.17, 1.3]; lag 0−1) compared to the warm season (0.16% [95% CI: −0.32, 0.64]). These results are the opposite of those observed in Samoli et al. (2013), although confidence intervals were large, associations were larger in magnitude in the warm season over the same lag period of 0−1 days (warm: 0.57% [95% CI: −0.16, 1.3]; cold: 0.26% [95% CI: −0.43, 0.95]). Instead of dividing the year into two seasons, Pascal et al. (2014) examined associations across the four seasons and reported seasonal associations more in line with the results of Samoli et al. (2013). The authors observed positive associations in the spring, summer, and autumn, with evidence of no association in the winter, with the summer and autumn having much larger associations, 4.6% (95% CI: 2.3, 6.9) and 3.3% (95% CI: 1.3, 5.1) at lag 0−1, respectively. Although Samoli et al. (2013) and Pascal et al. (2014) reported a relatively similar pattern of seasonal $PM_{10–2.5}$-mortality associations, the results from Lee et al. (2015a) complicate the interpretation of seasonal associations across studies.

In addition to examining seasonal associations, which in some respect are a proxy for examining the influence of temperature on the relationship between $PM_{10–2.5}$ and mortality, Pascal et al. (2014) also examined through a traditional stratified analysis if the $PM_{10–2.5}$-mortality association varied between warm (i.e., defined as days above the 97.5th percentile of the temperature distribution) and nonwarm days. The authors reported some evidence of a larger association on warm days (3.9% [95% CI: −3.3, 11.7]; lag 0−1) compared to nonwarm days (1.5% [95% CI: 0.3, 2.7]). These results were further reflected when examining the interaction ratio, which portrays the extra PM effect on warm days (1.04 [95% CI: 0.98, 1.12]).

Overall there is some evidence that warmer temperatures and seasons modify the $PM_{10–2.5}$-mortality association. However, the limited number of studies that examined both the potential modifying effects of season and temperature complicate the interpretation of results across studies.

11.3.5.2 Role of Exposure Assignment and Exposure Misclassification

Compared to $PM_{2.5}$, relatively few studies have examined the role of different parameters (e.g., distance to monitor) used to assign exposures on the $PM_{10–2.5}$ mortality relationship. Although

similar approaches to assign exposure have been used across PM size fractions, it remains unclear if different parameters impact the observed association and its magnitude. Malig and BD (2009) in the case-crossover study of 15 California counties examined the influence of reducing the buffer size around monitors from 20 to 10 km on the $PM_{10-2.5}$-mortality association when assigning exposure. The authors observed the strongest association at lag 2 when using the 20-km buffers (0.7% [95% CI: −0.1, 1.5]). When restricting the analysis to 10-km buffers around monitors, which reduced the number of cases examined by 40%, the results were almost identical (quantitative results not presented).

11.3.6 $PM_{10-2.5}$-Mortality Concentration-Response (C-R) Relationship and Related Issues

11.3.6.1 Lag Structure of Associations

Studies evaluated in the 2009 PM ISA that examined the relationship between short-term $PM_{10-2.5}$ exposure and mortality often selected lags to examine a priori and did not thoroughly examine the lag structure of associations. Across these studies positive associations were often observed with mortality at lags ranging from 0 to 1 day (U.S. EPA, 2009). Recent multicity studies provide additional insight on the lag structure of associations for short-term $PM_{10-2.5}$ exposure and mortality through systematic analyses focusing on both single- and multiday lags. As detailed in Section 11.1.8.1, the focus of this section is on those studies that conducted a systematic evaluation of different lags (e.g., single-day vs. distributed or average of multiple days) and include all single days evaluated in the distributed or multiday average lags (i.e., if a study examines a distributed or multiday average lag of 0−6 days it also examines single-day lags of 0 to 6 days).

Lee et al. (2015a) in the study of 11 East Asian cities examined the lag structure of associations for short-term $PM_{10-2.5}$ exposure and mortality by focusing on same-day exposure (lag 0) and multiday lags ranging from 0−1 to 0−4 days. Across this lag structure, the authors observed the strongest association, in terms of both magnitude and precision, at lag 0−1 and an association slightly smaller in magnitude across lags ranging from 0−2 to 0−4 days (quantitative results not presented). For each of the multiday lags; however, the confidence intervals were large. The pattern of associations observed in Lee et al. (2015a) is consistent with that reported in Stafoggia et al. (2017) in a study of eight European cities that examined single-day lags ranging from 0 to 10 days. The authors observed evidence of a positive association across lags 0 to 3 days, with the strongest association at lag 1 (quantitative results not presented).

Instead of focusing on single-day lags or a series of multiday lags, Samoli et al. (2013), in a study of 10 European Mediterranean cities, took a different approach to examining the lag structure of associations by focusing on distributed lags indicative of immediate (0−1), delayed (2−5), and prolonged

effects (0−5). The authors observed the strongest association at lag 0−1 (0.30% [95%: −0.10, 0.69]), with no evidence of an association at lags 2−5 and 0−5 days.

The results from studies that examined a series of single-day lags along with studies that examined multiday lags are consistent with the collective body of evidence detailed in the 2009 PM ISA. The combination of evidence from the 2009 PM ISA along with the limited number of studies that have systematically evaluated the lag structure of associations provide initial evidence indicating that mortality effects occur at lags ranging from 0 to 1 day.

11.3.6.2 Concentration-Response Relationship and Threshold Analyses

Studies evaluated in the 2009 PM ISA did not examine the C-R relationship and whether a threshold exists between short-term $PM_{10–2.5}$ exposure and mortality. Only the recent multicity study encompassing 10 European Mediterranean cities conducted by Samoli et al. (2013) provides some insight on the $PM_{10–2.5}$-mortality C-R relationship.

Similar to the analysis for $PM_{2.5}$ detailed in Section 11.1.10, Samoli et al. (2013) conducted a threshold analysis by selecting cutpoints at 5 $\mu g/m^3$ increments along the range of $PM_{10–2.5}$ concentrations from 0−20 $\mu g/m^3$. The authors assumed there was no risk of mortality below the defined threshold value. Samoli et al. (2013) did not observe any evidence of a threshold, which was reflected in the models with the lowest deviance being those that did not assume the presence of a threshold.

In understanding the relationship between short-term $PM_{10–2.5}$ exposure and mortality it is also important to characterize the relationship along the full distribution of ambient concentrations. Studies that examine the influence of extreme events can provide insight on the $PM_{10–2.5}$-mortality relationship at the high end of the $PM_{10–2.5}$ distribution. Lee et al. (2015a) in the analysis of 11 East Asian cities examined the influence of high particle concentrations on the $PM_{10–2.5}$-mortality association through an analysis focusing on (1) the highest 0.5% $PM_{10–2.5}$ concentrations and (2) dust storms. When including the highest 0.5% $PM_{10–2.5}$ concentrations in the analysis, the authors observed an attenuation of the $PM_{10–2.5}$ mortality association at lag 0−1 from 0.35% (95% CI: −0.02, 0.81) to 0.13% (95% CI: 0.01, 0.26). The authors reported a similar observation when examining associations between dust storm (0.07% [95% CI: −0.17, 0.31]; lag 0−1) and nondust storm (0.34% [95% CI: 0.05, 0.62]) periods, which collectively indicate a potential different relationship between short-term $PM_{10–2.5}$ exposure and mortality at higher particle concentrations. The results of Lee et al. (2015a) are supported by an analysis of areas with high $PM_{10–2.5}$ concentrations in the meta-analysis by Adar et al. (2014). When stratifying results by areas with mean concentrations <10 $\mu g/m^3$, 10 to <15 $\mu g/m^3$, and >15 $\mu g/m^3$, the authors observed the smallest associations for study areas with the highest mean $PM_{10–2.5}$ concentrations.

Summary

Although studies have not focused specifically on the shape of the $PM_{10–2.5}$-mortality C-R relationship, recent studies do not provide evidence of a threshold. Additionally, studies focusing on high concentrations provide initial evidence indicating that the shape of the C-R may plateau at higher concentrations; however, there are no statistically based analyses currently available that examine the shape of the C-R relationship to support the observations from these high concentration analyses.

11.3.7 Summary and Causality Determination

Since the completion of the 2009 PM ISA a number of multicity studies conducted primarily in Europe and Asia continue to provide evidence of consistent positive associations between short-term $PM_{10–2.5}$ exposure and total (nonaccidental) mortality. Although these studies contribute to increasing the confidence in the $PM_{10–2.5}$-mortality relationship, different methods are employed across studies in the measurement of $PM_{10–2.5}$ concentrations, which continues to form the main uncertainty in the associations observed and further support that the evidence is suggestive, but not sufficient to infer, a causal relationship. While uncertainty in the measurement of $PM_{10–2.5}$ remains, recent studies provide initial evidence that informs additional uncertainties and limitations identified in the studies evaluated in the 2009 PM ISA, specifically potential copollutant confounding; effect modification (e.g., temperature, season); and the shape of the C-R relationship and whether a threshold exists. The evidence for total mortality is supported by consistent positive associations with cardiovascular mortality with less consistent evidence for respiratory mortality; however, there is limited coherence and biological plausibility for cause-specific mortality when evaluating different health endpoints across the scientific disciplines (i.e., animal toxicological, controlled human exposure studies, and epidemiologic) for both cardiovascular (Chapter 6) and respiratory (Chapter 5) morbidity. This section describes the evaluation of evidence for total (nonaccidental) mortality, with respect to the causality determination for short-term exposures to $PM_{10–2.5}$ using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015b). The key evidence, as it relates to the causal framework, is summarized in Table 11-10.

Table 11-10 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10-2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{10-2.5}$ concentrations.	Increases in mortality in multicity studies conducted in the U.S., Europe, and Asia Total mortality associations, supported by consistent increases in cardiovascular mortality with less consistent evidence for respiratory mortality in multicity studies conducted in the U.S., Europe, and Asia.	Section 11.3.2 Figure 11-26 Figure 11-27 Section 5.3.7 Section 6.3.8	Mean 24-h avg: U.S.: 12.3 Europe: 7–16 Asia: 10.7[d]–101 Table 11-1
Epidemiologic evidence from copollutant models provides some support for an independent $PM_{10-2.5}$ association.	$PM_{10-2.5}$ associations are generally robust, but there are some instances of attenuation in copollutant models with gaseous pollutants and $PM_{2.5}$. However, there is limited information on the correlation between $PM_{10-2.5}$ and gaseous pollutants complicating the interpretation of results. Copollutant analyses with cardiovascular and respiratory mortality are limited to studies conducted in Europe and Asia and indicate that $PM_{10-2.5}$ associations generally remain positive, although attenuated in some instances. When reported, correlations with gaseous copollutants were primarily in the low ($r < 0.4$) to moderate ($r \geq 0.4$ or <0.7) range.	Section 11.3.4.1 Figure 11-28 Section 5.3.7.1.1 Figure 5-46 Section 6.3.8 Figure 6-32	
Uncertainty regarding exposure measurement error	Across studies $PM_{10-2.5}$ concentrations are measured using a number of approaches (i.e., directly measured from dichotomous sampler, different between PM_{10} and $PM_{2.5}$ at collocated monitors, and difference of area-wide concentrations of PM_{10} and $PM_{2.5}$), which have not been compared in terms of whether they have similar spatial and temporal correlations.	Table 11-9 Section 3.3.1.1	
Epidemiologic evidence provides some support for a no-threshold concentration-response (C-R) relationship.	Initial evidence from a study conducted in Europe for a no-threshold relationship, while a study conducted in Asia along with a meta-analysis indicating that the shape of the C-R curve may be different at higher concentrations.	Section 11.3.6.2	

Table 11-10 (Continued): Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10-2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Limited biological plausibility from cardiovascular and respiratory morbidity evidence.	Cardiovascular morbidity studies provide some evidence for ischemic events from epidemiologic studies, but limited experimental evidence resulting in limited coherence and biological plausibility for $PM_{10-2.5}$-related cardiovascular effects. Collectively, there is limited biological plausibility to support a relationship between short-term $PM_{10-2.5}$ exposure and cardiovascular mortality, which comprises ~33% of total mortality.[e] Respiratory morbidity studies provide some evidence for effects on pulmonary inflammation and function, which is supported by asthma-related hospital admissions and ED visits, but overall there is limited coherence and biological plausibility for $PM_{10-2.5}$-related respiratory effects. Collectively, there is limited biological plausibility to support a relationship between short-term $PM_{2.5}$ exposure and respiratory mortality, which comprises ~9% of total mortality.[e]	Section 6.3.13 Table 6-58 Section 5.3.8 Table 5-37	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015b).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to the causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

[d]Median concentration from Lee et al. (2015a).

[e]Statistics taken from NHLBI (2017).

The evidence from recent multicity studies of short-term $PM_{2.5}$ exposures and mortality demonstrates consistent positive associations with total (nonaccidental) mortality, with increases ranging from 0.25% (Chen et al., 2011) to 1.70% (Pascal et al., 2014) at lags of 0 to 2 day in single-pollutant models. However, across studies different approaches have been employed to measure $PM_{10-2.5}$ concentrations (i.e., directly measured from a dichotomous sampler, difference between PM_{10} and $PM_{2.5}$ at collocated monitors, and difference of area-wide concentrations of PM_{10} and $PM_{2.5}$), which have not been compared to determine if their spatial and temporal correlation are similar, contributing uncertainty to the comparison of results across studies (Section 2.4, Section 3.3.1). Recent studies expand the assessment of potential copollutant confounding of the $PM_{10-2.5}$-mortality relationship, and provide some evidence that $PM_{10-2.5}$ associations remain positive in copollutant models, but there is some evidence that associations are attenuated (Section 11.3.4.1). Overall, the assessment of potential copollutant confounding is limited due to the lack of information on the correlation between $PM_{10-2.5}$ and gaseous

pollutants and the small number of locations in which copollutant analyses have been conducted. Analyses of cause-specific mortality provide some supporting evidence for total (nonaccidental) mortality associations, but overall estimates are more uncertain (i.e., wider confidence intervals) and less consistent, specifically for respiratory mortality (Figure 11-27). For both cardiovascular and respiratory mortality there was a limited assessment of potential copollutant confounding, with the pattern of associations and uncertainties similar to those observed for total (nonaccidental) mortality. The assessment of cardiovascular (Chapter 6) and respiratory morbidity (Chapter 5) provides limited biological plausibility for $PM_{10–2.5}$-related cardiovascular and respiratory mortality.

In addition to examining potential copollutant confounding, a few studies also assessed whether statistical models adequately account for temporal trends and weather covariates. To date, this assessment remains limited, but initial evidence indicates that $PM_{10–2.5}$ associations may be sensitive to model specification. An examination of whether associations vary by season and temperature provide some evidence that $PM_{10–2.5}$-mortality associations are larger in magnitude during warmer temperatures and seasons, but this pattern was not evident across all studies (Section 11.3.5.1). Across the studies evaluated, a few conducted systematic evaluations of the lag structure of associations. These studies examined either a series of single-day lags or whether there was evidence of an immediate (lag 0−1), delayed (lag 2−5), or prolonged effect (lag 0−5), and provided initial evidence that the $PM_{10–2.5}$ is immediate (i.e., lags 0 to 1 day) (Section 11.3.6.1). At the completion of the 2009 PM ISA no studies had assessed the $PM_{10–2.5}$-mortality C-R relationship, and recent studies have only conducted cursory analyses that do not thoroughly inform the shape of the C-R curve or whether a threshold exists.

Overall, recent epidemiologic studies provide additional support of consistent positive associations between short-term $PM_{10–2.5}$ exposure and total (nonaccidental) mortality, but there remains a large degree of uncertainty due to the various approaches used to measure $PM_{10–2.5}$ concentrations. The lack of information on the spatial and temporal correlation between the various measurement approaches reduces the confidence in the associations observed across studies. Additionally, the evidence from the assessment of short-term $PM_{10–2.5}$ exposures and cardiovascular and respiratory morbidity provide limited biological plausibility for $PM_{10–2.5}$-related mortality. Although recent studies attempt to address previously identified uncertainties and limitations in the $PM_{10–2.5}$-mortality relationship, the overall assessment of potential copollutant confounding, model specification, the lag structure of associations, and the C-R relationship remains limited. **Collectively, this body of evidence is suggestive, but not sufficient to infer, that a causal relationship exists between short-term $PM_{10–2.5}$ exposure and total mortality.**

11.4 Long-Term $PM_{10–2.5}$ Exposure and Total Mortality

The 2009 PM ISA reported that the evidence was "limited to adequately characterize the association" between long-term $PM_{10–2.5}$ exposure and mortality (U.S. EPA, 2009), noting that findings

from the AHSMOG (Chen et al., 2005; McDonnell et al., 2000) and Veterans (Lipfert et al., 2006) cohorts provided limited evidence for an association, especially after adjustment for $PM_{2.5}$ in the models. Each of these studies subtracted $PM_{2.5}$ concentrations from PM_{10} concentrations to calculate a concentration for $PM_{10–2.5}$, contributing to uncertainty in their interpretation. Due to the dearth of studies examining the association between long-term $PM_{10–2.5}$ exposure and mortality, the 2009 PM ISA concluded that the evidence was "inadequate to determine if a causal relationship exists" (U.S. EPA, 2009).[81] Recent studies provide some additional evidence to inform the relationship between long-term $PM_{10–2.5}$ exposure and mortality, though they often have similar limitations to those noted for studies included in the 2009 PM ISA.

11.4.1 Biological Plausibility for Long-Term $PM_{10–2.5}$ Exposure and Total Mortality

The preceding chapters characterized evidence related to evaluating the biological plausibility by which long-term $PM_{10–2.5}$ exposure may lead to the morbidity effects that are the largest contributors to total (nonaccidental) mortality, specifically cardiovascular and respiratory morbidity and metabolic disease (Section 6.4.1, Section 5.4.1, and Section 7.4.1, respectively). This evidence is derived from animal toxicological, controlled human exposure, and epidemiologic studies. Section 6.4.1 outlines the available evidence for plausible mechanisms by which inhalation exposure to $PM_{10–2.5}$ could result in initial events, such as an inflammatory response in the lungs, and limited evidence for altered hemostasis and arterial thrombosis. Arterial thrombosis can progress to IHD and thus provides a plausible mechanism by which ED visits and hospital admissions related to IHD can occur. Similarly, Section 5.4.1 characterizes the available evidence by which inhalation exposure to $PM_{10–2.5}$ could progress from initial events to endpoints relevant to the respiratory system. This includes evidence for markers of oxidative stress and inflammation and enhanced allergen-induced responses and airway changes that could play a role in asthma development and/or exacerbation. However, the evidence for how the initial events and subsequent endpoints could lead to the observed increases in respiratory ED visits and hospital admissions is limited. Section 7.4.1 outlines the limited evidence for an initial event (i.e., pulmonary inflammation) that could initiate mechanisms by which inhalation exposure to $PM_{10–2.5}$ could progress to intermediate endpoints and eventually result in population outcomes such as metabolic disease. However, the evidence for how pulmonary inflammation could lead to metabolic disease is limited. Collectively, the progression demonstrated in the available evidence for cardiovascular and respiratory morbidity and metabolic disease provides limited support for potential biological pathways by which long-term $PM_{10–2.5}$ exposures could result in mortality.

[81] As detailed in the Preface, risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{10–2.5}$ concentrations, unless otherwise noted.

11.4.2 Associations between Long-Term $PM_{10-2.5}$ Exposure and Mortality

Several recent U.S. cohort studies examined the association between long-term $PM_{10-2.5}$ exposure and mortality in cohorts for which subjects were recruited based on their place of employment. Puett et al. (2009) examined the association between long-term $PM_{10-2.5}$ exposure and total (nonaccidental) mortality among a cohort of female nurses in the Nurses' Health Study from 13 states in the Northeast and Midwest from 1992 through 2002. Spatio-temporal models were used to assign exposure to $PM_{2.5}$ and PM_{10}, and the $PM_{10-2.5}$ concentrations were derived via subtraction. The authors observed positive associations with total (nonaccidental) and CHD mortality, with the strongest association observed for fatal CHD events. These associations were attenuated to below the null value in copollutant models that include $PM_{2.5}$. Using a design similar to that of the Nurses' Health Study, Puett et al. (2011) investigated the effect of long-term $PM_{10-2.5}$ (derived by subtraction of $PM_{2.5}$ from PM_{10}) exposure and mortality among men enrolled in the Health Professionals cohort. Near null associations were observed for both total (nonaccidental) and CHD mortality in this cohort.

A European pooled-analysis combined data from 22 existing cohort studies and evaluated the association between long-term $PM_{10-2.5}$ exposure and total (nonaccidental) (Beelen et al., 2014a), cardiovascular (Beelen et al., 2014b), and respiratory (Dimakopoulou et al., 2014) mortality. LUR models were used to assign exposure to $PM_{2.5}$ and PM_{10}, and the $PM_{10-2.5}$ concentrations were derived via subtraction. The authors applied a common statistical protocol to data from each of the 22 cohorts, from 13 different European countries, in the first stage of the analysis and combined the cohort-specific effects in a second stage. The authors observed a near-null association between long-term $PM_{10-2.5}$ exposure and total (nonaccidental) (Beelen et al., 2014a), cardiovascular (Beelen et al., 2014b), and respiratory (Dimakopoulou et al., 2014) mortality. The strongest association was observed for the subset of cardiovascular deaths attributable to cerebrovascular disease (HR: 1.17, 95% CI: 0.9, 1.52) (Beelen et al., 2014b), though copollutant models with $PM_{2.5}$ were not reported for this comparison. Using the same exposure models used for the pooled cohort study, Dehbi et al. (2016) assigned $PM_{10-2.5}$ exposure to two British cohort studies that were pooled together to examine CVD mortality. The British cohorts included follow-up between 1989 and 2015, though $PM_{10-2.5}$ exposure estimates were available for 2010−2011. The authors observed a negative association when exposure was considered on the continuous scale, but positive associations for each quartile when exposure was categorized. However, the confidence intervals were wide and overlapping for all of the results, and the inconsistency may indicate generally null results, but instability in the model. In a separate European cohort, Bentayeb et al. (2015) used the CHIMERE chemical transport model to estimate PM_{10} and $PM_{2.5}$, and then subtracted to estimate long-term $PM_{10-2.5}$ exposure. The authors observed positive association with total (nonaccidental), cardiovascular, and respiratory mortality, though the association with total (nonaccidental) mortality was attenuated in copollutant models with $PM_{2.5}$. The associations with cardiovascular and respiratory mortality were not evaluated in copollutant models.

Recent studies are characterized in Table 11-11. While there are more studies available in this review that examine the association between long-term $PM_{10-2.5}$ exposure and mortality, the body of evidence remains limited. In addition, to date all of the studies that have examined the relationship between long-term $PM_{10-2.5}$ exposure and mortality have used the difference method to derive concentrations for $PM_{10-2.5}$, contributing to the uncertainty associated with these effect estimates. Overall, there is no consistent pattern of associations for total, cardiovascular, or respiratory mortality. In the instances where positive associations were observed for long-term $PM_{10-2.5}$ exposure and mortality, and $PM_{2.5}$ copollutant model results were reported, the $PM_{10-2.5}$ effect estimates were often attenuated but still positive after adjusting for $PM_{2.5}$.

Table 11-11 Epidemiologic studies of long-term exposure to $PM_{10-2.5}$ and mortality.

Study	Cohort Location	Mean $PM_{10-2.5}$ µg/m³	Exposure assessment	Single Pollutant Hazard Ratio[a] 95% CI	Copollutant Examination
McDonnell et al. (2000)	AHSMOG (U.S.)	27.3	ZIP code average Subtraction method	Total (men): 1.03 (0.96, 1.10) Resp (men): 1.09 (0.94, 1.28) Lung Cancer (men): 1.12 (0.79, 1.60)	Correlation (*r*): NA Copollutant models with: $PM_{2.5}$: Total (men): 0.99 (0.91, 1.08) $PM_{2.5}$: Resp (men): 1.03 (0.86, 1.24)
Chen et al. (2005)	AHSMOG (U.S.)	25.4	ZIP code average Subtraction method	CHD (men): 0.96 (0.81, 1.14) CHD (women): 1.17 (0.98, 1.40)	Correlation (*r*): NA Copollutant models with: NA
Lipfert et al. (2006)	Veterans (U.S.)	16	County average Subtraction method	Total (men): 1.03 (1.01, 1.05)	Correlation (*r*): NA Copollutant models with: NA
†Puett et al. (2009)	Nurses' Health (U.S.)	7.7	Spatio-temporal models Subtraction method	Total (women): 1.01 (0.94, 1.09) CHD (women): 1.07 (0.85, 1.33)	Correlation (*r*): NA Copollutant models with: $PM_{2.5}$: Total (women): 0.98 (0.91, 1.06) $PM_{2.5}$: CHD (women): 0.95 (0.75, 1.22)
†Puett et al. (2011)	Health Professionals (U.S.)	10.1	Spatio-temporal models Subtraction method	Total (men): 0.95 (0.89, 1.03) CHD (men): 1.03 (0.90, 1.18)	Correlation (*r*): NA Copollutant models with: $PM_{2.5}$: Total (men): 0.98 (0.90, 1.06) $PM_{2.5}$: CHD (men): 1.05 (0.90, 1.22)

Table 11-11 (Continued): Epidemiologic studies of long-term exposure to $PM_{10-2.5}$ and mortality.

Study	Cohort Location	Mean $PM_{10-2.5}$ µg/m³	Exposure assessment	Single Pollutant Hazard Ratio[a] 95% CI	Copollutant Examination
†Beelen et al. (2014a)	ESCAPE (Europe)	4.0−20.7	LUR models Subtraction method	Total: 1.04 (0.98, 1.10)	Correlation (*r*): NA Copollutant models with: $PM_{2.5}$: Total: 1.01 (0.92, 1.11)
†Beelen et al. (2014b)	ESCAPE (Europe)	4.0−20.7	LUR models Subtraction method	CVD: 1.02 (0.91, 1.13) IHD: 0.92 (0.77, 1.11) MI: 0.88 (0.71, 1.10) CBVD: 1.17 (0.90, 1.52)	Correlation (*r*): NA Copollutant models with: NA
†Dimakopoulou et al. (2014)	ESCAPE (Europe)	4.0−20.7	LUR models Subtraction method	Resp: 0.95 (0.76, 1.14)	Correlation (*r*): NA Copollutant models with: NA
†Dehbi et al. (2016)	2 British Cohorts	6.4	Same exposure as ESCAPE	CVD: 0.94 (0.56, 1.60)	Correlation (*r*): NA Copollutant models with: NA
†Bentayeb et al. (2015)	Gazel (France)	8.0	CHIMERE chemical transport model Subtraction Method	Total: 1.22 (1.09, 1.37) CVD: 1.32 (0.89, 1.91) Resp: 1.27 (0.96, 1.72)	Correlation (*r*): NA Copollutant models with: $PM_{2.5}$: Total: 1.07 (0.85, 1.37)

[a]Hazard Ratio of mortality per 5 µg/m³ change in $PM_{10-2.5}$.

†Studies published since the 2009 PM ISA.

11.4.3 Summary and Causality Determination

Since the completion of the 2009 PM ISA a number of recent cohort studies conducted primarily in the U.S. and Europe provide no consistent evidence for positive associations between long-term $PM_{10-2.5}$ exposure and total (nonaccidental) mortality. In addition to the inconsistent results, all of the studies use the difference of PM_{10} and $PM_{2.5}$ (measured at monitors or estimated from models) to estimate $PM_{10-2.5}$, which continues to be a main uncertainty in the positive associations that are observed in some cohorts and further support that the evidence is suggestive of, but not sufficient to infer, a causal relationship. An additional uncertainty is related to potential copollutant confounding; positive associations observed in the Nurses' Health Study (Puett et al., 2009), AHSMOG (McDonnell et al., 2000) and ESCAPE (Beelen et al., 2014a) cohorts were attenuated to the null when $PM_{2.5}$ was included in the model. The strongest evidence for total mortality comes from the GAZEL cohort (Bentayeb et al., 2015) in France; the authors observed a 22% increase in total mortality associated with increases in $PM_{10-2.5}$. This association remained positive in copollutant models with $PM_{2.5}$, but was attenuated and less precise. There is limited information on biological plausibility and limited coherence across scientific disciplines (i.e., animal toxicological, controlled human exposure studies, and epidemiologic) for cardiovascular (Chapter 6) and respiratory (Chapter 5) morbidity and metabolic disease (Chapter 7). This section describes the evaluation of evidence for total (nonaccidental) mortality, with respect to the causality determination for long-term exposures to $PM_{10-2.5}$ using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015b). The key evidence, as it relates to the causal framework, is summarized in Table 11-12.

Overall, recent epidemiologic studies provide inconsistent evidence for positive associations between long-term $PM_{10-2.5}$ exposure and total (nonaccidental) mortality. A positive association between long-term $PM_{10-2.5}$ exposure and total mortality, which remained positive in copollutant models with $PM_{2.5}$ (Bentayeb et al., 2015), provides the strongest evidence for this relationship. However, there remains a large degree of uncertainty due to the various approaches used to measure $PM_{10-2.5}$ concentrations (see Chapter 3). The lack of information on the spatial and temporal correlation between the various measurement approaches reduces the confidence in the associations observed across studies. Additionally, the evidence from the assessment of long-term $PM_{10-2.5}$ exposures and cardiovascular and respiratory morbidity and metabolic disease provide limited biological plausibility for $PM_{10-2.5}$-related mortality. Although recent studies attempt to address previously identified uncertainties and limitations in the $PM_{10-2.5}$-mortality relationship, the overall assessment of potential copollutant confounding remains limited. **Collectively, this body of evidence is suggestive of, but not sufficient to infer, a causal relationship between long-term $PM_{10-2.5}$ exposure and total mortality.**

Table 11-12 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between long-term $PM_{10-2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Evidence from multiple epidemiologic studies is generally supportive but not entirely consistent	Positive associations from several cohort studies, but not a consistent pattern of associations for total mortality	Table 11-11	Mean concentrations across cities: 4.0−27.3 μg/m^3
Uncertainty regarding epidemiologic evidence from copollutant models to support and independent $PM_{10-2.5}$ association	$PM_{10-2.5}$ effect estimates often attenuated after adjustment for $PM_{2.5}$	Section 11.3.2	
Uncertainty regarding exposure measurement error	Across studies, $PM_{10-2.5}$ concentrations are measured using a number of approaches (i.e., directly measured from dichotomous sampler, difference between PM_{10} and $PM_{2.5}$ concentrations measured at collocated monitors, and difference of area-wide concentrations of PM_{10} and $PM_{2.5}$), which have not been compared in terms of whether they have similar spatial and temporal correlations	Table 11-11 Section 3.3.1.1	
Biological plausibility from studies of cardiovascular morbidity	Expanded body of evidence provides some evidence for associations between long-term $PM_{10-2.5}$ exposure and IHD and stroke	Section 6.5.2 and Section 6.5.5	Mean (across studies): 7.3−31.0 μg/m^3

$PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm and greater than a nominal diameter of 2.5 μm.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to the causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the $PM_{10-2.5}$ concentrations with which the evidence is substantiated.

11.5 Short-Term UFP Exposure and Total Mortality

The 2009 PM ISA concluded that the "epidemiologic evidence is inadequate to infer a causal relationship between short-term UFP exposure and mortality" (U.S. EPA, 2009). In both the 2004 PM

AQCD and the 2009 PM ISA a few studies examined the association between short-term UFP exposure and mortality with all of the studies being conducted in Europe. Across studies there was inconsistency in the lag structure of associations, which was not consistent with the lag structure observed for other PM size fractions, and the interpretation of the evidence was further complicated by the correlation between UFPs and gaseous copollutants, specifically from combustion sources. Additionally, at the completion of the 2009 PM ISA inherent limitations across all UFP epidemiologic studies was evident and also applicable to the mortality studies. Specifically, it was noted that there is a relatively limited amount of monitoring data within the U.S. that is reflected by no U.S. based studies focusing on short-term UFP exposure and mortality; limited information on the spatial and temporal variability in UFP concentrations; and limited data on the spatial and temporal evolution of UFP size distributions along with data on the composition of UFPs (U.S. EPA, 2009).

Within this ISA, the evaluation of the relationship between short-term exposure to $PM_{2.5}$ and $PM_{10–2.5}$ and mortality focuses on studies that further characterize the relationship, or addresses uncertainties and limitations in the evidence, respectively (Section 11.2.1 and Section 11.3.1). For UFPs, the literature base for all health effects, not just mortality, is much smaller than that for the other PM size fractions. An overall limitation in the health evidence that has complicated the interpretation of results across studies, both those evaluated in the 2009 PM ISA and recent studies that specifically examined associations between short-term UFP exposure and mortality, is the different exposure metrics used (i.e., number concentration [NC], mass concentration [MC], surface area concentration [SC]). As detailed in the Preface, the evaluation of the evidence for UFPs relies on studies that examine MC and SC for particles < 0.3 μm and NC any size range that includes particles <0.1 μm (see Preface).

As detailed in Section 11.1.2, within this section the discussion will focus on the evaluation of multicity studies, but a stronger reliance on large single-city studies due to most UFP and mortality studies to date occurring in individual cities. Additionally, compared to studies that examined short-term exposure to $PM_{2.5}$ and $PM_{10–2.5}$ and mortality, most recent studies of UFPs have not focused on total (nonaccidental) mortality, but instead on cause-specific mortality. As such, cause-specific mortality studies will be discussed in more detail within this section compared to the sections on $PM_{2.5}$ and $PM_{10–2.5}$. The multicity and single-city studies discussed throughout this section, along with study-specific details, air quality characteristics, including size fraction and exposure metric, and the location of UFP monitor(s) is detailed in Table 11-13.

Table 11-13 Study-specific details and UFP concentrations from studies in the 2009 PM ISA and recent studies.

Study/Location/Years/ Mortality Outcome(s)	UFP Metric/Size Range	Mean	Upper Percentiles	Location of UFP Monitor(s)	Copollutant Examination	Results
Breitner et al. (2009) Erfurt, Germany 1991–2002[a] Total	NC (cm^{-3}) 10–100 nm[b]	12,910	---	One monitor 1 km south of city center and 40 m from nearest major road[c]	Correlation (*r*): 0.62 NO_2, 0.51 CO, 0.57 PM_{10}, 0.48 $PM_{2.5}$ Copollutant models examined with: NO_2, CO, PM_{10}, $PM_{2.5}$	% Increase (95% CI) (per 8,439 cm^{-3}) 9/1995–2/1998: 5.5 (1.1, 10.5); lag 0–5 3/1998–3/2002: −1.1 (−6.8, 4.9); lag 0−5
Stölzel et al. (2007) Erfurt, Germany 1995–2001 Total cardio-respiratory	NC (cm^{-3}): 10–30 nm 30–50 nm 50–100 nm 10–100[d] nm	NC 10–30 nm: 9,016 30–50 nm: 2,801 50–100 nm: 1,731 10–100 nm: 13,491	NC: 10–30 nm 75th: 11,574 95th: 21,327 30–50 nm 75th: 3,502 95th: 6,870 50–100 nm 75th: 2,147 95th: 4,202 10–100 nm 75th: 17,030 95th: 31,253	One monitor 1 km south of city center and 40 m from nearest major road	Correlation (*r*)[e]: (Across NC size fractions) 0.60–0.61 NO_2 0.52–0.67 NO 0.50–0.62 CO 0.48–0.74 PM_{10} Copollutant models examined with: NO_2, NO, CO	% Increase (95% CI) (per 9,748 cm^{-3}) Total: 2.9 (0.3, 5.5); lag 4 Cardio-respiratory: 3.1 (0.3, 6.0); lag 4

Table 11-13 (Continued): Study-specific details and UFP concentrations from studies in the 2009 PM ISA and recent studies.

Study/Location/Years/ Mortality Outcome(s)	UFP Metric/Size Range	Mean	Upper Percentiles	Location of UFP Monitor(s)	Copollutant Examination	Results
Kettunen et al. (2007) Helsinki, Finland 1998–2004 Stroke	NC (cm^{-3}) <100 nm	Cold: 8,986[f] Warm: 7,587[f]	Cold: 75th: 13,970 Max: 52,800 Warm: 75th: 11,100 Max: 23,070	1998–2001: One monitor on 20 m high peninsular a few hundred meters from urban areas 3/2001–2004: hilltop 3 km from original site, 4th floor of office building, 100 m from major highway	Correlation (*r*): Cold 0.37 $PM_{2.5}$ 0.33 PM_{10} 0.18 $PM_{10-2.5}$ 0.47 CO −0.10 O_3 0.68 NO_2 Warm 0.30 $PM_{2.5}$ 0.44 PM_{10} 0.47 $PM_{10-2.5}$ 0.39 CO 0.03 O_3 0.61 NO_2 Copollutant models examined with: NR	% Increase (95% CI) (per 4,979 cm^{-3}) 8.5 (−1.2, 19.1); lag 1
†Lanzinger et al. (2016)g Five Central European cities (UFIREG) 2011–2014 Total cardiovascular respiratory	NC (cm^{3-}) 20–100 nm 20–800 nm[h]	20–100 nm: 4,197–5,880 20–800 nm: 5,799–7,775	Max: 20–100 nm: 13,920–28,800 20–800 nm: 16,710–29,470	One urban or suburban back-ground site in each city with no heavy traffic roads in immediate vicinity	Correlation (*r*): 20–100 nm: 0.26–0.54 NO_2 0.29–0.43 PM_{10} 0.40–0.51 $PM_{10-2.5}$ 0.25–0.37 $PM_{2.5}$ 20–800 nm: 0.45–0.62 NO_2 0.54–0.59 PM_{10} 0.45–0.58 $PM_{10-2.5}$ 0.49–0.50 $PM_{2.5}$ Copollutant models examined with: NR	% Increase (95% CI) (20−100 nm: per 2,750 cm^{-3} 20−800 nm: 3,675 cm^{-3}) Total: 20−100 nm 0.1 (−2.0, 2.4); lag 0−1 20−800 nm −0.2 (−2.4, 2.1); lag 0−1 Cardiovascular: 20−100 nm −0.2 (−5.5, 5.4); lag 0−5 20–800 nm −0.1 (−5.5, 5.6); lag 2−5 Respiratory: 20−100 nm 9.9 (−6.3, 28.8); lag 0−5 20−800 nm 5.8 (−6.4, 19.7); lag 2−5

Table 11-13 (Continued): Study-specific details and UFP concentrations from studies in the 2009 PM ISA and recent studies.

Study/Location/Years/ Mortality Outcome(s)	UFP Metric/Size Range	Mean	Upper Percentiles	Location of UFP Monitor(s)	Copollutant Examination	Results
†Stafoggia et al. (2017)[i] Eight European cities 1999–2013[i] Total cardiovascular respiratory	NC (cm^{-3})[j] 4–3,000 nm	5,105–34,046	75th: 6,382–44,208 95th: 9,998–73,044	One urban or suburban background site, except for Rome, which was oriented near traffic sources	Correlation (*r*): 0.13 0.51 PM_{10}, 0.07–0.56 $PM_{2.5}$, 0.09–0.41 $PM_{10-2.5}$, 0.28–0.69 NO_2, 0.07–0.67 CO, −0.52–0.19 O_3 Copollutant models examined with: PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, NO_2, CO, O_3	% Increase (95% CI) (per 10,000 cm^{-3}) Total: 0.35 (−0.05, 0.75); lag 6 (Quantitative results not presented for cardiovascular and respiratory mortality.)
†Samoli et al. (2016) London, U.K. 2011–2012 Total cardiovascular respiratory	NC (cm^{-3})[k] Total: <3,000 nm Source specific: <600 nm	Total: 12,123[f] Urban background: 1,893[f] Nucleation: 279[f] Secondary: 104[f] Traffic: 2,355[f]	90th: Total: 17,901 Urban background: 4,442 Nucleation: 991 Secondary: 622 Traffic: 3,950	One urban background site	Correlation (*r*): NR Copollutant models examined with: NR	% Increase (95% CI) (per 5,180 cm^{-3}) <3,000 nm Total: −0.06 (−1.16, 1.06); lag 1 Cardiovascular: −2.04 (−3.94, −0.10); lag 1 Respiratory: −1.86 (−4.50, 0.86); lag 2

Table 11-13 (Continued): Study-specific details and UFP concentrations from studies in the 2009 PM ISA and recent studies.

Study/Location/Years/ Mortality Outcome(s)	UFP Metric/Size Range	Mean	Upper Percentiles	Location of UFP Monitor(s)	Copollutant Examination	Results
†Breitner et al. (2011) Beijing, China 3/2004–8/2005 Cardiovascular ischemic heart disease cerebrovascular	NC (cm^{-3}) <30 nm 30–100 nm <800 nm SC (μm^2 cm^{-3}) 0.1–0.3 µm MC ($\mu g/m^3$) 0.1–0.3 µm	NC[f] <30 nm: 10,430 30–100 nm: 13,260 <800 nm: 33,500 SC[f] 0.1–0.3 µm: 567.0 MC[f] 0.1–0.3 µm: 27.8	NC <30 nm: 75th: 17,120 Max: 61,930 30–100 nm: 75th: 16,380 Max: 31,080 <800 nm: 75th: 40,690 Max: 86,820 SC 0.1–0.3 µm: 75th: 819.6 Max: 2,076.0 MC 0.1–0.3 µm: 75th: 40.2 Max: 105.1	One urban back-ground site a few hundred meters from a major road	Correlation (*r*): NR Copollutant models examined with: NR	% Increase (95% CI) Cardiovascular: NC; lag 0−4 <30 nm (per 7,448 cm^{-3}) 2.13 (−1.80, 6.22) 30−100 nm (per 4,150 cm^{-3}) 2.99 (−0.66, 6.77) <800 nm (per 12,060 cm^{-3}) 4.19 (−0.76, 9.37) SC; lag 0−4 0.1−0.3 µm (per 265.9 μm^2 cm^{-3}) 0.24 (−2.72, 3.29) MC; lag 0−4 0.1−0.3 µm (per 14.0 $\mu g/m^3$) 0.13 (−2.87, 3.23)

Table 11-13 (Continued): Study-specific details and UFP concentrations from studies in the 2009 PM ISA and recent studies.

Study/Location/Years/ Mortality Outcome(s)	UFP Metric/Size Range	Mean	Upper Percentiles	Location of UFP Monitor(s)	Copollutant Examination	Results
†Leitte et al. (2012) Beijing, China 3/2004–8/2005 Respiratory	NC (cm^{-3}) 3–10 nm 10–30 nm 30–50 nm 50−100 nm 3–100 nm 3−1,000 nm	3–10 nm: 4,700 10–30 nm: 8,600 30–50 nm: 5,700 50−100 nm: 7,700 3–100 nm: 27,000 3−1,000 nm: 34,000	95th: 3–10 nm: 11,000 10–30 nm: 14,000 30–50 nm: 8,200 50−100 nm: 11,400 3–100 nm: 39,000 3−1,000 nm: 46,000	One urban background site, 20 m above ground, and 500 m from major road	Correlation (*r*): Across NC size fractions −0.23–0.60 PM_{10}, −0.06–0.51 SO_2, −0.33–0.69 NO_2 Copollutant models examined with: PM_{10}, SO_2, NO_2	% Increase (95% CI); lag 0−4 3−10 nm (per 5,300 cm^{-3}) 4.6 (−5.4, 15.6) 10−30 nm (per 5,300 cm3−) 3.5 (−8.5, 17.1) 30−50 nm (per 2,700 cm^{-3}) −1.7 (−11.7, 9.4) 50−100 nm (per 3,800 cm^{-3}) 1.8 (−8.0, 12.7) 3−100 nm (13,000 cm^{-3}) 3.9 (−7.3, 16.4) 3−1,000 nm (per 14,000 cm^{-3}) 8.9 (−3.8, 16.4)

MC = mass concentration; NC = number concentration; SC = surface area concentration.

[a]Study period 1 October 1991 through 31 March 2002.

[b]Also examined associations with NC 0.01–0.03 µm, 0.03–0.05 µm, and 0.05–0.1 µm.

[c]Particle size distribution measured winter 1991-1992 and 1995 onward, UFP measurements imputed for missing time periods.

[d]Missing data imputed.

[e]Correlations reported only for other NAAQS pollutants.

[f]Median concentration.

[g]PM only measured in four of the five cities.

[h]For one city the range was 0.02–0.5 µm.

[i]Only three cities explicitly measured particles in the ultrafine range (i.e., <100 nm), and each city had to have at least 3 years of continuous data.

[j]NC used as a proxy for UFPs because only three cities explicitly measured UFPs.

[k]Monitor used for total NC had upper size limit of 3 µm while the monitor used for the source apportionment NC collection had an upper size limit of 0.6 µm.

†Studies published since the 2009 PM ISA.

11.5.1 Biological Plausibility for Short-Term UFP Exposure and Total Mortality

The preceding chapters characterized evidence related to evaluating (to the extent possible) the biological plausibility by which short-term UFP exposure may lead to the morbidity effects that are the largest contributors to total (nonaccidental) mortality, specifically cardiovascular and respiratory morbidity (Section 6.5.1 and Section 5.5.1, respectively). This evidence is derived from animal toxicological, controlled human exposure, and epidemiologic studies. Section 6.5.1 outlines the available evidence for plausible mechanisms by which inhalation exposure to UFP could result in cardiovascular effects. Similarly, Section 5.5.1 characterizes the available evidence by which inhalation exposure to UFP could progress from initial events to endpoints relevant to the respiratory system. While there is some evidence for initial events, including injury, inflammation and oxidative stress, the evidence for how these initial events could lead to the subsequent endpoints, and eventually increases in respiratory emergency department (ED) visits and hospital admissions is limited. Collectively, there is limited available evidence for cardiovascular and respiratory morbidity supporting potential biological pathways by which short-term UFP exposures could result in mortality.

11.5.2 Associations Between Short-Term UFP Exposure and Total Mortality in Multicity Studies

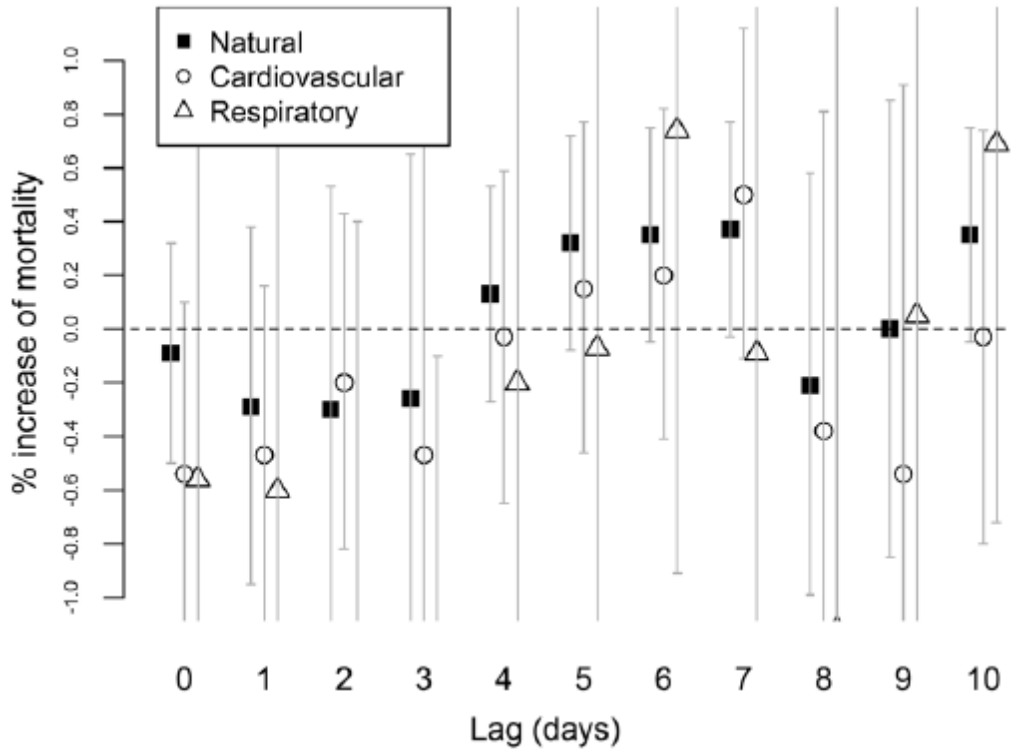
The majority of recent studies examining the association between short-term UFP exposure and mortality have primarily been conducted in individual cities. Lanzinger et al. (2016) and Stafoggia et al. (2017) represent the initial multicity studies that examine the relationship between short-term UFP exposure and mortality. Lanzinger et al. (2016) in the UFIREG project (Ultrafine particles—an evidence based contribution to the development of regional and European environmental and health policy) focused on examining short-term UFP exposure and mortality in five cities in Central and Eastern Europe, but was limited to approximately 2 years of data in each city. Stafoggia et al. (2017) examined short-term UFP exposure and mortality in a study that consisted of eight European cities mostly in Western Europe with at least 3 years of data in each city. Within Lanzinger et al. (2016) the UFP fraction was divided into two distinct metrics, and referred to as UFPs where NC was estimated for sizes ranging from 20 to 100 nm and a NC specific metric that included sizes ranging from 20 to 800 nm with one city having a smaller range of 20 to 500 nm. This approach differed from Stafoggia et al. (2017) where across cities only three explicitly measured particles within the traditional ultrafine range of <100 nm; as a result, NC was used as a proxy for UFPs in each city.

In a time-stratified case-crossover analysis, Lanzinger et al. (2016) examined immediate (lag 0−1), delayed (lag 2−5), and prolonged (lag 0−5) effects of UFP and NC exposure on mortality. Across all of the lags examined for UFP and NC, the authors observed no evidence of an association for total

(nonaccidental) or cardiovascular mortality. Lanzinger et al. (2016) reported a positive, but imprecise, association with respiratory mortality for UFP and NC across all lags with the association largest in magnitude for UFP at lag 0−5 (9.9% [95% CI: −6.3, 28.8] per 2,750 $cm^{-3}$and NC at lag 2−5 (5.8% [95% CI: −6.4, 19.7] per 3,675 cm^{-3}). No evidence of an association was observed with respiratory mortality and the other PM size fractions examined. Although some sensitivity analyses focusing on model specification were conducted based on the UFP—respiratory mortality association, the wide confidence intervals complicate the interpretation of these analyses.

While Lanzinger et al. (2016) focused on examining the lag structure of associations across different multiday lags, Stafoggia et al. (2017) focused on examining whether there was evidence of an association between short-term UFP exposure and mortality across a range of single-day lags (i.e., 0 to 10 days). Across the single-lag days examined, the authors reported evidence of positive associations with total (nonaccidental) mortality at lags 5 through 7 ranging from 0.32−0.37%, with associations largest in magnitude for respiratory (lag 6) and cardiovascular (lag 7) mortality also within this range, although there were wide confidence intervals (Figure 11-30). Subsequent copollutant and sensitivity analyses focused specifically on associations reported for lag 6, where single-pollutant models resulted in a 0.35% increase in total (nonaccidental) mortality (95% CI: −0.05, 0.75) for a 10,000 particle/cm^3 increase in 24-hour average NC.

The results from copollutant analyses indicate that associations with total (nonaccidental) mortality are relatively unchanged in models with CO (0.30%) and O_3 (0.27%), while there was some evidence of an attenuation in models with PM_{10} (0.22%). The authors reported no evidence of an association with NC in copollutant models with $PM_{2.5}$, $PM_{10-2.5}$, and NO_2, providing some evidence of potential confounding. Complicating the overall interpretation of results from Stafoggia et al. (2017) is that further analysis of the pooled results across cities identified that the positive association observed at lag 6 was largely driven by the city of Rome. As a result, when excluding Rome from the meta-analysis there was no evidence of an association between short-term NC exposure and total (nonaccidental) mortality.



Note: Natural = total (nonaccidental) mortality.
Source: Permission pending, Stafoggia et al. (2017).

Figure 11-30 Percent increase in total (nonaccidental), cardiovascular, and respiratory mortality across eight European cities for a 10,000 particle/cm^3 increase in 24-hour average number concentration (NC) across lags 0 to 10 days.

11.5.3 Associations Between Short-Term UFP Exposure and Total Mortality in Single-City Studies

Recent single-city studies all examined a number of different size fractions of particles within the ultrafine range along with exposure metrics, as detailed in Table 11-13. In many cases the size fractions examined are a reflection of the monitor used. For example, some monitors that measure NC result in a larger size distribution being measured than others (Section 2.4.3). As a result, the NC metric is considered a proxy for UFP exposure due to the potential for particles larger than the traditional 100 nm cutoff for UFPs being included in the measurement (Section 2.4.3.1). Overall, the inconsistency in the size fractions examined across studies complicates the interpretation of results, but collectively can inform if there is evidence of a relationship between short-term UFP exposure and mortality.

The single-city studies conducted to date that examined short-term UFP exposure and mortality are limited to Europe and Asia. Samoli et al. (2016) in a study conducted in London, U.K. used a

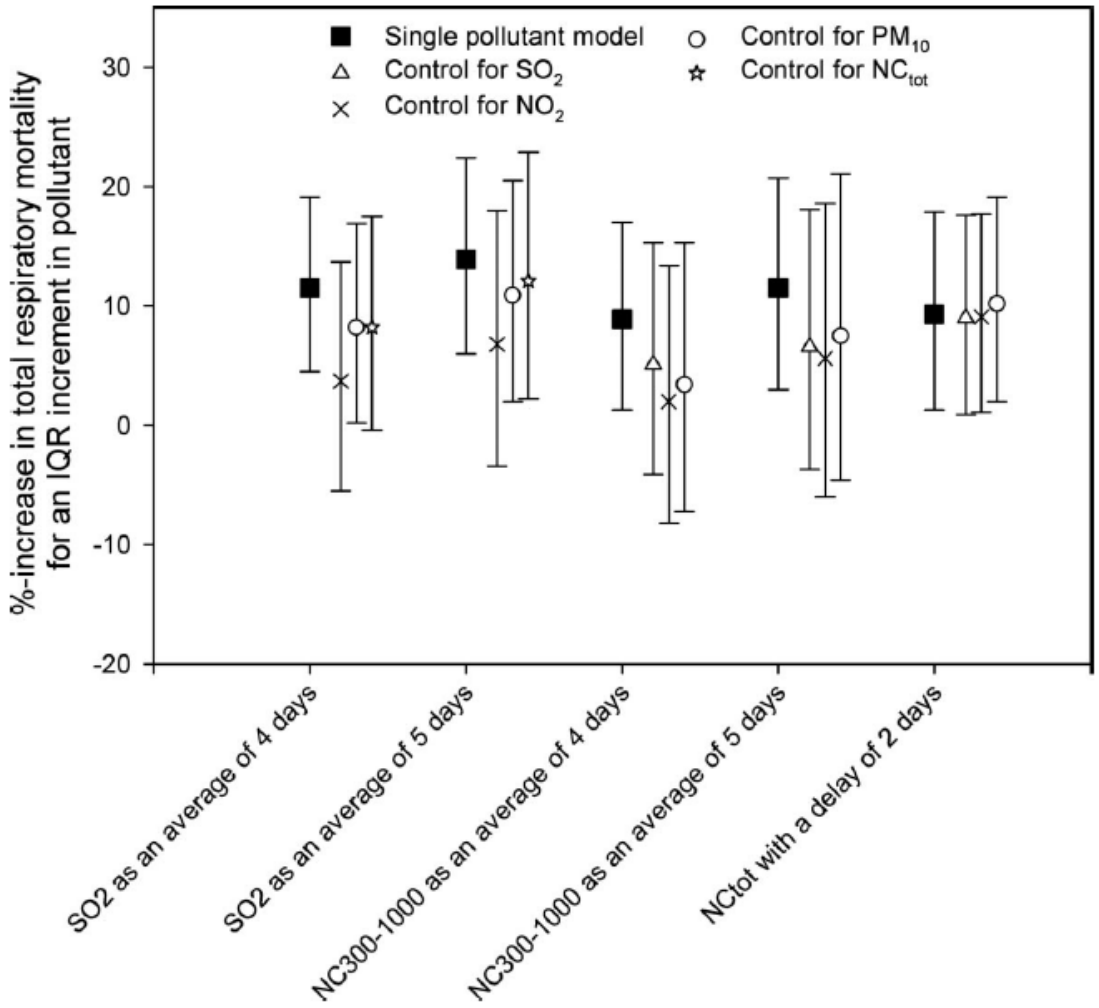
traditional source apportionment method (i.e., positive matrix factorization) to identify UFP sources based on NC data. The source apportionment analyses identified four sources each with a different peak in the size distribution: urban background (30 nm), nucleation (70 nm), secondary (20 nm), and traffic (250 nm). In analyses focusing on total (nonaccidental) and cardiovascular mortality at lag 1 and respiratory mortality at lag 2, the authors reported no evidence of an association with total NC. When examining source-specific NC, a small positive association was observed for total (nonaccidental) mortality and nucleation and traffic sources (~0.20% increase), but confidence intervals are wide. There was no evidence of an association with any NC sources and cardiovascular mortality with evidence of a positive association between respiratory mortality and only the urban background source (1.4% increase [95% CI: −0.97, 3.89] for a 1,806 number/cm^3 increase). When measuring NC, although a large percentage of particles are <0.1 µm (see Section 2.4.3.1), the authors used two different types of monitors with different size ranges for the NC and source-specific NC analysis, resulting in some degree of uncertainty when comparing the NC and source-specific NC results.

The single-city studies conducted in China systematically examined various UFP size fractions and exposure metrics. Breitner et al. (2011) and Leitte et al. (2012) were both conducted in Beijing, China over the same study duration, but focused on different UFP size fractions and metrics as well as mortality outcomes. Both Breitner et al. (2011) and Leitte et al. (2012) examined some particle size ranges that are outside the scope of the UFP - mortality evaluation and are detailed in Section 11.1.9. Breitner et al. (2011) in a study focusing on cardiovascular-related mortality, in addition to focusing on NC, converted NC to SC, assuming spherical particles with constant density, and MC, assuming a density of 1.5 g/cm^3. For cardiovascular mortality, the authors observed positive associations, but with wide confidence intervals for all NC metrics at lag 0-4 days (see Table 11-13). Positive, but uncertain, associations were also observed for $SC_{0.1\text{-}0.3}$ and $MC_{0.1\text{-}0.3}$ at lag 0−4 days ($SC_{0.1–0.3}$: 0.24% [95% CI: −2.72, 3.29] per IQR [265.9 µ$m^2cm^{3–}$]; $MC_{0.1–0.3}$: 0.13% [95% CI: −2.87, 3.23] per IQR [14.0 µg/m^3]). When comparing the multiday lag results to single-day lags, there was variability in the magnitude and direction of the association across single-day lags across metrics, while the multiday average lag was consistently positive. A similar pattern of associations was observed for ischemic heart disease mortality. Copollutant models focused only on the Aitken mode particles and NC_1 at lag 2. Across the copollutant models, when including the other size fractions examined in the model ranging up to 1 µm, both Aitken mode particles (0.03−0.1 µm) and NC1 (<0.8 µm) associations were robust. Breitner et al. (2011) also examined whether the UFP associations were modified by specific types of air masses identified through cluster analysis. The authors did not observe any evidence that air mass origin modified NC associations, however, mortality associations at lag 2 for the SC and MC metrics were stronger for air masses representative of stagnant air masses and air masses originating from Southern China.

Unlike Breitner et al. (2011), Leitte et al. (2012) only focused on NC metrics and respiratory mortality. Across the different UFP size fractions, the authors reported consistent positive associations between respiratory mortality and NC for all particle fractions between 3 nm and 1 µm at lag 2, but confidence intervals were wide. Focusing on lag 0−3 days, the strongest association was observed for

NC_{total}, which was defined as particles ranging in size from 3 nm−1 µm where Leitte et al. (2012) reported an 8.9% (95%CI: −3.8, 23.3%) increase in respiratory mortality per IQR increase (14,000 cm^{3-}). In comparison, for UFP, which was defined as particles ranging in size from 3−100 nm, the authors observed a 3.9% (95%CI: −7.3, 16.4%) increase per IQR increase (13,000 cm^{3-}). When comparing the results from single-day lags to multiday averages (i.e., 0−4 and 0−5 days), the magnitude of the association between all of the size fractions, except the 30−50 nm size fraction, and respiratory mortality were larger in magnitude, but the confidence intervals were also larger compared to the single-day lag estimates. Whereas Breitner et al. (2011) only focused on copollutant models with other UFP size fractions, Leitte et al. (2012) examined gaseous pollutants, for NC_{total} and found associations remained relatively unchanged in models with NO_2 and SO_2 (Figure 11-31).

Leitte et al. (2012) also examined potential modification of the respiratory mortality and UFP relationship by different air masses, focusing on the NC_{total} fraction, and similar to the cardiovascular mortality results in Breitner et al. (2011) observed some evidence that particularly stagnant air masses as well as air masses originating from some areas of China may modify the NC_{total} association.



Source: Permission pending, Leitte et al. (2012).

Figure 11-31 Association between short-term number concentration (NC)300−1,000 and NC_{total} exposure in single and copollutant models and respiratory mortality in Beijing, China.

11.5.4 Summary and Causality Determination

Compared to the examination of other PM size fractions, a smaller number of studies have examined the association between short-term UFP exposure and total (nonaccidental) mortality. At the completion of the 2009 PM ISA, the overall body of evidence was limited and based on a few single-city studies that provided some evidence of positive associations, but at lags longer than those observed for other PM size fractions. Recent evidence from both multi- and single-city studies provides additional insight on the relationship between short-term UFP exposure and mortality, but the uncertainties and limitations in the evidence identified in the 2009 PM ISA remain, including, but not limited to: the metric

to examine UFP exposures (i.e., NC, SC, or MC); the size range to consider when examining UFP exposures; exposure measurement error due to the spatial and temporal variability in UFPs; and the correlation between UFPs and gaseous pollutants, which collectively continue to support that the evidence is inadequate to infer a causal relationship. Although there is evidence of positive associations for NC for different size fractions in a few studies, confidence intervals are often wide, and studies did not monitor and, subsequently examine, the same UFP size fractions complicating the interpretation of results across studies. Additionally, there is limited and inconsistent cardiovascular (Chapter 6) and respiratory (Chapter 5) morbidity evidence to provide biological plausibility to support the positive associations observed in some studies for total mortality. This section describes the evaluation of evidence for total (nonaccidental) mortality, with respect to the causality determination for short-term exposures to UFPs using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015b). The key evidence, as it relates to the causal framework, is summarized in Table 11-14.

Recent multi- and single-city studies that examined the association between short-term UFP exposure and total (nonaccidental) mortality provide inconsistent evidence of a positive association, which is further supported by studies that examined cardiovascular and respiratory mortality. The evaluation of the evidence from recent studies is complicated by the different UFP size fractions examined and exposure metrics used (i.e., NC, SC, and MC). Across studies, the majority primarily examined UFP associations using the NC metric, but the range of size fractions examined varied preventing a complete comparison of the pattern of associations across studies. Of the few studies that examined copollutant confounding, the focus was on examining associations with NC. In the assessment of copollutant confounding, the NC size fractions examined varied from focusing on a specific size fraction range (e.g., 0.03−0.1 μm) to total NC. The copollutant model results provided evidence that the NC associations were both robust and sensitive to adjustment depending on the PM size fraction and gaseous pollutant included in the model.

Across epidemiologic studies that examined short-term UFP exposure and mortality, an inherent limitation is the use of primarily one monitoring site to estimate exposure, which potentially contributes to exposure measurement error. The potential for exposure measurement error is reflected in the limited number of studies demonstrating greater spatial variability in UFP concentrations (i.e., NC) as well as changes in the particle size distribution at increasing distances from sources (Section 2.5.1.1.5, Section 2.5.1.2.4, Section 3.4.5) There is also limited information on the temporal variability in UFP concentrations (i.e., NC) over an urban area (Section 2.5.2.2.3).

Table 11-14 Summary of evidence that is inadequate to infer the presence or absence of a causal relationship between short-term UFP exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	UFP Concentrations Associated with Effects[c]
Inconsistent epidemiologic evidence from a limited number of studies at relevant UFP concentrations	Some evidence of positive, but imprecise, increases in mortality in multicity and single-city studies conducted in Europe and Asia, with no studies conducted in the U.S. Limited evidence of positive associations for cardiovascular and respiratory mortality in multi- and single-city studies conducted in Europe, and Asia, with no studies conducted in the U.S.	Section 11.5.2 Section 11.5.3 Table 11-13 Section 5.5.8 Section 6.5.8	24−h avg: NC: Variability in UFP size ranges examined prevents providing a range. SC (μm^2 cm^{-3}) 0.1–0.3 µm: 567.0 MC ($\mu g/m^3$) 0.1–0.3 µm: 27.8
Limited epidemiologic evidence from copollutant models for an independent UFP association	Some evidence that UFP associations using the NC metric are relatively unchanged with CO and O_3 and other NC size ranges, but potentially attenuated with $PM_{2.5}$, $PM_{10-2.5}$, and NO_2.	Section 11.5.2 Section 11.5.3	
Uncertainty regarding exposure metric and UFP size fraction	Inconsistency in the UFP metric used (i.e., NC, SC, and MC) and UFP size fraction examined complicating interpretation of results across studies.	Section 11.4.1	
Uncertainty regarding exposure measurement error	All studies relied on one monitor to measure UFPs, which is inadequate based on limited data demonstrating both that there is greater spatial variability in UFPs (i.e., NC) and that the particle size distribution changes with distance from source. Additionally, there is limited information on the temporal variability in UFP concentrations.	Section 2.5.1.1.5 Section 2.5.1.2.4 Section 2.5.2.2.3 Section 3.4.5 Table 11-13	
Limited and inconsistent evidence for biological plausibility from cardiovascular and respiratory morbidity	Limited evidence from studies examining short-term UFP exposure and respiratory and cardiovascular effects provide limited biological plausibility for a relationship between short-term UFP exposure and cardiovascular- and respiratory-related mortality.	Section 5.5 Section 6.7	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015b).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to the causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the UFP concentrations and metric (i.e., number concentration [NC], surface area concentration [SC], mass concentration [MC]) with which the evidence is substantiated.

Overall, recent epidemiologic studies that examined short-term UFP exposure and mortality provide limited and inconsistent evidence of a positive association in both single and copollutant models. There is also limited evidence of biological plausibility from the assessment of short-term UFP exposures and respiratory and cardiovascular morbidity to support potential UFP-related mortality (Section 5.5, Section 6.7). Additionally, across studies there is a lack of consistency in terms of the UFP metric and size fractions examined, which complicate the interpretation of results, along with the potential for exposure measurement error due to uncertainty in the spatial and temporal variability in UFP concentrations. **Collectively, the epidemiologic evidence is inadequate to infer the presence or absence of a causal relationship between short-term UFP exposure and total mortality.**

11.6 Long-Term UFP Exposure and Total Mortality

The 2009 PM ISA reported that no epidemiologic studies evaluated the effects of long-term UFP exposure and mortality, concluding that the evidence was "inadequate to determine if a causal relationship exists between long-term UFP exposure and mortality." A recent study provides some additional evidence to inform the relationship between long-term UFP exposure and mortality, though the overall evidence base remains limited.

11.6.1 Biological Plausibility for Long-Term UFP Exposure and Total Mortality

The preceding chapters characterized evidence related to evaluating the biological plausibility by which long-term UFP exposure may lead to the morbidity effects that are the largest contributors to total (nonaccidental) mortality, specifically cardiovascular and respiratory morbidity (Section 6.6.1 and Section 5.6.1, respectively). This evidence is derived from animal toxicological, controlled human exposure, and epidemiologic studies. Section 6.6.1 outlines the available evidence for plausible mechanisms by which inhalation exposure to UFPs could result in initial events to endpoints relevant to the cardiovascular system. Similarly, Section 5.6.1 characterizes the available evidence by which inhalation exposure to UFPs could progress from initial events to endpoints relevant to the respiratory system. This evidence is limited to several experimental studies of oxidative stress and inflammatory changes that do not provide consistent evidence for initial events or progression along a plausible pathway from UFP exposure to respiratory health endpoints. Collectively, there is limited available evidence for cardiovascular and respiratory morbidity supporting potential biological pathways by which long-term UFP exposures could result in mortality.

11.6.2 Associations between Long-Term UFP Exposure and Total Mortality

In 2009, Hoek et al. (2009) published an expert elicitation in which 11 European experts in epidemiology, toxicology and clinical science were asked to quantify the relationship between UFP exposure and health endpoints, including mortality. The experts emphasized that the lack of studies examining long-term UFP exposure and mortality contributed greatly to the uncertainty of this relationship. The experts were asked to estimate the "percent change in annual, total (nonaccidental) mortality in the general EU [European Union] population resulting from a permanent 1,000 particles/cm^2 reduction in annual average UFP across Europe (given a population-weighted baseline concentration of 20,000 particles/cm^2)." While there was substantial variability, the median response from the experts was a 0.30% decrease in annual, total (nonaccidental) mortality, though none of the experts excluded the possibility that UFPs had no effect. In a recent study, Ostro et al. (2015) examined the association between UFP (<0.1 μm) mass concentrations and mortality among women in the California Teachers Cohort. The authors used a chemical transport model to predict UFP concentrations with a 4-km spatial resolution, observing a positive association with IHD mortality (HR: 1.10; 95% CI: 1.02, 1.18, per 0.969 μg/m^3 increase). Associations with total (nonaccidental), cardiovascular, and respiratory mortality were near the null value.

Overall, the literature base for long-term UFP exposure and mortality remains very small, with one study (Ostro et al., 2015) reporting results for UFP mass concentration. There are no studies that examine UFP number concentration. An expert elicitation conducted in Europe (Hoek et al., 2009) asked experts in epidemiology, toxicology and clinical sciences to review the available evidence for the health effects of UFPs. The experts concluded that long-term exposure could affect mortality risk, but due to the small literature base and associated uncertainties, they could not rule out the possibility of no UFP effect on mortality.

11.6.3 Summary and Causality Determination

This section describes the evaluation of evidence for total (nonaccidental) mortality, with respect to the causality determination for long-term exposures to UFPs using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015b). The key evidence, as it relates to the causal framework, is summarized in Table 11-15. Compared to the examination of other PM size fractions, a smaller number of studies have examined the association between long-term UFP exposure and total (nonaccidental) mortality. At the completion of the 2009 PM ISA, there were no available studies examining long-term UFP exposure and total mortality. Recent evidence from the CA Teachers cohort provides little insight on the relationship between long-term UFP exposure and mortality due to generally null associations and the uncertainties and limitations in the evidence base. Additionally, there is limited and inconsistent cardiovascular (Chapter 6) and respiratory (Chapter 5) morbidity evidence to provide biological

plausibility to support an association between UFPs and total mortality. **Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between long-term UFP exposure and total mortality.**

Table 11-15 Summary of evidence that is inadequate to infer the presence or absence of a causal relationship between long-term UFP exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Limited and inconsistent epidemiologic evidence	Single study observes generally null association with total mortality	Ostro et al. (2015)	1,293 ng/m^3
Uncertainty regarding potential confounding by copollutants	No studies examine potential confounding of UFP associations by copollutants	Section 11.6.2	
Uncertainty regarding exposure measurement error	Chemical transport model to predict UFP concentrations with a 4-km spatial resolution	Ostro et al. (2015)	
Uncertainty regarding biological plausibility	Little evidence for long-term UFP exposure and cardiovascular or respiratory morbidity	Section 5.6 and Section 6.7	

UFP = ultrafine particle.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to the causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the UFP concentrations with which the evidence is substantiated.

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CHAPTER 12 POPULATIONS AND LIFESTAGES POTENTIALLY AT INCREASED RISK OF A PARTICULATE MATTER-RELATED HEALTH EFFECT

Summary of Populations and Lifestages Potentially at Increased Risk of a Particulate Matter-Related Health Effect

- The preceding health effects chapters in this ISA characterized a large body of evidence examining $PM_{2.5}$-related health effects and demonstrate that there is strong evidence for a range of health effects due to short- and long-term $PM_{2.5}$ exposures that are observed in both the general population as well as specific populations (e.g., people with a pre-existing disease) and lifestages (i.e., children and older adults). ***Thus, extensive evidence in the health effects chapters indicates that both the general population as well as specific populations and lifestages are at risk for $PM_{2.5}$-related health effects.***
- More specific consideration is often given to specific lifestages and populations, such as children, those with pre-existing diseases, or certain sociodemographic characteristic (e.g., low socioeconomic status) to determine if these unique populations and lifestages might be at increased risk of an air pollutant-related health effect relative to others in the population that do not have that characteristic.
- While preceding chapters focus on whether there is evidence broadly of $PM_{2.5}$-related health effects, the objective of this chapter is to evaluate the extent to which the evidence indicates that a population or lifestage is at **disproportionately greater risk,** using an established framework to assess the available evidence. ***Thus, this chapter is addressing the specific question: are specific populations or lifestages at increased risk of a $PM_{2.5}$-related health effect compared to a reference population?***
- In addressing this question, the evaluation builds on evidence from the 2009 PM ISA and takes into consideration a broad range of recent evidence from epidemiologic, controlled human exposure, and animal toxicological studies, in addition to information on differential exposure or dosimetry. Conclusions are drawn based on an integrated evaluation of evidence in the context of the framework.

12.1 Introduction

The NAAQS are intended to protect public health with an adequate margin of safety, which includes protection for the population as a whole and for those groups potentially at increased risk for health effects in response to exposure to a criteria air pollutant (e.g., PM) [see Preamble to the ISA (U.S. EPA, 2015b)]. There is interindividual variation in both physiological responses, as well as exposures to ambient air pollution. A variety of terms have been used in the scientific literature to describe risk factors and subsequently populations or lifestages that may be at increased risk of an air pollutant-related health effect, including susceptible, vulnerable, sensitive, at risk, and response-modifying factor (Vinikoor-Imler

et al., 2014) [see Preamble to the ISA (U.S. EPA, 2015b)]. Acknowledging the inconsistency in definitions for these terms across the scientific literature and the lack of a consensus on terminology in the scientific community, "at-risk is the all-encompassing term used within this chapter for groups with specific factors that increase the risk of an air pollutant (e.g., PM)-related health effect in a population", as initially detailed in the 2013 O_3 ISA (U.S. EPA, 2013b). Therefore, while there is strong evidence for health effects to occur in the exposed general population and in some specific populations or lifestages, this chapter focuses on the evaluation and characterization of evidence informing if there are populations or lifestages potentially at increased risk of a PM-related health effect with specific emphasis on studies that compare responses to a reference population, where appropriate [see Preamble to the ISA (U.S. EPA, 2015b)].

As discussed in the Preamble to the ISAs (U.S. EPA, 2015b), the risk of health effects from exposure to an ambient air pollutant, including PM, may be modified as a result of intrinsic (e.g., pre-existing disease, genetic factors) or extrinsic factors (e.g., sociodemographic or behavioral factors), differences in internal dose (e.g., due to variability in ventilation rates or exercise behaviors), or differences in exposure to air pollutant concentrations (e.g., more time spent in areas with higher ambient concentrations). For the purposes of informing decisions on the NAAQS, the focus of this chapter is on identifying those populations or lifestages at increased risk of a PM-related health effect. It is recognized that, in many cases, subsets of the population are at increased risk of a PM-related health effect due to a combination or co-occurrence of factors [e.g., residential location and socioeconomic status (SES)], but evidence on the interaction among factors remains very limited. Thus, the following sections identify, evaluate, and characterize the overall confidence that individual factors potentially result in increased risk for PM-related health effects [see Preamble to the ISAs (U.S. EPA, 2015b)].

The preceding chapters of this ISA focus on assessing whether exposure to PM of various size fractions is causally related to health effects regardless of population or lifestage. It is the collective body of evidence spanning populations and lifestages that ultimately forms the basis of the causality determinations detailed within each of the health chapters. These chapters clearly conclude that there is a large body of evidence that demonstrates health effects with PM, particularly $PM_{2.5}$, across populations with diverse characteristics (e.g., children, older adults, people with a pre-existing cardiovascular disease, etc.). While the health chapters assess the degree to which there is evidence of a causal relationship between PM exposure and health effects, this chapter is focusing solely on the question: ***Are there specific populations and lifestages at increased risk of a PM-related health effect compared to a reference population?***

This analysis is one aspect to be considered in the latter evaluation of the extent to which the NAAQS provide public health protection with an adequate margin of safety.

12.2 Approach to Evaluating and Characterizing the Evidence for Populations or Lifestages Potentially at Increased Risk

The systematic approach used to identify, evaluate, and characterize evidence for factors that may increase the risk of a population or specific lifestage to an air pollutant-related health effect, including PM, is described in more detail in the Preamble (U.S. EPA, 2015b). The evidence evaluated in this chapter includes relevant studies discussed in Chapters 5-11 of this ISA relevant to the evaluation of populations and lifestages potentially at increased risk of a PM-related health effect and builds on the evidence presented in the 2009 PM ISA (U.S. EPA, 2009). The evaluation of the evidence focuses on those health outcomes and size fractions of PM for which a "*causal*" or "*likely to be a causal*" relationship was concluded in Chapters 5-11 of this ISA with additional supporting evidence from studies of health outcomes for which the causality determination is "suggestive" or "inadequate". More specifically, this chapter focuses on the health effects related to $PM_{2.5}$ based on the strength of the evidence as described in the health chapters. In addition, focus is given to the endpoints (e.g., mortality, asthma exacerbation, lung development, etc.) that formed the basis of the conclusions. In addition, it is important to recognize that the 2009 PM ISA (U.S. EPA, 2015b) focused broadly on the extent to which evidence indicated that certain populations or lifestages were "susceptible" to a PM-related health effect, regardless of size fraction. As part of the 2013 O_3 ISA (U.S. EPA, 2013a), a framework was developed to systematically evaluate the collective body of evidence and inform whether a specific population or lifestage is at increased risk for an air pollutant-related health effect compared to a reference population, where applicable[82]. As such, it is important to note that the conclusions detailed within this ISA are more nuanced than the dichotomous conclusions of whether a population or lifestage is susceptible for a PM-related health effect as reflected in the 2009 PM ISA (U.S. EPA, 2009).

As described in the Preamble and the PM IRP and demonstrated in previous ISAs (U.S. EPA, 2017, 2016a, b, 2015a, 2013a, b), evidence is integrated across scientific disciplines (i.e., epidemiology, controlled human exposure, and animal toxicology) and health effects, and when available, with relevant dosimetric information (Chapter 4) as well as exposure differences (Chapter 3) in the evaluation process. Epidemiologic studies that include stratified analyses to compare populations or lifestages exposed to similar $PM_{2.5}$ concentrations within the same study design directly inform the question of disproportionate risk. A more detailed presentation of this evidence is included in a supplement to this chapter (U.S. EPA, 2018). Other epidemiologic studies that do not stratify results but instead examine a specific population or lifestage can provide further evidence of increased risk particularly when a health effect is only relevant for a unique population or lifestage (e.g., lung function development in children). When evaluating results

[82] In some cases, studies do not include a reference population for comparison because there are outcomes that are only relevant to some specific populations and lifestages. For example, lung function development is only examined in studies of children because this outcome cannot be measured in adults as lung development is already complete. Another example is studies of asthma hospitalization or emergency department visits, where studies often examine these events only for the population with asthma because those without asthma would not have an asthma exacerbation.

across epidemiologic studies, similar to the characterization of epidemiologic evidence in Chapters 5-11, statistical significance is not the sole criterion by which effect modification and evidence of increased risk is determined; emphasis is placed on patterns or trends in results across these epidemiologic studies.[83] Experimental studies in human subjects or animal models that focus on factors, such as genetic background or health status (e.g., pre-existing asthma), are also important lines of evidence to evaluate to establish coherence of effects across disciplines. These studies can also inform the independent effects of PM as well as biological plausibility of effects observed in epidemiologic studies. Additionally, dosimetry studies can further inform biological plausibility by demonstrating whether the deposition of PM within the body might vary in a particular population or lifestage. Differential exposure to PM in populations and lifestages is also considered when available, though these types of evidence tend to be sparser.

As stated, the objective of this chapter is to identify, evaluate, and characterize the extent to which various factors may increase the risk of a PM-related health effect in a population or lifestage compared to a reference population, where applicable, building on the conclusions drawn in previous chapters in the ISA. More specifically, Table 12-1 presents the framework applied to the available evidence in drawing conclusions on increased risk. The broad categories of factors evaluated include pre-existing disease (Section 12.3), genetic background (Section 12.4), sociodemographic factors (Section 12.5), and behavioral and other factors (see Section 12.6). Furthermore, factors that are considered in this chapter are not predetermined, but are included based on the availability of evidence in the scientific literature. The classifications of evidence are characterized in Table 12-1. A summary of the characterization of the evidence for each factor considered within this chapter is presented in Section 12.7.

It is important to note that while a broad range of evidence is evaluated, there are uncertainties and limitations inherent in the approach used within this chapter to identify populations or lifestages potentially at disproportionately increased risk of a PM-related health effect. First, publication bias, or the tendency not to report quantitatively null results in epidemiologic studies is more frequent in stratified results than main effects, and this can introduce uncertainty when evaluating increased risk or risk modification in general. However, in the evaluation and characterization of the evidence within this chapter, where the evidence is considered "adequate" to classify a group as being at increased risk (Table 12-1) even when considering the strengths and limitations, the collective body of evidence is strong enough to outweigh this uncertainty. In addition, there is variability in the indicators or metrics used to define the populations and/or lifestages that are examined, which can be an important limitation (e.g., well-controlled vs. uncontrolled pre-existing disease, body mass index, indicators of socioeconomic status, various age ranges). Another aspect to consider is variability within the populations or lifestages, such as behavioral differences, biological differences (e.g. obese vs. non-obese), and adherence to treatment for pre-existing disease). These limitations and uncertainties can impact the extent to which the

[83] As detailed in the Preface, risk estimates are for a 10 $\mu g/m^3$ increase in 24-hour avg $PM_{2.5}$ concentrations or a 5 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations, unless otherwise noted.

evidence can reliably indicate whether there is disproportionate risk in a population or lifestage compared to a reference population and is considered where relevant.

Table 12-1 Characterization of evidence for factors potentially increasing the risk for particulate matter-related health effects.

Classification	Health Effects
Adequate evidence	There is substantial, consistent evidence within a discipline to conclude that a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. Where applicable, this evidence includes coherence across disciplines. Evidence includes multiple high-quality studies.
Suggestive evidence	The collective evidence suggests that a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage, but the evidence is limited due to some inconsistency within a discipline or, where applicable, a lack of coherence across disciplines.
Inadequate evidence	The collective evidence is inadequate to determine whether a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. The available studies are of insufficient quantity, quality, consistency, and/or statistical power to permit a conclusion to be drawn.
Evidence of no effect	There is substantial, consistent evidence within a discipline to conclude that a factor does not result in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. Where applicable, the evidence includes coherence across disciplines. Evidence includes multiple high-quality studies.

12.3 Pre-Existing Diseases/Conditions

Individuals with pre-existing disease may be considered at greater risk of an air pollution-related health effect than those without disease because they are likely in a compromised biological state that can vary depending on the disease and severity. The 2009 PM ISA (U.S. EPA, 2009) concluded that those with pre-existing cardiovascular (CV) and respiratory diseases are generally more susceptible to the health effects associated with exposure to PM, but that evidence for diabetes and obesity was limited. Of the recent epidemiologic studies evaluating effect measure modification by pre-existing disease or condition, most focused on pre-existing CV disease (Section 12.3.1), pre-existing diabetes and metabolic syndrome (Section 12.3.2), obesity (Section 12.3.3), elevated cholesterol (Section 12.3.4), and pre-existing respiratory disease (Section 12.3.5). Table 12-2 presents the prevalence of these diseases from the National Health Interview Survey conducted by the Centers for Disease Control and Prevention's (CDC's) National Center for Health Statistics (Blackwell and Villarroel, 2018), including the proportion of adults with a current diagnosis categorized by age and geographic region. The large proportions of the U.S. population affected by many chronic diseases, including various cardiovascular diseases, indicates

the potential public health impact, and thus, the importance of characterizing if certain subpopulations may be at increased risk for $PM_{2.5}$-related health effects.

Table 12-2 Prevalence of cardiovascular diseases, diabetes, obesity, and respiratory diseases among adults by age and region in the U.S. in 2016.

	Adults (18+)	Age (%)[a]				Region (%)[b]			
Chronic Disease/Condition	N (in thousands)	18−44	45−64	65−74	75+	North east	Midwest	South	West
All (N, in thousands)	245,142	113,401	83,703	28, 532	19,507	44,851	54,359	87,402	58,531
Selected cardiovascular diseases/conditions									
All heart disease	28,064	3.8	12.2	22.6	36.5	10.2	11.8	11.0	9.4
Coronary heart disease	15,230	1.2	6.0	13.9	25.1	5.4	6.4	6.3	4.5
Hypertension	66,443	9.2	34.4	55.7	59.1	23.5	26.0	27.0	21.9
Stroke	7,449	0.6	3.2	6.6	11.1	2.4	2.5	3.2	2.8
Metabolic disorders/conditions									
Diabetes	23,104	2.8	12.5	23.0	19.4	8.5	9.3	9.3	7.9
Obesity (BMI ≥30 kg/m^2)	70,723	27.5	34.7	31.5	21.2	25.9	33.4	32.1	24.6
Overweight (BMI 25−30 kg/m^2)	82,870	31.8	36.9	40.5	38.3	35.8	33.1	34.2	35.8
Selected respiratory diseases									
Asthmatic	20,383	8.1	9.2	8.3	6.0	9.4	9.0	7.3	8.3
COPD—chronic bronchitis	8,940	2.0	5.0	5.3	4.9	3.1	3.7	4.0	2.6
COPD—emphysema	3,524	0.2	1.8	3.6	4.0	1.2	1.5	1.4	0.9

BMI = body mass index; COPD = chronic obstructive pulmonary disease.

[a]Percentage of individual adults within each age group with disease, based on N (at the top of each age column).

[b]Percentage of individual adults (18+) within each geographic region with disease, based on N (at the top of each region column).

[c]Asthma prevalence is reported for "still has asthma."

Source: Blackwell and Villarroel (2018); National Center for Health Statistics, Summary Health Statistics: National Health Interview Survey, 2016.

12.3.1 Cardiovascular Disease

Overview

- Approximately 12% of adults in the U.S. have a CV disease, and CV disease is the leading cause of death in the U.S, accounting for one in four deaths.
- A limited number of epidemiologic studies included in the current and previous ISAs have conducted stratified analyses; while they do not clearly demonstrate increased risk across all pre-existing CV diseases. There is some evidence that those with hypertension are at increased risk for $PM_{2.5}$-related health effects compared to those without hypertension, but there are inconsistencies.
- Strong evidence demonstrates that there is a causal relationship between CV effects and short- and long-term exposures to $PM_{2.5}$. Some of the evidence is from studies of panels or cohorts with pre-existing CV disease, which provide supporting evidence but do not directly inform an increase in risk.
- **Overall, the evidence is suggestive that those with pre-existing CV disease, particularly hypertension, may be at increased risk for $PM_{2.5}$ related health effects compared to those without a pre-existing CV disease.**

Cardiovascular disease is the primary cause of death in the U.S., and approximately 12% of adults report a diagnosis of heart disease [Table 12-2; (Blackwell and Villarroel, 2018)]. While evidence demonstrates that a causal relationship exists between short- and long-term $PM_{2.5}$ exposure and cardiovascular effects based on recent evidence, building from studies evaluated in the 2009 PM ISA (U.S. EPA, 2009), evidence addressing whether or not individuals with pre-existing cardiovascular disease are at increased risk for $PM_{2.5}$-associated health effects compared to those without pre-existing CV disease is complex. The evidence examining differential risk for $PM_{2.5}$-related health effects in individuals with pre-existing cardiovascular disease in the 2009 PM ISA (U.S. EPA, 2009) was limited and inconsistent, though studies from the recent literature provide some additional evidence that pre-existing cardiovascular disease may modify the risk of $PM_{2.5}$ for cardiovascular outcomes.

As described in Chapter 6, both previous evidence from the 2009 PM ISA (U.S. EPA, 2009) and recent evidence demonstrate that there is a causal relationship between short- and long-term $PM_{2.5}$ exposure and cardiovascular effects. Both conclusions were informed by evidence for $PM_{2.5}$-related mortality, and hospital admissions and emergency department visits for IHD associated with short-term exposures to $PM_{2.5}$. It is well-recognized that these serious population-level effects are preceded by altered cardiovascular function, though there are no studies that examine differential risk for these serious effects in individuals with and without underlying cardiovascular conditions or diseases. There is, however, evidence from studies examining these serious health effects in only adults with pre-existing cardiovascular disease that demonstrate that $PM_{2.5}$-associated CV effects are observed in this population (Chapter 6). Thus, while this evidence does not inform if those with pre-existing CV disease are at increased risk for a $PM_{2.5}$-related health effect compared to those without pre-existing CV disease, it does indicate that these individuals are at-risk.

Recent studies examining whether there is evidence of increased risk for $PM_{2.5}$-related health effects in people with pre-existing cardiovascular disease have considered an array of specific cardiovascular diseases/conditions (Supplemental Table S12-1) (U.S. EPA, 2018). As was the case for the 2009 PM ISA, hypertension is the most commonly examined cardiovascular disease in epidemiologic studies that conducted stratified analyses. Puett et al. (2009) and Goldberg et al. (2013) both reported positive associations between long-term $PM_{2.5}$ exposure and mortality in the Nurses' Health Study and among older adults in Montreal, Canada, respectively. However, Puett et al. (2009) did not find associations to differ consistently by hypertension status; only associations with fatal CHD, and not mortality or first CHD, were increased for those with hypertension compared to those without. Other studies examining $PM_{2.5}$-related ischemic stroke and incident diabetes also did not find evidence for increased risk among those with hypertension with short-term exposures (Wellenius et al., 2012a; O'Donnell et al., 2011) or long-term exposure (Hansen et al., 2016) (Chen et al., 2013). However, studies examining effect modification for $PM_{2.5}$-associated changes in subclinical CVD outcomes (e.g., blood pressure, inflammation, endothelial dysfunction) provide some evidence that effects in those with hypertension are larger with $PM_{2.5}$ exposure. Both Auchincloss et al. (2008) and Krishnan et al. (2012) conducted analyses within the MESA cohort and observed positive associations for pulse pressure, BAD, and FMD with long-term $PM_{2.5}$ exposure; associations were larger for study participants with hypertension, with the exception of BAD. Wellenius et al. (2013) also found in a study of community-dwelling older adults in Boston that those with hypertension had greater $PM_{2.5}$-related increases in flow velocity and cerebrovascular resistance, measures related to stroke and neurological conditions, with long-term exposure. Interleukin-6 and C-reactive protein, markers of inflammation, were also more strongly associated with long-term exposure to $PM_{2.5}$ in those with hypertension compared to those without (Hajat et al., 2015; Ostro et al., 2014).

Beyond hypertension, recent studies have also evaluated whether there is evidence that people with pre-existing coronary heart disease (CHD) are at increased risk of a PM-related health effect compared to those without CHD. However, all studies are from a single panel of adults from the Heinz Nixdorf Recall study. More specifically, participants in this panel ranged from 45−75 years of age and were from Ruhr area, Germany. Hennig et al. (2014), Viehmann et al. (2015), Hoffmann et al. (2009a), and Fuks et al. (2011) observed positive associations between 12-month $PM_{2.5}$ exposures and CRP, fibrinogen, and BP. When examining effect measure modification by CHD status, only Viehmann et al. (2015) found larger effects in those with CHD compared to those without. Hertel et al. (2010) also examined associations for CRP, and while positive associations across averaging times were observed, effect measure modification by CHD was not clear results varied for 2-day up to 28-day averages of $PM_{2.5}$.

Studies examining effect modification by pre-existing CV diseases other than hypertension or CHD are sparse and vary across outcomes making it difficult to draw conclusions. In addition to the differences across studies in the outcomes and populations examined, results across these studies are inconsistent and do not suggest that individuals with pre-existing CV disease, at a broad level, are at

increased risk for health effects related to short- or long-term exposures to $PM_{2.5}$. However, there is some evidence that those with hypertension, specifically, may be at increased risk compared to those without hypertension.

Evidence from controlled human exposure and animal toxicological studies evaluating whether or no pre-existing CV disease increases risk for $PM_{2.5}$-associated health effects is limited. A single CHE study from the recent literature is available that examined whether use of a respiratory filter could attenuate the cardiovascular effects of acute diesel exhaust (DE) exposure in patients with heart failure (HF) or healthy individuals (Vieira et al., 2016). BP was not significantly changed with DE exposure compared to air controls. When the FILTER-HF patients and healthy controls exercised for 6 minutes, BP increased with exercise in both groups but there were no statistically significant differences with DE exposure with or without filtration and results were similar in those with and without HF. No differences in HRV, HR, endothelial dysfunction, or arterial stiffness were observed for those with or without HF. In addition, the 2009 PM ISA(U.S. EPA, 2009) characterized evidence from studies that evaluated pulmonary outcomes in spontaneously hypertensive rats. These studies found some evidence for pulmonary inflammation following 4-hour to 3-day exposures to CAPs from RTP, NC; various sites in the Netherlands; a high-traffic area in Taiwan, and Detroit (Rohr et al., 2010; Campen et al., 2006; Cassee et al., 2005; Kodavanti et al., 2005; Lei et al., 2004) but lack of a comparison to a normotensive strain limits the utility of these studies in informing differential effects for pre-existing CV disease.

Taken together, the collective evidence is suggestive that individuals with pre-existing CV disease are at increased risk for $PM_{2.5}$-associated health effects compared to those without pre-existing CV disease. The evidence from epidemiologic studies conducting stratified analyses, controlled human exposure, and animal toxicological studies is not clear in describing increased risk across all pre-existing CV disease, but evidence for those with hypertension demonstrates a potential for increased risk. In addition, there is strong evidence described in Chapter 6 supporting a causal relationship between short-term $PM_{2.5}$ exposure and CV effects, based primarily on evidence for ischemic heart disease. As noted, the pathophysiology underlying the serious CV outcomes associated with $PM_{2.5}$ exposure is linked to a variety of underlying CV conditions, though they may be asymptomatic and undiagnosed. This uncertainty in disease diagnoses, and in addition, the variability in disease status complicate the examination of increased risk in these populations.

12.3.2 Pre-existing Diabetes and Metabolic Syndrome

Overview

- Diabetes mellitus is an important component of metabolic syndrome, as well as a risk factor for cardiovascular disease.
- In the 2009 PM ISA, there was limited evidence comparing $PM_{2.5}$-associated health effects in individuals with and without diabetes.
- Recent stratified epidemiologic analyses of short- and long-term $PM_{2.5}$ exposure do not consistently demonstrate increased risk among those with diabetes.
- **Overall, the evidence is inadequate to determine whether individuals with pre-existing diabetes are at increased risk for $PM_{2.5}$-related health effects compared to individuals without diabetes.**

Diabetes mellitus is a group of diseases characterized by high blood glucose levels and affects an estimated 30 million Americans, or 8.8% of the adult population, in 2016 (Blackwell and Villarroel, 2018). In addition, 84 million Americans are estimated to be living with prediabetes, a condition characterized by elevated fasting plasma glucose levels that is also a key risk factor for cardiovascular disease and a component of metabolic syndrome (CDC, 2017). As described in Chapter 7 (Section 7.2.2) metabolic syndrome components (i.e., fasting blood glucose, high blood pressure, dyslipidemia, and obesity) often co-occur and can contribute to atherosclerotic plaque progression causing damage to the vascular system and potentially promoting cardiovascular disease and heart failure. Furthermore, studies have demonstrated cardiovascular and metabolic effects in humans or animal models of diabetes as characterized in Chapter 6 and 7. It is conceivable that biological effects in individuals with diabetes may be further exacerbated by exposures to $PM_{2.5}$. Thus, this section characterizes the evidence informing if individuals with pre-existing metabolic disease, including diabetes, are at increased risk for $PM_{2.5}$-related health effects compared to the individuals without metabolic disease or diabetes.

The 2009 PM ISA (U.S. EPA, 2009) concluded there was some evidence suggesting increased PM-related health effects among those with diabetes; however, much of the evidence was inconsistent across several studies of hospital admission and emergency department visits and short-term PM_{10} exposure, with only one study evaluating the effects of $PM_{2.5}$ (Goldberg et al., 2006). Controlled human exposure and toxicological studies found limited evidence of differences in biomarkers by diabetes status, though the 2009 PM ISA (U.S. EPA, 2009) noted that it was unclear how differences in biomarker responses contribute to overall potential for cardiovascular risk in those with diabetes compared to those without diabetes. Recent epidemiologic and toxicological studies have focused on differential $PM_{2.5}$-related health effects for diabetes status and provide some evidence of increased risk, but there are inconsistencies in results across studies of mortality and cardiovascular outcomes (Supplemental Table S12-2) (U.S. EPA, 2018).

Several studies examined whether diabetes status modified associations between mortality and long-term $PM_{2.5}$ exposure. There was little evidence that $PM_{2.5}$-associated mortality was modified by diabetes status for long- or short-term $PM_{2.5}$ exposure across studies. Several multistate or statewide U.S. based studies of long-term $PM_{2.5}$ exposure reported slight variations in associations, though estimates were generally imprecise (i.e., wide 95% confidence intervals) and changes in risk were small (Wang et al., 2016b; Pope et al., 2014; Puett et al., 2009). One exception was a study of seven southeastern U.S. states, where Wang et al. (2017) observed an increase in risk for mortality associated with long-term $PM_{2.5}$ exposure among Medicare patients who also had a history of diabetes hospital admission compared to those that did not. Furthermore, this modification persisted across simultaneous stratifications of sex and race combinations. Too few studies were available to compare if there were differences by mortality cause. Among studies of short-term $PM_{2.5}$ exposure and mortality, only Goldberg et al. (2013) examined differential risk for $PM_{2.5}$-related mortality by diabetes status. This study demonstrated a slight increase in risk for nonaccidental mortality for cases with diabetes compared to all cases.

A number of studies also examined effect measure modification by diabetes status across an array of cardiovascular outcomes and long-term $PM_{2.5}$ exposure. Studies of incident hypertension and self-reported heart disease found little evidence for differences between individuals with or without diabetes (Hoffmann et al., 2009b; Johnson and Parker, 2009). Chan et al. (2015) and Fuks et al. (2011) observed larger $PM_{2.5}$-related decreases in blood pressure in those with diabetes; however, these differences were modest and imprecise (i.e., wide 95% confidence intervals). In contrast, in a study of the of the Nurses' Health Study cohort by Hart et al. (2015) examining incident CVD among women positive associations were observed for those with diabetes (HR: 1.44, 95% CI: 1.23, 1.68) compared to those without diabetes (HR: 0.94, 95% CI: 0.86, 1.03). Additionally, in a multicity study, Chen et al. (2014) observed a 41% increase in risk of incident hypertension among those with diabetes compared to those without; however, effect estimates were imprecise.

Among evaluations of short-term $PM_{2.5}$ exposure, some studies demonstrated higher risk of cardiovascular effects among individuals with diabetes compared to those without diabetes; while other studies did not observe changes in association based on diabetes status. Across studies, there is limited evidence of differential risk for changes in blood pressure (Wellenius et al., 2012b), heart failure (Haley et al., 2009), or transmural infarctions (Rich et al., 2010). One exception is a multicity study of ischemic stroke hospital admissions as determined by registry data in Ontario, Canada, which reported a positive association among those with diabetes, but observed little evidence of an association among those without diabetes (O'Donnell et al., 2011). Additionally, a panel study in Boston, MA observed little evidence of changes in blood pressure for individuals with well-controlled diabetes compared to a positive change in blood pressure among individuals with poorly controlled diabetes (Hoffmann et al., 2012), which indicates the potential for severity and control of diabetes to be an important factor beyond the presence or absence of the disease.

Several recent epidemiologic studies evaluated cardiovascular effects and measures of inflammation related to atherosclerosis in individuals exposed to PM and found larger, though imprecise, associations in participants with diabetes compared to those without. In a study of the MESA cohort, Allen et al. (2009) observed positive associations between $PM_{2.5}$ levels (2 year average) and elevated risk for calcification among individuals with diabetes. Furthermore, in those diabetic individuals with some or no calcification there was a positive change in the Agatston Score (a metric for coronary artery calcification). In other studies of the MESA cohort, Roux et al. (2008) observed no differences in associations between 20 year $PM_{2.5}$ averages and health measures of atherosclerosis by diabetes status. Additionally, Roux et al. (2008) and Van Hee et al. (2011) did not observe effect measure modification for $PM_{2.5}$-associated changes in QT-prolongation or ventricular conduction delay by diabetes status. In a German population-based cohort study (Heinz Nixdorf Recall study), Bauer et al. (2010) found a slightly weaker association between $PM_{2.5}$ exposure and carotid intima-media thickness (CIMT) for those with diabetes compared to those without.

Other studies specifically evaluated effect measure modification of associations between long- and short-term $PM_{2.5}$ exposure and markers of inflammation and coagulation (e.g., IL-6, CRP, and fibrinogen) by diabetes status. Specifically, in a study of 6 U.S. cities, Ostro et al. (2014) found the association between CRP and long-term $PM_{2.5}$ exposure to be modified by diabetes, with particularly large increases in CRP when comparing diabetes status among older adults. In contrast, Hoffmann et al. (2009a) conducted stratified analyses of the German Heinz Nixdorf Recall Study and found no distinct effect by diabetes status on PM associations with fibrinogen or CRP. In a study of short-term $PM_{2.5}$ exposure using the same German population-based cohort, Hertel et al. (2010) observed no distinct effect by diabetes status on the PM association with CRP.

Overall, evidence is inadequate to determine whether individuals with pre-existing diabetes are at increased risk for $PM_{2.5}$-associated health effects compared to those without diabetes. A number of recent studies provide inconsistent evidence for increased risk across a range of health effects associated with exposure to $PM_{2.5}$. Epidemiologic studies of diabetes predominantly evaluated associations between mortality and cardiovascular outcomes and long-term $PM_{2.5}$ exposure. Several studies reported elevated risk among those with diabetes; however, results were inconsistent within and across health outcomes. One important limitation for many studies was the small proportion of participants with diabetes, contributing to imprecise effect estimates (i.e., wide 95% confidence intervals). Additionally, as observed by Hoffmann et al. (2012), there may differences in response to PM exposure between those with well-controlled versus poorly controlled diabetes; however, few studies include this level of detail. Interpretation of the evidence is further complicated by the lack of information on individuals with prediabetes, which may exhibit similar underlying metabolic characteristics as those with diabetes. Relying solely on a clinical diagnosis may underestimate the population at increased risk and potentially introduce bias by similarly grouping those in a healthy metabolic state with those in a prediabetic metabolic state.

12.3.3 Obesity

Overview

- Obesity affects nearly a third of adults in the U.S. and is associated with low-grade inflammation that potentially interact with PM-related inflammation.
- Evidence indicates the potential for dosimetric differences for $PM_{2.5}$ among adults and children by obesity status.
- Evidence from recent stratified epidemiologic analyses of long-term $PM_{2.5}$ exposure and mortality suggest increased risk for those who are obese compared to those who are not; evidence for other outcomes is inconsistent.
- Variability in the definition of obesity limits comparability between studies and the ability to distinguish risk between those who are overweight and obese.
- **Overall, the evidence is suggestive of increased risk for $PM_{2.5}$-related health effects among those who are obese compared to those who are not.**

In the U.S., obesity is defined as a BMI of 30 kg/m^2 or greater, with a BMI between 25 and 30 kg/m^2 indicating an overweight individual. It is a public health issue of growing importance as obesity rates in adults have continually increased over several decades in the U.S., reaching an estimated 30% in 2016 (Blackwell and Villarroel, 2018). Furthermore, 36% of adults in the U.S. are considered overweight while 34% are at a healthy weight (BMI 18.5−25 kg/m^2) (Blackwell and Villarroel, 2018). Obesity or high BMI could potentially increase the risk of PM related health effects through multiple mechanisms. For example, persistent low grade inflammation associated with obesity or excess nutrients and energy (CN and AR, 2011; Gregor and Hotamisligil, 2011; Lumeng and Saltiel, 2011) may work in conjunction with PM related inflammation that is thought to facilitate atherosclerotic plaque progression (Section 6.3.1, Figure 6-11). Obesity is closely related to diabetes, and is one component of metabolic syndrome, where co-occurring factors may also be associated with PM exposure (Section 7.2.1, Figure 7-2) and further facilitate cardiovascular risk (Section 6.3.1). Nutritional access and poor diet (Section 12.6.2) may also be potential risk factors that act in combination with obesity. Additionally, those who are obese may experience greater particle deposition in the lung as there is evidence of increased ventilation rates for overweight or obese adults and children, as well as a lower nasal breathing fraction and increase deposition fraction among obese children (Section 4.1.3, Section 4.2.4.4).

The 2009 PM ISA evaluated several studies that reported differences in subclinical cardiovascular and inflammatory markers between obese and nonobese participants in association with short-term exposure to $PM_{2.5}$(Dubowsky et al., 2006; Schwartz et al., 2005; Bennett and Zeman, 2004). A number of recent studies examining effect measure modification $PM_{2.5}$-related health effects by obesity statues are available and have reported some evidence of increased risk for mortality among obese individuals; however, evidence in studies across the range of effects examined including cardiovascular disease, incident diabetes, reproductive, and development outcomes do not consistently indicate differential risk by obesity status (Supplemental Table S12-3) (U.S. EPA, 2018).

Several studies examined effect measure modification of associations between mortality and long-term $PM_{2.5}$ exposure by obesity status. Overall, there was a trend across studies of increased risk among those who were overweight or obese compared to those of normal weight, though there are some exceptions to this trend across studies, and effect estimates are imprecise (i.e., wide 95% confidence intervals). A number of multicity studies in the U.S., Canada, and Europe reported increased risk for mortality among those who were obese (Villeneuve et al., 2015; Beelen et al., 2014a; Beelen et al., 2014b; Weichenthal et al., 2014; Puett et al., 2009). However, Turner et al. (2011) reported decreasing risk as BMI increased, including a 14% decrease in risk for those overweight compared to normal BMIs and a negative association among obese individuals. Furthermore, it is possible there is some variation by underlying cause of mortality. For example, Pinault et al. (2016) observed marginal decreases in risk for all-cause and cardiovascular mortality among those who were obese, though they reported a 35% increase in risk for respiratory mortality among obese participants. In contrast to these results, a pooled analysis of European cohorts observed that as BMI increased the association between $PM_{2.5}$ and respiratory mortality declined, while the opposite was true for all-cause and cardiovascular mortality (Beelen et al., 2014a; Beelen et al., 2014b; Dimakopoulou et al., 2014).

Studies have also examined a differential risk for a variety of cardiovascular effects by obesity status. In general, studies found little evidence for differences between obese and nonobese individuals, and when changes in association were present, they tended to be modest and imprecise. For example, a registry study of long-term $PM_{2.5}$ exposure and incident hypertension in Ontario, Canada (Chen et al., 2014) reported a decrease in risk for obese participants (HR: 1.07, 95% CI: 0.91, 1.26) compared to nonobese participants (HR: 1.17, 95% CI: 1.04, 1.33). Likewise, an examination of the Nurses' Health Study reported an increased risk in incident cardiovascular disease for obese participants (HR: 1.12, 95% CI: 0.99, 1.30) compared to nonobese participants (HR: 0.99, 95% CI: 0.88, 1.12) (Hart et al., 2015). A number of studies also examined changes in blood pressure with both long-term (Chan et al., 2015; Fuks et al., 2011) and short-term (Hoffmann et al., 2012; Wellenius et al., 2012b) exposures to $PM_{2.5}$ and observed no consistent pattern by obesity status for changes in blood pressure. Other studies examined outcomes such as prevalence of heart disease (Johnson and Parker, 2009) or measures of atherosclerosis (Hoffmann et al., 2009b) and did not observe an increase in risk among those who were obese compared to those with healthy weight.

Several of the studies that examined cardiovascular endpoints related to atherosclerosis and modification by diabetes status, as previously described (Section 12.3.2), also examined potential modification by obesity and observed limited evidence of increased risk among obese participants compared to those or healthy weight. In a study of the MESA cohort, Allen et al. (2009) identified positive $PM_{2.5}$ associations with elevated risk for calcification among obese individuals compared to those of normal weight. Furthermore, in those obese individuals with some or no calcification a positive change in the Agatston score (measure of coronary artery calcification) was observed. A similar study of the MESA cohort estimated the effect of 20 year $PM_{2.5}$ averages on atherosclerosis health measures and found no differences in association by BMI category (Roux et al., 2008). In a German population-based

cohort study (Heinz Nixdorf Recall study) Bauer et al. (2010) found a slightly stronger association between $PM_{2.5}$ exposure and carotid intima-media thickness (CIMT) for obese participants compared to those of normal weight.

Other studies specifically evaluated effect modification by obesity status on associations between markers of inflammation and coagulation, including IL-6, CRP, and fibrinogen. Hoffmann et al. (2009a) and Hertel et al. (2010) conducted analyses from German Heinz Nixdorf Recall Study cohort and found no distinct effect by obesity status on $PM_{2.5}$ associations with fibrinogen or CRP. A Study of Women's Health Across the Nation (SWAN), demonstrated increased CRP for middle aged obese women, though estimates had wide confidence intervals (Ostro et al., 2014).

A limited number of studies investigated effect measure modification by obesity for associations between $PM_{2.5}$ and other health endpoints, such as incident diabetes and reproductive outcomes. Among studies of incident diabetes, results were inconsistent. A study in Ontario, Canada reported decreased risk of developing diabetes among the overweight and obese (Chen et al., 2013), while multicity studies in Denmark (Hansen et al., 2016) and Germany (Weinmayr et al., 2015) reported increased risk among the obese compared to healthy weight. Among studies of reproductive outcomes, insufficient studies were available to report any trends for a specific outcome; however, there was little evidence of modification by obesity status in studies of endometriosis (Mahalingaiah et al., 2014), and gestational diabetes (Robledo et al., 2015). Conversely, in a small study of preeclampsia among predominantly Hispanic women in Los Angeles, Mobasher et al. (2013) reported higher risks among nonobese women based on $PM_{2.5}$ exposures in the first trimester compared to obese women.

Overall, the available evidence is suggestive of increased risk among those who are obese compared to those who are not obese for $PM_{2.5}$-associated health effects. There is a relatively consistent evidence across a small evidence base demonstrating increased risk of $PM_{2.5}$-associated mortality among those who are obese or overweight compared to those of healthy weight. Results from other outcomes were less consistent, although some studies observed increased risk in markers of atherosclerosis as well as incident diabetes. An important limitation across studies was the variability in categorizing obesity, with thresholds defining obesity ranging from a BMI of 27 to 30.6 kg/m^2. Furthermore, many studies did not distinguish between being overweight or obese and included overweight individuals either with obese individuals or with healthy weight individuals.

12.3.4 Elevated Cholesterol

Overview

- Elevated cholesterol is a common chronic condition in the U.S. adult population and is an important risk factor for other serious health conditions associated with $PM_{2.5}$ exposure, such as cardiovascular disease and diabetes.
- The 2009 PM ISA did not evaluate cholesterol status, but some recent studies have examined differences $PM_{2.5}$-associated health effects in the context of lipid disorders. This limited epidemiologic evidence provides evidence of increased risk with short- and long-term $PM_{2.5}$ exposure for those with elevated cholesterol compared to normal cholesterol.
- Additional epidemiologic studies stratifying by cholesterol medication (i.e., statins) usage provide limited evidence of increased risk of cardiovascular disease among statin users compared to those not taking statins.
- **Overall, the evidence is inadequate to determine if adults with elevated cholesterol are at increased risk for $PM_{2.5}$-related health effects.**

Elevated blood cholesterol is a common chronic health condition in the U.S., with the prevalence of hypercholesterolemia in the U.S. adult population approximately 26.0%, as reported by the 1999−2006 National Health and Nutrition Examination Surveys (Fryar et al., 2010). Metabolic disruption, such as dyslipidemia, can increase the risk of other health conditions, such as cardiovascular disease and diabetes. Additionally, as examined in Chapter 6 and Chapter 7, there is some evidence that short-term (Section 6.3.5, Section 7.1.3.3) and long-term (Section 6.3.12, Section 7.2.5.5) $PM_{2.5}$ exposures are associated with changes in blood lipids. While elevated blood cholesterol is an important health risk factor, few studies have explicitly investigated if blood cholesterol status increases the risk of other health outcomes associated with $PM_{2.5}$ exposure.

The PM 2009 ISA (U.S. EPA, 2009) did not evaluate studies examining potential differences in populations based on cholesterol. A limited number of epidemiologic studies have investigated differences between populations with and without high cholesterol, or by statin usage, and observed some evidence of higher risk for $PM_{2.5}$ related mortality and cardiovascular outcomes (Supplemental Table S12-4) (U.S. EPA, 2018). While these studies indicate those with elevated cholesterol, or those who use statins, may have potentially higher risks, overall, there were insufficient studies available to determine if cholesterol status consistently modifies health outcomes associated with $PM_{2.5}$ exposure.

In a study of 13 northeastern U.S. states, using data from the NHS cohort, Puett et al. (2009) evaluated the potential for effect measure modification by hypercholesterolemia status with $PM_{2.5}$ exposure over the 12-months prior to all-cause mortality, or a fatal coronary heart disease (CHD) event. In stratified analyses, the authors observed increased risk among those with hypercholesterolemia (HR: 1.53, 95% CI: 1.15−2.03) compared to those without hypercholesterolemia (HR: 1.04, 95% CI: 0.77−1.40). Puett et al. (2009) observed a similar trend among a smaller subset of fatal CHD cases. A

small study of myocardial infarction hospital admissions in Rochester, NY also observed a larger positive association among patients with history of dyslipidemia (Gardner et al., 2014).

In addition to studies with information on direct measures of blood cholesterol or patient history of dyslipidemia, several studies stratified study populations by use of statins or lipid-lowering medication. Long-term exposure studies in the U.S. and Germany (Bauer et al., 2010; Allen et al., 2009), as well as a meta-analysis of randomized controlled trials in Los Angeles (Künzli et al., 2010) observed increased risk of atherosclerosis associated with $PM_{2.5}$ exposure among those using statins compared to those not using statins. Studies of other health measures and long-term $PM_{2.5}$ exposure, such as history of peripheral vascular disease (Hoffmann et al., 2009b), and platelet counts (Viehmann et al., 2015) also observed increased risk among individuals using statins. A U.S. based study, using data from the MESA cohort, did not observe any substantial changes in $PM_{2.5}$-related flow-mediated dilation; however, they observed a positive association in baseline arterial diameter among those using statins compared to no change for those not using statins (Krishnan et al., 2012). Conversely, studies of short- and long-term exposure that investigated systemic inflammation found decreased responses for biomarkers of systemic inflammation among those using statins (Viehmann et al., 2015; Ostro et al., 2014; Hertel et al., 2010); however, many statins have anti-inflammatory properties complicating interpretation of these results.

Overall, the limited evidence is inadequate to determine if elevated cholesterol increases risk for $PM_{2.5}$-related health effects compared to cholesterol in the normal range. A single long-term exposure study reported elevated risk among those with hypercholesterolemia for $PM_{2.5}$-related mortality, while a single short-term study reported elevated risk of ST-Elevation Myocardial Infarction. Several studies examining biomarkers or preclinical measures of atherosclerosis and vascular function provide some evidence of elevated cardiovascular disease risk among statin users; however, the evidence base is small. Other studies examined if statin usage modified $PM_{2.5}$-related systemic inflammation; however, many statins have known anti-inflammatory properties, making these studies less informative in determining whether those with elevated cholesterol exhibited differential subclinical responses due to $PM_{2.5}$ exposure. Further limitations among studies of statins include the relatively low proportion of participants who used statins, leading to less precise estimates (i.e., wide 95% confidence intervals), as well as the difficulty in interpreting how representative statin prescription information is for control of blood lipid disorders among populations using statins.

12.3.5 Pre-existing Respiratory Disease

Overview

- The most common chronic respiratory diseases in the U.S. are asthma and COPD. Asthma affects a substantial fraction of the U.S. population, and it is the leading chronic disease among children. COPD primarily affects older adults and contributes to compromised respiratory function and underlying pulmonary inflammation.
- There is strong evidence indicating $PM_{2.5}$-associated respiratory effects among those with asthma, which forms the primary evidence base for the likely to be causal relationship between short-term exposures to $PM_{2.5}$ and respiratory health effects (Chapter 5).
- Few studies are available from the recent literature or in the 2009 PM ISA that inform whether those with asthma are at disproportionate risk for $PM_{2.5}$-related health effects compared to those without asthma.
- While there is some evidence of $PM_{2.5}$-related health effects in individuals with COPD, there are few studies from the current and previous ISAs with stratified analyses to compare effects in individuals with and without COPD
- **Overall, there is suggestive evidence that individuals with respiratory disease, particularly asthma, may be at increased risk for $PM_{2.5}$-related health effects compared to those without respiratory disease.**

Asthma

Approximately 8.3% of adults and 8.4% of children (age <18 years) in the U.S. currently have asthma (Blackwell and Villarroel, 2018), and it is the leading chronic illness affecting children. With regard to consideration of those with asthma potentially being at increased risk for a $PM_{2.5}$-related health effect, it is important to note that individuals with asthma, and children, tend to have a higher degree of oronasal breathing, which can result in greater penetration of PM into the lower respiratory tract (Section 4.1.3). Furthermore, there is limited evidence demonstrating that individuals with asthma may have altered clearance of particles (Section 4.3.4).

The 2009 PM ISA concluded that individuals with asthma may be more susceptible to health effects related to PM based on a limited number of epidemiologic studies for respiratory effects and controlled human exposure and animal toxicological studies demonstrating biological plausibility for asthma exacerbation with exposures to $PM_{2.5}$. Consistent with this, recent evidence evaluated in this ISA supports that there is likely to be a causal relationship between short-term exposure to $PM_{2.5}$ and respiratory effects, based primarily on evidence for asthma exacerbation in epidemiologic studies (Section 5.1.2) with supporting evidence across disciplines that provides biological plausibility (Section 5.1.1). Given this evidence, it is clear that individuals with asthma experience $PM_{2.5}$-related respiratory effects; however, evidence informing an increase in risk compared to those without asthma is limited.

There continue to be few studies that provide comparisons between individuals with and without asthma (Supplemental Table S12-5) (U.S. EPA, 2018). The 2009 PM ISA (U.S. EPA, 2009) included only a handful of epidemiologic and controlled human exposure studies examining $PM_{2.5}$ or CAPs exposures that provided some evidence for increased risk. Recent evidence is also limited to a few epidemiologic studies with stratified analyses for asthma for a variety of disparate outcomes. Of these studies, Watanabe et al. (2015) and Prieto-Parra et al. (2017) are most informative as they examined respiratory outcomes (i.e., lung function and symptoms) in children with and without asthma. Both studies demonstrated positive associations with short-term exposures to $PM_{2.5}$ for those without asthma, but symptoms and lung function decrements were of greater magnitude in children with asthma.

Other studies examined nonrespiratory outcomes. A study measuring cytokine responsiveness in blood samples collected from children with and without asthma in Germany demonstrated $PM_{2.5}$-related proinflammatory responses in children with asthma that were not observed in children without asthma for short-term exposures. In a multicity U.S. study in adults, $PM_{2.5}$ associated lung cancer mortality was greater in those with asthma compared to those without provide some evidence for increased risk in those with asthma compared to those without (Klümper et al., 2015; Turner et al., 2011). Bunch et al. (2011) conducted a study in Utah of hospital admissions with a primary diagnosis of atrial fibrillation and observed generally positive associations with $PM_{2.5}$ in those with and without asthma. In a study of diabetes incidence in Ontario, Canada, Chen et al. (2013) observed individuals with asthma to be at slightly decreased risk for diabetes with long-term exposures to $PM_{2.5}$ compared to those without.

Chronic Obstructive Pulmonary Disease (COPD)

Chronic lower respiratory disease, including COPD, was ranked as the third leading cause of death in the U.S. in 2011 (Hoyert and Xu, 2012). COPD comprises chronic bronchitis and emphysema and affects approximately 6.8 million adults in the U.S., respectively (Table 12-2). Given that people with COPD have compromised respiratory function and underlying systemic inflammation, it is plausible that they could be at increased risk for an array of $PM_{2.5}$-related health effects. Furthermore, there was some evidence to suggest differences in dosimetry, including greater deposition and impaired mucociliary clearance, that is also described in this ISA (Sections 4.2.4.7 and 4.3.4).

The 2009 PM ISA (U.S. EPA, 2009) described inconsistent results across a small evidence base examining differential $PM_{2.5}$-related respiratory effects in individuals with COPD and those without. In the current review, there continues to be limited evidence examining differential risk by COPD status and most of the available studies have focused on cardiovascular outcomes (Supplemental Table S12-5) (U.S. EPA, 2018). Wang et al. (2017) and Turner et al. (2011) observed greater risk for mortality associated with long-term exposures to $PM_{2.5}$ for those with COPD in a multicity study in the U.S. However, studies for cardiovascular hospitalizations (i.e., atrial fibrillation, myocardial infarction, acute coronary syndrome, and heart failure), incident hypertension, and diabetes incidence did not consistently demonstrate that those with COPD are at greater risk than those without in studies of short- and long-term

$PM_{2.5}$ exposures (Chen et al., 2014; Chen et al., 2013; Bunch et al., 2011; Belleudi et al., 2010; Rich et al., 2010; Haley et al., 2009). There are no recently published controlled human exposure studies that have examined health effects in individuals with COPD.

Despite limited evidence from epidemiologic and experimental studies examining $PM_{2.5}$-related health effects in those with and without pre-existing COPD, the evidence characterized in Chapter 5 demonstrates that there is evidence of COPD exacerbation associated with short-term exposure to $PM_{2.5}$ (Section 5.1.4), contributing to the conclusion of a "likely to be causal" relationship. In particular, epidemiologic studies report positive associations between $PM_{2.5}$ and hospital admissions and emergency department visits for COPD, with supporting evidence from panel studies demonstrating COPD exacerbation. Epidemiologic evidence is supported by limited experimental evidence of COPD-related effects, which provides biological plausibility for COPD in response to $PM_{2.5}$ exposure. This evidence indicates that $PM_{2.5}$-associated effects are observed in those with COPD, but it does not indicate if this risk is disproportionate compared to those without COPD.

Taken together, the collective evidence is suggestive that those with pre-existing respiratory diseases, particularly asthma and COPD, are at increased risk for $PM_{2.5}$-related health effects compared to those without pre-existing respiratory diseases. For asthma, there is strong evidence across disciplines indicating that there is likely to be a causal relationship for respiratory effects and $PM_{2.5}$ exposures based on asthma exacerbation, but few studies have conducted stratified analyses to inform increased risk. For COPD, the evidence base is limited to a few studies with inconsistent results for no respiratory outcomes.

12.4 Genetic Factors

Overview

- Variability in genetic background is known to contribute to the wide range of biological responses and diseases that are observed in the human population.
- Although limited, recent epidemiologic evidence is consistent with that characterized in the 2009 PM ISA, demonstrating differential risk for $PM_{2.5}$-related responses in individuals with variants in genes in the glutathione pathway that has a key role in oxidative stress.
- This is coherent with evidence supporting the biological plausibility for $PM_{2.5}$-related health effects as oxidative stress is an important early response following exposure.
- Several other genetic variants and epigenetic factors have been examined, but evidence is limited for each.
- **Overall, the evidence is suggestive that individuals with variants in the glutathione pathway are at increased risk for $PM_{2.5}$-related health effects compared to those without a variant genotype.**

Genetic variation in the human population is known to contribute to numerous diseases and differential physiologic responses. The potential for genetic background to modify responses to exposure to PM was evaluated in the 2009 PM ISA (U.S. EPA, 2009) and the biological plausibility of individuals with certain genotypes known to result in reduced function in genes encoding antioxidant enzymes being at increased risk for respiratory effects related to ambient air pollution was described. Though the evidence base for any particular genetic polymorphism was limited, the 2009 ISA concluded that evidence suggested that specific genetic polymorphisms could potentially increase the susceptibility of an individual to health effects related to PM exposure. In the recently published literature, several additional studies are available that examine genes related to antioxidant defense, inflammation, and lipid metabolism (Supplemental Table S12-6) (U.S. EPA, 2018).

Glutathione is the primary antioxidant defense in the body and is critical to protecting against oxidative stress. Because of this, variant genotypes in the glutathione pathway have been the most commonly studied with regard to health effects related to PM because oxidative stress is known to be one of the early biological responses following exposure (Sections 5.1.2, 5.2.1, 6.1.1, and 6.2.1). The 2009 PM ISA described results from a few studies that observed those with GSTM1 null genotypes to be at increased risk for cardiovascular effects related to $PM_{2.5}$ exposures (Schneider et al., 2008; Chahine et al., 2007; Schwartz et al., 2005). Of the recent epidemiologic evidence examining genetic variants in the oxidative stress pathway, only one study provides additional evidence for cardiovascular outcomes. Hampel et al. (2010) demonstrated that in adults with prior MI, $PM_{2.5}$-related QTc prolongation was greater in individuals with the minor allele for NFE2L2 rs1364725 compared to those with the major allele. Other recent evidence examines respiratory outcomes in children and provides additional support for effect measure modification by genetic background. For example, in a study of elementary and middle school children in Taiwan, $PM_{2.5}$-related increases in leukocytes and neutrophils in nasal lavage samples were greater in those with GSTM1 null genotypes compared to GSTM1 positive (Chen et al., 2016). Another study examined haplotypes in the glutathione synthetase gene (GSS) utilizing data from the Children's Health Study in southern California. While stratification for GSS haplotype 010000 demonstrated larger decrements in FVC in association with long-term $PM_{2.5}$ concentrations compared to other haplotypes, slightly smaller decrements in FEV1 and MMEF were observed for haplotype 010000 (Breton et al., 2011). Fuertes et al. (2013) conducted a pooled-analysis of 6 birth cohorts across Europe to examine associations in doctor-diagnosed allergic rhinitis at 7−8 years of age among variants for SNPs in GSTP1, TNF, TLR2, and TLR4. This study found positive associations for $PM_{2.5}$ and allergic rhinitis across all children, and magnitude of association in children with the minor alleles for GSTP1 (rs1138272) was slightly larger than those homozygous for the major allele. In addition, the magnitude of association between $PM_{2.5}$ and allergic rhinitis was slightly larger for those having minor alleles for SNPs in TNF (rs1800629) and TLR4 (rs10759930), implicating an inflammatory response with long-term exposure to $PM_{2.5}$.

Other studies examined a diverse range of genetic variants and outcomes. Wilker et al. (2011) examined modification of the $PM_{2.5}$-associated changes in adhesion molecules by genetic variants in

micro-RNA processing genes in the participants from the Normative Aging Study. Relatively little is known about the role of these genes relative to inflammation, but this study demonstrated that those having the minor allele for GEMIN4 (rs1062923) had lower levels of ICAM-1 and VCAM-1 in association with short-term $PM_{2.5}$ exposures. Ren et al. (2010) also used data from the NAS to evaluate genetic background, though the focus of this study $PM_{2.5}$-related HRV and modification by polymorphisms in lipid metabolism and endothelial function. A number of polymorphisms were examined in APOE, LPL, and VEGF and results demonstrated that the minor allele for the SNPs examined was associated with smaller reductions in HRV. Lastly, Hampel et al. (2012) examined effect modification by SNPs associated with cardiovascular outcomes as identified in the literature and demonstrated inconsistent results for CHT1 rs333229, rs2966762, rs1871841 and $PM_{2.5}$-related decrements in HRV, though the relevance of these SNPs is not clear.

Some recently published animal studies have also examined genetic variants, particularly in relation to PM-induced metabolic effects. Experimental genetic knockout studies in mice exposed to $PM_{2.5}$ support a role for TLR4 activation of Nox2 leading to a systemic inflammation (Kampfrath et al., 2011). In another study of mice deficient in the CC-chemokine receptor 2 (CCR2) gene, defective monocyte recruitment during immune responses were protected from $PM_{2.5}$ and high fat diet induction of hepatic steatosis, insulin resistance, systemic and peripheral inflammation (Liu et al., 2014). Other studies utilized a mouse model deficient in the neutrophil NADPH oxidase gene (required for superoxide anion production) and found that they were protected from CAPs-induced increases in superoxide production, insulin resistance, increase in abdominal mass and visceral adiposity, and fibrosis in mice (Zheng et al., 2015; Xu et al., 2010).

Recent evidence has also included the examination of DNA methylation and the underlying role it may play in $PM_{2.5}$-related health effects. Across the studies of DNA methylation (Peng et al., 2016; Lepeule et al., 2014; Bind et al., 2012; Salam et al., 2012), hypermethylation of a number of genes have been examined including iNOS, ICAM1, CRAT, ICAM, IFN-gamma, IL-6, iNOS, OGG1, GCR, F3, and TLR2. While there is some evidence that hypermethylation of these genes may play a role in mediating $PM_{2.5}$-related health effects when compared to hypomethylation, evidence is too limited to draw conclusions.

Overall, the evidence is suggestive that individuals with genetic variants in the glutathione pathway are at increased risk for $PM_{2.5}$-related health effects compared to those without variant genotypes. There is consistent evidence from a handful of studies in the recent literature and the 2009 PM ISA demonstrating that variants in the glutathione pathway may increase the risk of a PM-related health effect that is supported by evidence for biological plausibility and a role for oxidative stress in initial responses to exposures to $PM_{2.5}$. A variety of other variants have been examined in addition to studies of DNA methylation in $PM_{2.5}$-related health effects, but the evidence is too limited to determine if they modify risk.

12.5 Sociodemographic Factors

12.5.1 Lifestage

The 2009 ISA for Particulate Matter (U.S. EPA, 2009) discussed some evidence for increased risk of health effects related to PM exposure among different lifestages (i.e., children and older adults). Lifestage refers to a distinguishable time frame in an individual's life characterized by unique and relatively stable behavioral and/or physiological characteristics that are associated with development and growth (U.S. EPA, 2014). Differential health effects of PM across lifestages could be due to several factors. With regard to children, the human respiratory system is not fully developed until 18−20 years of age, and therefore, it is biologically plausible that children may have intrinsic risk for respiratory effects due to potential perturbations in normal lung development. Older adults, typically considered those 65 years of age or greater, have weakened immune function, impaired healing, decrements in pulmonary and cardiovascular function, and greater prevalence of chronic disease (Table 12-2), which may contribute to, or worsen health effects, related to PM exposure. Also, exposure or internal dose of PM may differ across lifestages due to varying ventilation rates, increased oronasal breathing at rest, and time-activity patterns. The following sections present the evidence comparing lifestages from the recent literature, which builds on the evidence presented in the 2009 Particulate Matter ISA (U.S. EPA, 2009).

12.5.1.1 Children

Overview

- Children makeup a substantial fraction of the population and often have unique risks because of their continuous growth and development.
- Limited recent evidence indicates that children may have higher $PM_{2.5}$ exposures than adults and that there are dosimetric differences in children compared to adults.
- Strong evidence demonstrates $PM_{2.5}$-associated health effects in children, particularly from recent epidemiologic studies of short-term $PM_{2.5}$ exposure and impaired lung function growth, decrements in lung function, and asthma development.
- Evidence from stratified analyses in the current and previous ISAs demonstrates generally positive associations with $PM_{2.5}$ exposure of similar magnitudes for children and adults.
- **Overall, evidence is adequate that children are at increased risk for $PM_{2.5}$-related health effects, with the strongest evidence from associations with effects specifically examined in children (e.g., lung function growth and asthma development).**

Children may be particularly at risk for health effects related to ambient $PM_{2.5}$ exposures compared to adults due to (1) children's developing respiratory system, (2) children's increased ventilation rates relative to body mass compared to adults, and (3) the increased proportion of oral

breathing observed among children, particularly boys, relative to adults. Such oral breathing can result in higher exposures compared to nasal breathing (Section 4.2.4.2). In addition, children tend to spend more time outdoors, and, consequently, have the potential for greater exposure to ambient $PM_{2.5}$. Consistent with these opportunities for greater exposure, Bell and Ebisu (2012) observed higher $PM_{2.5}$ exposures among children and young adults (0−19 years) compared to adults (20−64 years). According to the 2010 census, 24% of the U.S. population is less than 18 years of age, with 6.5% less than age 6 (Howden and Meyer, 2011). The large proportion of children within the U.S. supports the public health significance of characterizing the risk of PM-related health effects among children.

While there is some evidence to inform dosimetric and exposure differences among children (Sections 4.2.4 and 4.3.4), there has been little evidence from stratified analyses to demonstrate children being at increased risk of the health effects associated with $PM_{2.5}$ exposure compared to adults. That is, positive effect estimates are often observed in stratified analyses of children, but these effect estimates are similar in magnitude to those observed for adults (Supplemental Table S12-7) (U.S. EPA, 2018). For example, recent studies of short-term $PM_{2.5}$ exposure and respiratory hospital admissions or ED visits report consistent, positive associations among analyses restricted to children; the magnitude of these associations is similar to those observed for adults (Atkinson et al., 2016; Samoli et al., 2016; Xu et al., 2016). Overall, the evidence from recent studies is consistent with previously evaluated evidence. The 2004 PM AQCD, summarizing studies examining either PM_{10} or $PM_{2.5}$, concluded that the "rather small group of studies does not show striking differences in effect estimates from analyses across age group strata" (U.S. EPA, 2004). The 2009 PM ISA(U.S. EPA, 2009) presented evidence from a single study of $PM_{2.5}$ (Mar et al., 2004) that observed stronger respiratory effects in children (7−12 years) compared to adults (20−51 years).

Other epidemiologic studies did not stratify results by lifestage, but instead restricted the analyses to children, and provide evidence for the occurrence of effects for a particular lifestage (i.e., effects that can only be observed in children). This is the case for a number of longitudinal studies of long-term $PM_{2.5}$ exposure and lung development (Section 5.2.2.1.1), lung function (Section 5.2.2.2.1), and asthma development (Section 5.2.3.1) in children. Recent longitudinal studies, particularly those from the Children's Health Study (CHS), are consistent with and extend the evidence that was available in the 2009 PM ISA demonstrating that long-term $PM_{2.5}$ exposure is associated with impaired lung function growth, decrements in lung function, and increased incidence of asthma development in children. Toxicological studies provide support for these associations in children as pre- and post-natal exposure to ambient levels of urban particles were found to impair mouse lung development. Recent results from the CHS not only corroborate previous results, but they also indicate improvements in lung development in association with declining $PM_{2.5}$ concentrations (Gauderman et al., 2015). In addition, a number of recent prospective and retrospective cohort studies based in North America and Europe provide evidence that long-term $PM_{2.5}$ exposure is associated with asthma development in children (Section 5.2.3.1).

Additional studies compared different age groups within the childhood lifestage. (Ding et al., 2016) evaluated asthma ED visits in Chongqing, China and observed higher effect estimates among 2−5 year old children compared to 0−1 or 6−18 year old children, though the inability to reliably diagnose asthma in younger children may contribute to the heterogeneity in these results. When considering ED visits due to pneumonia in Jinan, China, (Lv et al., 2016) reported higher effect estimates for infants (<1 year old) and young children (1−4 years old) compared to older children (5−15 years old).

In summary, the evidence demonstrating $PM_{2.5}$-associated health effects in children is adequate to conclude that children are at increased risk for $PM_{2.5}$-related health effects. There is strong evidence that children are at increased risk to the effects of $PM_{2.5}$ exposure, based primarily on studies examining effects specific to children. Epidemiologic studies of long-term $PM_{2.5}$ exposure demonstrate associations with impaired lung function growth (Section 5.2.2.1.1), decrements in lung function (Section 5.2.2.2.1), and increased incidence of asthma development in children (Section 5.2.3.1). The evidence from stratified analyses provides limited evidence that children are at increased risk of $PM_{2.5}$-related health effects compared to adults. In addition, there is some evidence indicating that children receive higher $PM_{2.5}$ exposures than adults and there are dosimetric differences in children compared to adults that can contribute to higher doses. Finally, there is emerging evidence from two Chinese studies suggesting that ages 1 to 5 years could be a critical window among children during which they experience respiratory health effects associated with short-term $PM_{2.5}$ exposure.

12.5.1.2 Older Adults

Overview

- Older adults represent an increasing portion of the U.S. population and often have pre-existing diseases/conditions that may compromise biological function.
- Limited recent evidence does not indicate that older adults have higher $PM_{2.5}$ exposures than younger adults, though older adults could receive higher doses due to dosimetric differences.
- Consistent evidence demonstrates $PM_{2.5}$-associated health effects in older adults, particularly between short- and long-term $PM_{2.5}$ exposure and mortality as well as cardiovascular or respiratory morbidity.
- Evidence from stratified analyses in the current and previous ISAs demonstrates similar associations with $PM_{2.5}$ exposure in older adults and younger adults.
- Animal toxicological and controlled human exposure studies provide additional evidence for the occurrence of effects among this particular lifestage, but do not inform whether or not this lifestage is at increased risk to the health effects of $PM_{2.5}$.
- **Overall, while $PM_{2.5}$-associated effects are observed in older adults, evidence is inadequate to determine if older adults are at increased risk for effects compared to younger adults.**

Older adults are a potentially at increased risk population due to the higher prevalence of pre-existing cardiovascular and respiratory diseases found in this age range compared to younger life stages. The increased risk in this lifestage can likely be attributed to the gradual decline in physiological processes that occurs with aging (U.S. EPA, 2006). Therefore, some overlap exists between populations considered to be at-risk due to pre-existing disease and lifestage (i.e., older adults) (Kan et al., 2008). According to the 2014 National Population Projections issued by the U.S. Census Bureau, approximately 14.9% of the U.S. population is age 65 years or older, and by 2040, this fraction is estimated to grow to 21.7% (U.S. Census Bureau, 2014); accessed November 9, 2017. Thus, this lifestage represents a substantial proportion of the U.S. population demonstrating the public health importance of characterizing the potential for increased risk for health effects related to $PM_{2.5}$ exposure in this age group.

The 2009 ISA for Particulate Matter (U.S. EPA, 2009) indicated that compared with younger adults, older adults (typically ages 65 years and older) may be susceptible to PM-related cardiovascular effects. The evidence from epidemiologic, controlled human exposure and animal toxicological studies were generally consistent and coherent in supporting this conclusion, though some geographic heterogeneity in the pattern of associations among studies conducted in U.S. and non-U.S. locations was acknowledged. Additional evidence for associations between short-term PM exposure and respiratory morbidity and mortality was also available, and generally limited to results from epidemiologic studies.

Recent studies contribute to the existing body of evidence evaluating whether: (1) older adults experience higher exposures to $PM_{2.5}$ compared to younger adults; (2) stratified analyses conducted in epidemiologic studies support increased risk of health effects among older adults compared to younger adults; (3) animal toxicological, controlled human exposure, and epidemiologic analyses restricted to older populations provide coherence for the occurrence of effects for this particular lifestage, and (4) there is evidence for variability in associations among different age groups within the older adults lifestage.

Clearance of $PM_{2.5}$ from all regions of the respiratory tract decreases with increasing age beyond young adulthood in both humans and laboratory animals, indicating that older adults could receive higher doses of $PM_{2.5}$ compared to younger adults (Section 4.3.4). However, there is little evidence indicating that older adults are systemically exposed to higher concentrations of $PM_{2.5}$ than other lifestages. Miranda et al. (2011) observed that older adults (i.e., 65+ years) were less likely to live in counties with the highest daily or annual $PM_{2.5}$ concentrations. Consistent with this, Bell and Ebisu (2012) observed similar $PM_{2.5}$ exposures among older adults (65+ years) compared to adults (20−64 years).

A relatively large number of recent epidemiologic studies of short- and long-term $PM_{2.5}$ exposure and cardiovascular and respiratory health effects, as well as mortality, report generally consistent, positive associations among analyses restricted to older adults, though the magnitude of these associations is similar to those observed for younger adults (Supplemental Figure S12-8) (U.S. EPA, 2018). Studies of short-term $PM_{2.5}$ exposure and cardiovascular or respiratory effects generally consist of evaluations of hospital admission, emergency department visits, or mortality conducted in the U.S., Canada, Europe, or China. Generally, positive associations were observed for both younger adults and older adults with no

indication that the associations observed for older adults were consistently greater in magnitude. A number of studies of long-term $PM_{2.5}$ exposure evaluated associations with cardiovascular effects among older adults and younger adults and did not observe stronger magnitude of effects among the older adults. Evaluations of subclinical cardiovascular effects (e.g., blood pressure, measures of vascular functions, concentrations of circulating biomarkers) were somewhat less consistent in demonstrating positive associations with long-term $PM_{2.5}$ concentrations compared to cardiovascular mortality. Similar to the results of studies of long-term $PM_{2.5}$ exposure and cardiovascular mortality, both short- and long-term $PM_{2.5}$ exposures were consistently associated with total (nonaccidental) mortality, but there was no indication that these associations were of greater magnitude in older adults compared to younger adults (Supplemental Figure S12-8) (U.S. EPA, 2018).

Though there are a relatively large number of epidemiologic studies evaluating the associations between $PM_{2.5}$ concentrations and health effects as detailed in (Supplemental Figure S12-8), it is noteworthy that there is substantial variability in the age ranges included as the reference group. For example, sometimes the reference group included all individuals less than a certain age (e.g., 60, 65, or 70 years), while other times the reference group included individuals from a smaller, more restricted range of ages (e.g., 35−64, 40−69, or 45−64 years). Such variability in the reference groups makes it difficult to make comparisons about the magnitude of effects across studies, though it should not affect inferences about whether older adults are at increased risk of $PM_{2.5}$-related health effects compared to younger adults. Additionally, it is possible that the results of stratified analyses could be affected by publication bias; several studies conducted stratified analyses by lifestage but did not report quantitative results when no differences were observed across strata. While likely to exist, such publication bias is unlikely to influence any inferences drawn from the body of evidence evaluated here, as these studies also did not generally observe differences in associations across age strata. Finally, some studies compared associations for older adults to those for all ages (including the older adults). Since these are not truly stratified analyses, and there is overlap between the two groups, results from those studies are not considered here nor included in Supplemental Figure S12-8 (U.S. EPA, 2018)

Several animal toxicological, controlled human exposure, and epidemiologic studies did not stratify results by lifestage, but instead restricted the analyses to older individuals, and can provide coherence and biological plausibility for the occurrence of effects among this particular lifestage. When considering animal toxicological studies, the 2009 PM ISA reported that exposure to $PM_{2.5}$ CAPs was associated with arrhythmias in older, but not younger rats. Recent studies extend the evidence that was available in the 2009 PM ISA from controlled human exposure studies demonstrating that $PM_{2.5}$ CAPs exposure is associated with decreases in HRV in older, healthy adults. In Copenhagen, Denmark, Hemmingsen et al. (2015) exposed older overweight, but healthy men and women to traffic-related air pollution (TRAP) that was nonfiltered or particle filtered and observed decreased high frequency measurements and increased low frequency measurements when nonfiltered TRAP was compared to particle filtered. In a dietary intervention study, Tong et al. (2012) reported that after a 28-day

supplementation period with olive oil, there was a lower HF/LF ratio immediately after CAP exposure in older adults. There were no changes in HRV time domain measurements found in this study.

Recent epidemiologic panel studies have observed associations with cardiovascular morbidity and $PM_{2.5}$ exposure among older adults (Sections 6.2.2.2, 6.2.6.2, and 6.2.11.1). In one study of older adults with ischemic heart disease in nursing homes in Los Angeles, CA, $PM_{2.5}$ concentrations were associated with ST-segment depression (Delfino et al., 2011). In addition, panel studies of older adult populations report generally consistent evidence for an association between short-term $PM_{2.5}$ exposure and BP, particularly studies including participants living in nursing homes or senior communities which allow for improved exposure assessment (Jacobs et al., 2012; Wellenius et al., 2012b; Liu et al., 2009). Among studies of inflammatory markers, the evidence was less consistent. Some panel studies of older adults observed positive associations between $PM_{2.5}$ and inflammatory IL6 and TNF in a (Wittkopp et al., 2013; Delfino et al., 2009), while others did not (Wang et al., 2016a; Rich et al., 2012; Liu et al., 2009).

Additional studies compared different age groups within the older adult lifestage. For example, Bell et al. (2015) observed higher magnitude effect estimates among those 85+ years compared to those aged 65−74 or 75−84 years for cardiovascular mortality, but not for respiratory mortality and short-term $PM_{2.5}$ exposure. Conversely, Madsen et al. (2012) observed higher effects among those aged 65−74 compared to those aged 74−85 or 85+ when examining short-term $PM_{2.5}$ exposure and total mortality. When evaluating long-term $PM_{2.5}$ exposure and total mortality and cardiovascular mortality, Crouse et al. (2015) observed positive associations for both men and women across age groups (i.e., 60−69, 70−79, 80−89 years). This is inconsistent with evidence reported in the 2009 PM ISA, where limited evidence indicated declines in effect estimates for mortality with increasing age, starting at 60 until there was generally a null association among individuals 85+ years. Overall, there is no consistent evidence that risk varies for different age groups within the older adult lifestage.

Overall, there continues to be evidence supporting that $PM_{2.5}$-associated health effects are present in older adults; however, the evidence is inadequate to determine whether older adults are at increased risk of $PM_{2.5}$-related health effects when compared to younger adults. Among epidemiologic studies of short- and long-term $PM_{2.5}$ exposure, there is little evidence to support increased risk of health effects among older adults compared to younger adults. While there is limited evidence that changes in physiology could result in decreased ability to clear $PM_{2.5}$ from the respiratory tract, there is no evidence that older adults are exposed to high $PM_{2.5}$ concentrations than younger adults. Animal toxicological, controlled human exposure, and epidemiologic studies continue to support that older adults are at risk to the effects of $PM_{2.5}$ exposure, especially cardiovascular effects. This evidence comes mainly from epidemiologic panel studies of short-term $PM_{2.5}$ exposure observing associations with cardiovascular morbidity among older adults residing in nursing homes, decreases in HRV in controlled human exposure studies of older adults, and increased arrhythmias in older rats in animal toxicological studies. Studies that did not stratify results by lifestage, but instead restricted the analyses to older individuals, provide coherence and biological plausibility for the occurrence of effects among this

particular lifestage. Finally, there is no consistent evidence to indicate that any age groups within the older adult lifestage have higher risks than others.

12.5.2 Sex

Overview

- Males and females in the U.S. have differing health concerns; for example, health effects related to reproduction (e.g., sperm motility in males and pregnancy outcomes in females) are sex-specific.
- For health outcomes concerning both sexes, there is some evidence of higher mortality in males than in females from long-term exposures to $PM_{2.5}$.
- For other health outcomes from long-term $PM_{2.5}$ exposure, and for outcomes from short-term $PM_{2.5}$ exposure, there is no clear pattern of increased risk for either sex.
- **Overall, the evidence in inadequate to determine if males are at increased risk for $PM_{2.5}$-related health effects compared to females.**

A large number of health conditions resulting in morbidity and mortality have been shown to differ by sex. The Centers for Disease Control and Prevention estimate that a male born in the U.S. in 2012 has a life expectancy of 76.4 years, while a female has a life expectancy of 81.2 years (Arias et al., 2016). Due to both biological and social differences it is reasonable to consider that the risks of exposure to air pollution may differ between sexes. For example, exposure risks related to gestation and fetal development will primarily concern females and differences between sexes in time spent at the workplace or at home (U.S. BLS, 2017) will potentially contribute to differences in PM exposure. Sex-specific biological risks related to fertility are described in Chapter 9 of this document. Briefly, health outcomes specifically concerning males include potentially decreased sperm motility (Radwan et al., 2015; Hammoud et al., 2009). Outcomes specifically concerning females involve pregnancy-related morbidity; this includes outcomes such as gestational hypertension, preterm birth, and low birth weight. Overall, evidence in Chapter 9 was considered suggestive of a causal relationship between $PM_{2.5}$ exposure and these sex-specific reproductive health concerns.

The 2009 PM ISA (U.S. EPA, 2009) concluded that neither sex had a consistently stronger association between PM exposure and health effects. Evidence from the recent literature generally supports this conclusion, though there may be specific outcomes that differ in risk by sex. Due to the lower life expectancy of males in the U.S., females have been selected as the "reference" category; however, either sex could be considered a potential "at-increased-risk" group of interest.

There is some evidence for differences in mortality due to PM exposure by sex, with males having potentially stronger associations than females (Supplemental Table S12-9) (U.S. EPA, 2018). Di et al. (2017) analyzed long-term $PM_{2.5}$ exposure and mortality in the U.S. Medicare population and found

a higher association for males (RR: 1.087, 95% CI: 1.083, 1.090) than for females (RR: 1.060, 95% CI: 1.057, 1.063). However, this was not the case for Medicaid-eligible (low-income) Medicare recipients, who did not display this difference between the sexes. While this is among the more comprehensive studies on this topic, other results of national U.S.-based long-term exposure studies have been inconsistent. A study by Wang et al. (2017) which includes an overlapping study population with that of Di et al. (2017) focuses on Medicare beneficiaries in the Southeastern U.S. only, and consistent with Di et al. (2017), the mortality-PM association within this region was also stronger for males than for females. Other studies report results ranging from males having roughly the same risk (Thurston et al., 2015) to slightly lower risk (Zeger et al., 2008) than females. In Canada, Crouse et al. (2015) reported higher PM-associated mortality among males in each age bracket considered and higher mortality among males as a group overall. The short-term $PM_{2.5}$-related effect differences on mortality by sex are negligible, with Huang et al. (2012) and Madsen et al. (2012) reporting slight increases for all-cause mortality in males and Samoli et al. (2013) reporting a slight decrease for males for non-accidental mortality.

Other studies have examined effect measure modification by sex for $PM_{2.5}$-associated cardiovascular effects. In a study of hospitalizations for U.S. Medicare beneficiaries, Bell et al. (2015) reported higher risks for females than for males from short-term $PM_{2.5}$ exposure for cardiovascular outcomes overall, as well as for heart rhythm disturbance and heart failure specifically. However, this observation was found to vary geographically, and this disparity was more pronounced in the Northeast than in other regions of the U.S. (Bell et al., 2015). In contrast, a study of short-term $PM_{2.5}$ exposure in Little Rock, Arkansas demonstrated that males had a greater association than females for cardiovascular-related emergency room visits (Rodopoulou et al., 2015). Short-term exposure studies conducted outside the U.S. have reported associations larger in magnitude for cardiovascular mortality in females (Milojevic et al., 2014) and congenital heart disease in males (Ye et al., 2016). However, in general for short-term exposure to $PM_{2.5}$, there is little evidence supporting the presence of disparities in cardiovascular outcomes between males and females. Specifically, in studies examining cardiovascular outcomes overall (Lanzinger et al., 2016; Kloog et al., 2014), cardiovascular mortality (Su et al., 2015), cardiac arrest (Silverman et al., 2010), heart failure (Haley et al., 2009), hypertension (Brook and Kousha, 2015), infarctions (Weichenthal et al., 2016; Rich et al., 2010), pulmonary embolism (Dales et al., 2010), and venous thrombosis (Dales et al., 2010) there was little difference in the magnitude of associations between males and females.

Similarly, evidence does not indicate disparities in cardiovascular outcomes from long-term $PM_{2.5}$ exposure. As with short-term exposures, disparities may vary by the specific characteristics of the population. A study of the U.S. population as a whole found little difference in CVD mortality by sex (Thurston et al., 2015), yet a study focused on families in the agricultural sectors of Iowa and North Carolina found somewhat higher mortality risk in males (Weichenthal et al., 2014). In general, however, recent long-term $PM_{2.5}$ exposure studies show only minor differences in outcomes by sex for heart disease (Wong et al., 2015; Johnson and Parker, 2009), hypertension (Chen et al., 2014; Johnson and Parker,

2009), blood pressure (Fuks et al., 2011), and cardiovascular disease or cardio-metabolic disease in general (Crouse et al., 2015; Wong et al., 2015).

There is little evidence for disparities in respiratory outcomes between males and females from long-term $PM_{2.5}$ exposures. A study of 50−71 year-olds in the U.S. found only a minor increase in respiratory mortality for women compared to men (Thurston et al., 2015). Conversely, a meta-analysis of European studies found a minor increase in men compared to women (Dimakopoulou et al., 2014). Wong et al. (2015) found little evidence of effect modification by sex for respiratory outcomes in Hong Kong. For short-term $PM_{2.5}$ exposure, Bell et al. (2015) found somewhat increased association in females for respiratory hospital admissions overall as well as for respiratory tract infections specifically. Other studies have found only negligible differences between males and females for respiratory hospital admissions (Lanzinger et al., 2016; Liu et al., 2016; Rodopoulou et al., 2015), pediatric asthma (Gleason et al., 2014), and peak expiratory flow (Watanabe et al., 2015).

Overall, the evidence is inadequate to determine if males are at increased risk for $PM_{2.5}$-associated health effects compared to females. There is some evidence that males may have higher mortality risk due to long-term $PM_{2.5}$ exposure than females. However, for other health outcomes associated with long-term $PM_{2.5}$ exposure as well as for morbidities resulting from short-term $PM_{2.5}$ exposure, there is inconsistent evidence that either males or females are at higher risk. In considering this evidence, it is also important to note that certain health outcomes are sex-specific. For example, there is some evidence for effects related to gestation that apply only to females and are not represented in sex-stratified studies, but this evidence is also inconsistent.

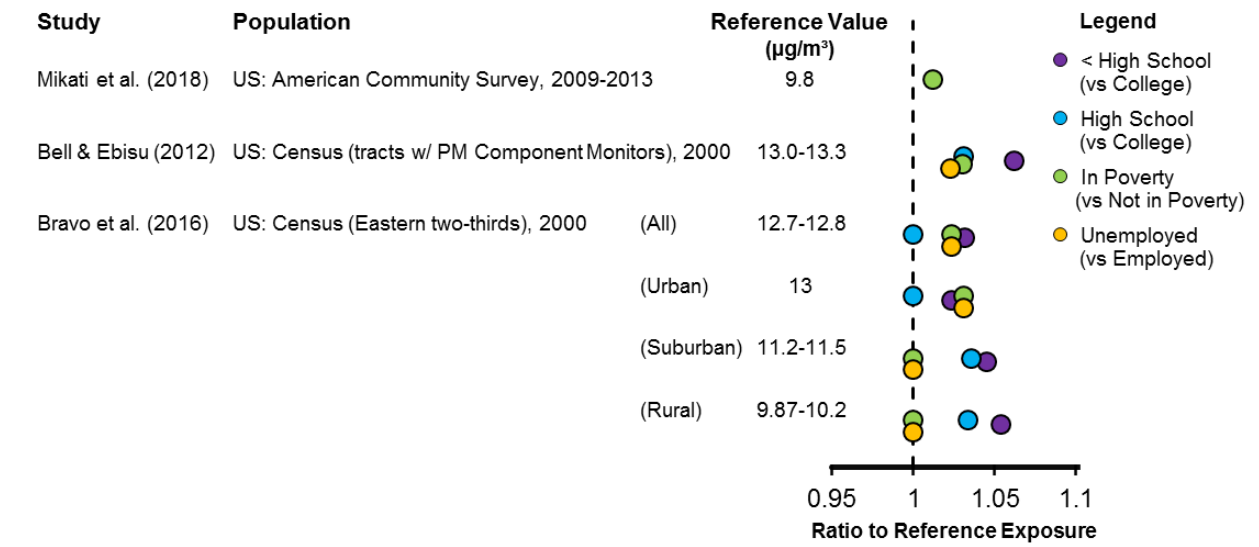
12.5.3 Socioeconomic Status

Overview

- Socioeconomic status (SES)—a composite measure that can include metrics such as income, education, or occupation—plays a role in access to healthy environments as well as access to healthcare in the U.S. Thus, SES may underlie differential risk for $PM_{2.5}$-related health effects.
- There is some evidence that demonstrates that having low income or living in lower-income areas results in stronger associations between mortality and long-term $PM_{2.5}$ exposures compared to higher-income counterparts.
- There is no clear pattern of differential risk when comparing effects in those with low educational attainment compared to higher educational attainment.
- **Taken together, the combination of exposure disparities and health evidence is suggestive that low SES populations are at increased risk for $PM_{2.5}$-related health effects compared to higher SES populations.**

Socioeconomic status (SES) is a composite measure that can represent various interrelated factors including income, education, or occupation—both in terms of the individual and in terms of the surrounding population's composition. The variety of metrics that fall under the umbrella of SES makes it difficult to make direct comparisons; for example, an income that is considered low in a particular city may be higher on the distribution of income at the national level. Furthermore, differences in social conditions from country to country make comparisons with studies taking place outside the U.S. difficult. However, it is still important to consider differential risk for $PM_{2.5}$-related health effects for SES. According to the U.S. Census Bureau, 12.7% of the U.S. population are living in poverty as of 2016 (Semega et al., 2017); 10.9% of the population aged 25 years and older does not have a high school diploma (U.S. Census Bureau, 2017a). Lower SES can impact place of residence and thus exposure to pollutants; it may be correlated with pre-existing health conditions that are potentially aggravated by air pollution; and it may result in inequities in access to resources such as healthcare.

Disparity in exposure to $PM_{2.5}$ due to differences in ambient $PM_{2.5}$ at the place of residence is one way in which SES may be related to PM risk (Figure 12-1). Mikati et al. (2018) compared modeled ambient $PM_{2.5}$ data for census tract populations across the U.S. and reported exposure to slightly higher concentrations of $PM_{2.5}$ for those living below the poverty line. Bell and Ebisu (2012) reported that those with less than a high school education, the unemployed, and those below the poverty line are exposed to higher concentrations of $PM_{2.5}$ (and to several $PM_{2.5}$ components) than do their higher-SES counterparts. Bravo et al. (2016) reported that lower educational attainment (no college degree) was associated with exposure to high $PM_{2.5}$ concentrations in suburban and rural areas (as well as urban areas when limiting to those without a high school diploma), and poverty status and unemployment were associated with exposure to high $PM_{2.5}$ concentrations in urban areas.



Note: Group for reference exposure listed in parentheses under legend.
Source: Permission pending, Mikati et al. (2018), Bell and Ebisu (2012), Bravo et al. (2016).

Figure 12-1 Differences in $PM_{2.5}$ exposure by socioeconomic status (SES).

The 2009 PM ISA (U.S. EPA, 2009) found some evidence for increased risk of mortality due to short-term $PM_{2.5}$ exposure in low-SES individuals. More recent studies have added to our understanding of the relationship between SES and PM-related health effects., including evidence where a variety of SES metrics and categories have been simplified into "high," "medium," and "low" status.

Several studies examined differential risk for $PM_{2.5}$-related mortality by SES level (Supplemental Table S12-11) (U.S. EPA, 2018). An expansive study examining the association between long-term exposure to $PM_{2.5}$ and mortality in the cohort of all Medicare beneficiaries in the U.S. reported that low-SES individuals, as measured by Medicaid eligibility, had a higher risk of $PM_{2.5}$-related mortality than high-SES individuals (Di et al., 2017). Another pair of studies focusing on the Medicare population reported that those living in low-income neighborhoods or low-SES cities have a slightly higher risk of long-term $PM_{2.5}$-related mortality than those in higher-income neighborhoods or higher-SES cities (Wang et al., 2017; Kioumourtzoglou et al., 2016). Residents of low-SES ZIP codes have slightly higher risk of mortality from long-term PM exposure than residents of high-SES ZIP codes in the Eastern, Central, and Western U.S. (Zeger et al., 2008). Studies conducted in Canada have reported similar results (Crouse et al., 2015; Brook et al., 2013). Mortality outcomes from a study of short-term $PM_{2.5}$ exposure in Norway reported slightly decreased risk in low-SES areas compared to higher-SES areas (Madsen et al., 2012).

Studies focusing on educational attainment have reported mixed results. Lee et al. (2015) reported that the risk of mortality from short-term $PM_{2.5}$ for those in their study area of GA, NC, and SC was more than doubled in the group that had eight or fewer years of education compared to the group having more

than eight years of education. While at least one European study reported lower risk of $PM_{2.5}$-related mortality for low-education individuals (Beelen et al., 2014a), other studies in the U.S. have reported either negligible differences by education status (Thurston et al., 2015) or higher risk of $PM_{2.5}$-related mortality for lower-education individuals (Kloog et al., 2013).

There is little evidence that the effect of $PM_{2.5}$ exposure on cardiovascular health outcomes is modified by SES. Coogan et al. (2016) conducted an analysis focused on long-term $PM_{2.5}$ exposure in a cohort of black women; among this subset of the population, risk of hypertension as a result of $PM_{2.5}$ was somewhat more pronounced in women outside the highest quintile of neighborhood SES, raising the possibility that race and SES interact. Kloog et al. (2014) reported that the increase in hospital admissions from short-term $PM_{2.5}$ exposure was greater in low income groups than in high income groups; however, other studies reporting CVD effects for both short-term (Haley et al., 2009) and long-term exposure (Johnson and Parker, 2009) have not reported this to be the case. A German study on the effects of long-term $PM_{2.5}$ exposure on blood pressure found no increase in risk for the unemployed compared to the employed (Fuks et al., 2011).

Results of CVD studies using education attainment as a metric of SES have been inconsistent (Supplemental Table S12-10) (U.S. EPA, 2018). Thurston et al. (2015) reported little difference in long-term $PM_{2.5}$-related CVD mortality between those with less than a high school education and those with greater than a high school education. Those with exactly a high school level education, however, had somewhat higher associations than either of these two groups. Increased CVD risk within an intermediate educational group was also reported by Coogan et al. (2016) which showed that participants with some college education had higher risk of hypertension from long-term $PM_{2.5}$ exposure than did college graduates or those without any college education. Johnson and Parker (2009) reported slightly higher associations for heart disease and for hypertension from long-term $PM_{2.5}$ exposure in lower-education individuals. Studies outside the U.S. have not shown that lower education individuals are more at risk for cardiovascular outcomes (Chen et al., 2014; Fuks et al., 2011).

The evidence that SES modifies the association between respiratory morbidity from PM exposure is also weak. Multiple Atlanta-based studies examining short-term $PM_{2.5}$ exposure and asthma reported results including slightly higher odds of asthma attacks for those in high-poverty ZIP codes and for those who were eligible for Medicaid, as well as those with lower maternal educational attainment (O'Lenick et al., 2017; Strickland et al., 2014; Sarnat et al., 2013). Another study based in New Jersey found little distinction in outcomes between low, moderate, and high-SES participants (Gleason et al., 2014). Thurston et al. (2015) reported that long-term exposure and respiratory mortality were not more strongly associated for lower-education groups than for those with more than a high school education.

Taken together, the combination of exposure disparities and health evidence is suggestive that low SES populations are at increased risk for $PM_{2.5}$-related health effects compared to populations of higher SES. Several studies show increased risk of overall $PM_{2.5}$-related mortality for

lower-income groups, but the metrics for income vary widely across studies. In addition, there is also weak evidence for differential risk for $PM_{2.5}$-related outcomes by educational attainment.

12.5.4 Race

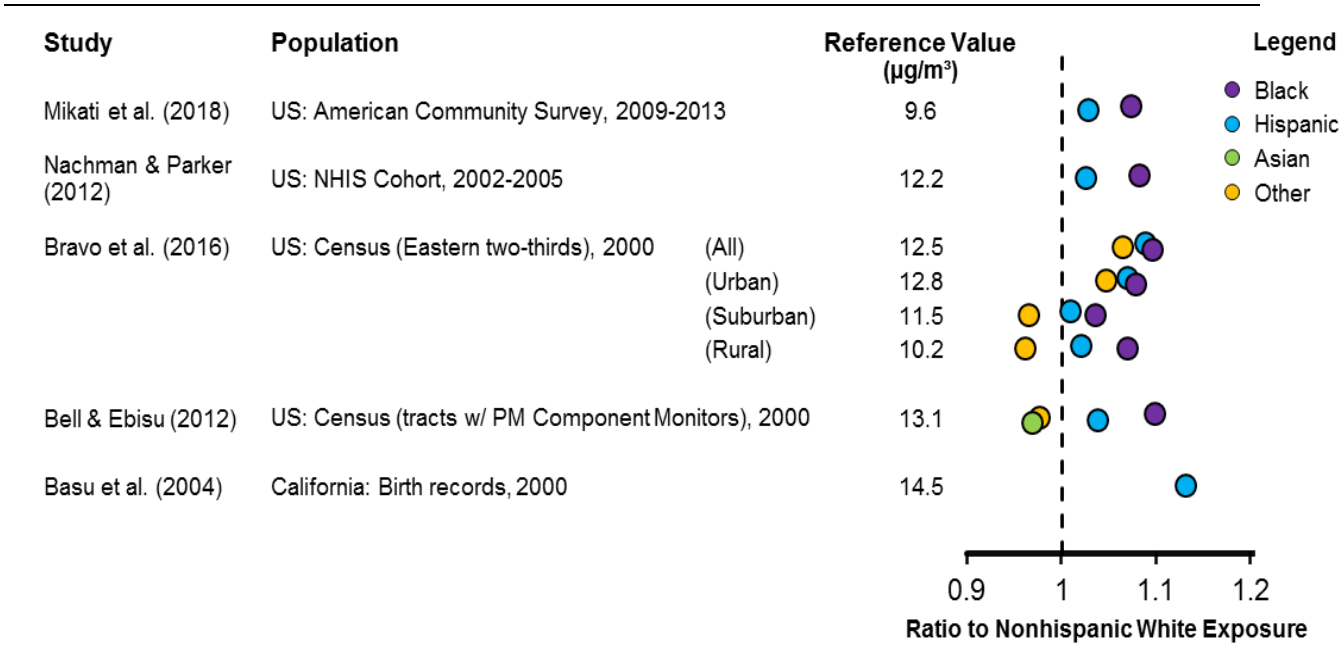
Overview

- People of different racial and ethnic backgrounds often have different health status disparities. The 2009 PM ISA found little evidence for increased $PM_{2.5}$-related risk by race and some evidence of increased risk by Hispanic ethnicity.
- Recent evidence demonstrates that there are consistent racial and ethnic disparities in $PM_{2.5}$ exposure across the U.S., particularly for blacks and African Americans compared to Nonhispanic whites.
- Recent studies provide evidence consistent with increased $PM_{2.5}$-related mortality from long-term exposure in blacks/African Americans; for $PM_{2.5}$-related health effects besides mortality there is also a general pattern of racial and ethnic disparities.
- **Overall, there is adequate evidence that race and ethnicity modify $PM_{2.5}$-related risk and that nonwhites, particularly Blacks, are at increased risk for $PM_{2.5}$-related health effects, in part due to disparities in exposure.**

Race and ethnicity are not biological categories but instead represent social definitions that broadly correspond to national origins (U.S. Census Bureau, 2017b). The U.S. Census Bureau considers racial categorization (e.g., white; black or African American; Hispanic; American Indian or Alaskan Native; Asian; Native Hawaiian or other Pacific Islander) to be distinct from ethnic categorization (e.g., Hispanic origin), but studies often examine race and ethnicity as a single concept (U.S. Census Bureau, 2017a). Furthermore, studies conducted outside of the U.S. may differ in the cultural and historical backgrounds that define race and ethnicity. Because of the fluidity of these categorizations, direct comparisons of results stratified by race and ethnicity between studies can be difficult. The evaluation of evidence for race and/or ethnicity in this section is done according to classifications made by original study authors.

The 2009 PM ISA (U.S. EPA, 2009) found little evidence that race and some evidence that ethnicity might be effect measure modifiers of PM-related mortality. However, this conclusion did not include an assessment of whether there is evidence of racial and ethnic disparities in PM exposure. Disparities in exposure to PM are one potential cause of disparity in PM-related health effects by race and ethnicity. Mikati et al. (2018) compared modeled ambient $PM_{2.5}$ data with census tract populations across the U.S. and reported higher exposures for Hispanics (9.9 $\mu g/m^3$) and higher exposures for Nonhispanic blacks (10.3 $\mu g/m^3$) than for Nonhispanic whites (9.6 $\mu g/m^3$). Nachman and Parker (2012) found that blacks in the nationally-representative 2002−2005 National Health Interview Survey were exposed to higher concentrations of ambient $PM_{2.5}$ (13.2 $\mu g/m^3$) than were Hispanics (12.5 $\mu g/m^3$) or Nonhispanic

whites (12.2 µg/m^3). Hispanics in this sample had only slightly higher exposures than Nonhispanic whites, but in some specific areas, the disparities may be larger. For example, a study of year 2000 birth records in the state of California reported a higher mean $PM_{2.5}$ concentration at monitors within five miles of Hispanic residences (18.2 µg/m^3) compared to Nonhispanic white (15.8 µg/m^3) residences over the gestation period (Basu et al., 2004). Disparities appear to persist in urban, suburban, and rural environments (Bravo et al., 2016). Hispanics and Blacks as well as Asians are also exposed to higher concentrations of certain components of $PM_{2.5}$ (such as elemental and organic carbon) than are Nonhispanic whites (Bell and Ebisu, 2012). In addition, Johnson and Parker (2009) reported that more blacks and Hispanics lived in high-exposure (≥15.8 µg/m^3) census block groups than whites.



Note: Group for reference exposure is Nonhispanic Whites.

Source: Permission pending, Mikati et al. (2018), Nachman and Parker (2012), Bravo et al. (2016), Bell and Ebisu (2012), Basu et al. (2004).

Figure 12-2 Differences in $PM_{2.5}$ exposure by race.

A further limitation to the discussion of race in the 2009 PM ISA (U.S. EPA, 2009) was the small number of studies available at the time. For instance, evidence for modification of short-term $PM_{2.5}$ mortality risk by Hispanic ethnicity primarily came from two studies in California: Ostro et al. (2006) and Ostro et al. (2008). However, a number of studies published since the 2009 PM ISA have considered effect measure modification by race and ethnicity.

A number of epidemiologic studies that examined the association between long-term $PM_{2.5}$ exposure and mortality reported that race/ethnicity modifies this relationship (Supplemental Table S12-12) (U.S. EPA, 2018). There is evidence for elevated risk among Nonwhites compared to Whites. Kioumourtzoglou et al. (2016), (Wang et al., 2017), and (Arnaud, 2011) all examined long-term $PM_{2.5}$-related mortality in the U.S. Medicare population and found racial disparities in in mortality risk. Kioumourtzoglou et al. (2016) found higher long-term $PM_{2.5}$-related mortality among residents of cities at the 75th percentile of proportional black population than among those in cities at the 25th percentile. Di et al. (2017) observed that whites had a lower risk for long-term $PM_{2.5}$-related mortality (RR: 1.063; 95% CI: 1.060, 1.065) than the overall population while Hispanics (RR: 1.116; 95% CI: 1.100, 1.133) and Asians (RR: 1.096; 95% CI: 1.075, 1.117) had higher risk; blacks, meanwhile, had greater risk (RR: 1.208; 95% CI: 1.199, 1.217) than either of these groups. Furthermore, the researchers showed that this discrepancy was not explained by low economic status alone; blacks with a high enough income to be ineligible for Medicaid retained greater risk than Medicaid-eligible whites. However, within a 1997−2009 National Health Interview Survey cohort, Parker et al. (2017) did not find significant differences by race or ethnicity in all-cause or heart disease mortality. Wang et al. (2017), which focused on the Medicare population only in the Southeastern U.S., found a greater mortality risk from long-term $PM_{2.5}$ exposure for blacks than for whites in this region. A study focused only on mortality records in the states of Georgia, North Carolina, and South Carolina reported a greater increase in short-term $PM_{2.5}$-associated mortality among the black population as well (Lee et al., 2015).

Beyond studies of mortality, other recently published literature has examined whether there is evidence of effect measure modification by race/ethnicity on the relationship between long-term $PM_{2.5}$ exposure and cardiovascular effects. Johnson and Parker (2009) reported that only Hispanics had a significantly elevated risk for heart disease associated with long-term $PM_{2.5}$ exposure; only whites had a significantly elevated risk for hypertension.

Studies focused on smaller geographic areas have reported inconsistent results. Among the 2000−2002 Multiethnic Study of Atherosclerosis cohort recruited from six cities across the U.S., Hicken et al. (2016) observed a larger mean difference in left-ventricular mass index (an outcome related to hypertension) associated with long-term $PM_{2.5}$ exposure in Blacks as opposed to Whites. However, they did not report such a difference between groups for left-ventricular ejection fraction (another outcome related to hypertension). Similarly, a study of over 80,000 cases of cardiovascular-related ED visits in Central Arkansas did not find a significant racial difference in outcomes for short-term $PM_{2.5}$ exposures (Rodopoulou et al., 2015); nor did a study of transmural myocardial infarctions in New Jersey (Rich et al., 2010).

In addition, there is evidence that associations between $PM_{2.5}$ exposures and respiratory outcomes are stronger for nonwhites than whites. Nachman and Parker (2012) observed that asthma prevalence associated with long-term $PM_{2.5}$ exposure was statistically significantly higher in Nonhispanic blacks, but not in Hispanics, than in Nonhispanic. There is also some evidence of effect measure modification by race

for short-term $PM_{2.5}$ exposures and respiratory effects. Short-term $PM_{2.5}$-related respiratory risks focused on individual cities are inconsistent. Glad et al. (2012) observed a slight increase in odds of asthma ED visits for African Americans compared to whites associated with short-term $PM_{2.5}$ exposure in Allegheny County, PA from 2002−2005. Alhanti et al. (2016), on the other hand, investigated asthma-related ED visits in Atlanta, GA, Dallas, TX, and St. Louis, MO between 1993−2009 and did not observe pronounced differences between whites and nonwhites in associations with $PM_{2.5}$ either overall or within any specific age ranges or individual cities.

Strickland et al. (2014) focused on pediatric asthma in Atlanta from 2002−2010 and the relationship with a population-weighted city average for short-term $PM_{2.5}$ from several monitors. They observed higher risk associated with $PM_{2.5}$ on pediatric asthma ED visits for African Americans compared to non-African Americans, and this difference was more prominent than differences based on other measures such as education or Medicaid status. Gleason et al. (2014) focused on pediatric asthma ED visits in a 2005−2007 New Jersey cohort and did not find any significant difference in outcomes by black or white race, but did observe a significantly increased odds ratio of events in those of Hispanic ethnicity as opposed to Nonhispanic ethnicity. The Central Arkansas study by Rodopoulou et al. (2015) reported lower short-term $PM_{2.5}$-related risk of respiratory emergency room visits for African Americans.

While evidence for reproductive effects is only suggestive of, but not sufficient to infer, a causal relationship with exposure to PM2.5 (Chapter 9), a limited number of studies evaluated whether race/ethnicity modified the relationship between $PM_{2.5}$ exposure and reproductive outcomes, including adverse birth outcomes and maternal effects during pregnancy; they provide mixed evidence for greater risk among nonwhites. Bell et al. (2007) conducted a study of births in Massachusetts and Connecticut between 1999−2002, assigning $PM_{2.5}$ as the average of all monitors in a county. They noted a larger decrease in birthweight for black mothers than they did for white mothers. Pereira et al. (2014) overlapped with the time and geography of Bell et al. (2007) by considering preterm birth in Connecticut from 2000−2006. $PM_{2.5}$-related preterm birth was lower for children of white mothers (OR: 1.02; 95% CI: 0.88, 1.20) than for children of black mothers (OR: 1.39; 95% CI: 0.99, 1.96) or Hispanic mothers (OR: 1.31; 95% CI: 1.00, 1.73). Among Hispanic mothers, odds of preterm birth were uniquely high for $PM_{2.5}$ exposure within the first trimester (OR: 1.25; 95% CI: 1.08, 1.44). Green et al. (2015) modeled zip code-level $PM_{2.5}$ exposure in California from 1999−2009 and compared to over 5.5 million birth records in the state. They did not find differential effects for stillbirth by race or ethnicity. Vinikoor-Imler et al. (2012) analyzed the risk of gestational hypertension associated with $PM_{2.5}$ exposure in North Carolina between 2000−2003. They reported a significantly lower risk of gestational hypertension for Hispanics than for whites, but a significantly higher risk for blacks.

Overall, there is adequate evidence that nonwhites, particularly blacks, are at increased risk for $PM_{2.5}$-related health effects based on studies examining differential exposure and health effects. There is strong evidence demonstrating that black and Hispanic populations, in particular, have higher $PM_{2.5}$ exposures than Nonhispanic white populations. In addition, there is consistent evidence across

multiple studies demonstrating an increase in risk for Nonwhite populations. More specifically, effect measure modification by race in high-quality studies of $PM_{2.5}$-associated mortality (Di et al., 2017; Wang et al., 2017) are complemented by studies examining effect modification on $PM_{2.5}$-associated morbidity.

12.5.5 Residential Location

Overview

- New methods in exposure assessment allow for the estimation of $PM_{2.5}$ exposures for both urban and rural populations, evidence indicates that $PM_{2.5}$ is generally lower in rural areas compared to urban areas.
- Studies examining exposure differences in populations with close proximity to roadways indicate $PM_{2.5}$ concentrations are generally not elevated close to roadways.
- Evidence is inconsistent across stratified epidemiologic analyses examining health effects compared to degree of urbanicity (e.g., urban or rural residence).
- There is some evidence from epidemiologic and toxicological studies that demonstrates an increase in risk for those exposed to traffic particles or live near a roadway.
- With fewer available $PM_{2.5}$ monitor sites in smaller metropolitan and rural locations compared to larger metropolitan areas, the ability to validate modeled ambient $PM_{2.5}$ in less populated locations remains an important limitation; furthermore, the diversity in residential classification metrics limits the ability to interpret trends across studies.
- **Overall, the evidence is inadequate to determine if residential location increases risk for $PM_{2.5}$-related health effects.**

12.5.5.1 Urban/Rural Residential Locations

Many studies examining the health effects of $PM_{2.5}$ exposure have traditionally focused on urban populations due to the predominantly urban siting of monitors in the national monitoring network; however, those living outside major metropolitan areas may be exposed to different mixtures of particulate matter than those in urban areas (Xu et al., 2015) and this may vary across regions in the U.S. (Sections 2.5.3 and 3.4.4.1). Residential location may also be an important surrogate for other factors, including differing access to services, lifestyle, and other environmental exposures that could potentially influence $PM_{2.5}$-health associations (Grabich et al., 2016). Recent developments in estimating exposure through hybrid models drawing from satellite observations, chemical transport model output, and ambient concentration measurements to estimate ambient $PM_{2.5}$ concentrations have enabled a greater proportion of rural populations to be included in recent epidemiologic studies (Section. 3.3.2). These studies have not only examined whether overall associations between $PM_{2.5}$ and health outcomes are present with the addition of rural populations, but have also examined differences in associations between urban and rural populations. These new methods also provide the opportunity to examine if there are differences in associations by degree of urban density or urbanicity, as many previous studies relied on a limited number of fixed site monitors in large metropolitan areas.

Few studies in the 2009 PM ISA reviewed the potential for modification by residential location, and those that did often incorporated residential information only as a general surrogate for socioeconomic status. However, a study in Phoenix did note that the largest association between mortality and short-term $PM_{2.5}$ exposure was in an area of medium urban density in central Phoenix (Wilson et al., 2007). Recent studies have examined whether degree of urbanicity modifies the association between $PM_{2.5}$ exposure and a variety of health effects. These studies report inconsistent results with the majority of studies focusing on mortality and long-term $PM_{2.5}$ exposure.

$PM_{2.5}$ concentrations are generally lower in rural areas compared to urban areas in the U.S., based both on limited monitoring data, as well as remote-sensing and hybrid modeled $PM_{2.5}$ estimates (Section 2.5.3). Several epidemiologic studies reported average $PM_{2.5}$ stratified by varying definitions of urban and rural residential location and generally observed similar trends of lower $PM_{2.5}$ in rural areas. Average annual rural $PM_{2.5}$ in the U.S. ranged from 10.2−12.9 $\mu g/m^3$, while urban $PM_{2.5}$ ranged from 11.5−15.5 $\mu g/m^3$ (Bravo et al., 2017; Garcia et al., 2015; Strickland et al., 2015). Moreover, there are compositional characteristics of urban ambient $PM_{2.5}$ that are consistent with traffic emissions and have been shown to change when moving away from the urban center (Section 2.5.1.2.5).

There is some evidence of stronger associations between $PM_{2.5}$ exposure and mortality in urban areas compared to rural areas; however, evidence is inconsistent across various metrics that use different categorization schemes based on the population size of a city or city urbanicity (Supplemental Table S12-13) (U.S. EPA, 2018). Di et al. (2017) and Kioumourtzoglou et al. (2016) both examined long-term $PM_{2.5}$ exposure and mortality using nationwide Medicare data, though the latter focused on the variation of urbanicity, rather than a comparison to nonmetropolitan areas.. Using modeled $PM_{2.5}$ across the entire continental U.S., as well as the largest Medicare study population to date, Di et al. (2017) observed stronger positive associations between $PM_{2.5}$ exposure and mortality in areas of moderate population density compared to areas of high population density. Meanwhile, Di et al. (2017) observed a smaller positive association among areas of low population density. Kioumourtzoglou et al. (2016) observed no strong evidence of modification in a pooled analysis of 207 U.S. cities by degree of urbanicity or population density within cities. However, in region specific metaregression the authors observed that as population density and urbanicity increased, there were larger effects for $PM_{2.5}$-mortality in the Northeast, Midwest, and Northwest compared to the South, Southeast, Central, Southwest, and Western regions of the U.S.

Additional multicity studies in the U.S, including six Northeastern states (Shi et al., 2015), seven Southeastern states (Wang et al., 2017), and Massachusetts (Kloog et al., 2013) also used hybrid models to estimate long-term $PM_{2.5}$ exposure and observed some evidence of decreased risk of mortality in rural populations compared to urban populations. This difference in effect also persisted in models simultaneously stratified by race and sex (Wang et al., 2017). Conversely, a study of diabetes-related mortality and long-term $PM_{2.5}$ exposure in Canada observed a larger, but imprecise (i.e., wide 95% confidence intervals), association in rural areas compared to large or mid-population cities (Brook et al.,

2013). A study in California also observed higher rates of cardiovascular, cardiopulmonary, and overall mortality in rural compared to urban zip codes, though the strength of this pattern varied substantially by $PM_{2.5}$ exposure assignment method (Garcia et al., 2015). In addition to studies of long-term $PM_{2.5}$ exposure, a study of mortality and short-term $PM_{2.5}$ exposure in Georgia, North Carolina, and South Carolina observed higher risks in rural zip codes compared to metropolitan urban cores (Lee et al., 2015).

A limited number of studies evaluated if urbanicity characteristics modified the association between other health effects and $PM_{2.5}$, such as cardiovascular effects, respiratory effects and reproductive outcomes. In a study of long-term $PM_{2.5}$ exposure, Johnson and Parker (2009) observed attenuated associations in less-urban areas for self-reported cardiovascular disease, but larger associations for self-reported hypertension in urban areas.

Among a limited number of studies for short-term $PM_{2.5}$ exposure, studies of cardiovascular effects were inconsistent, while studies of respiratory effects tended to see increasing risk in less urban areas. Kloog et al. (2014) observed a negative association in urban areas, and no association in rural areas using Medicare data on cardiovascular hospital admissions. Conversely, using Medicare data in 708 U.S. counties, Bravo et al. (2017) reported increasing associations between short-term $PM_{2.5}$ exposure and cardiovascular hospitalization in more urban areas, though larger associations in less urban areas for respiratory hospital admissions. In the state of Georgia, Strickland et al. (2015) observed positive associations in less urban areas compared to null or negative associations in large metropolitan areas for less frequent respiratory hospital admissions, such as bronchitis, pneumonia, and sinusitis, though estimates were imprecise (i.e., wide 95% confidence intervals). Among more frequent respiratory outcomes, such as asthma, there was less evidence of effect modification. In contrast to other studies of respiratory outcomes, there was a trend of stronger associations for respiratory hospital admissions in urban areas in Southern California, compared to less urban counties in the Central Valley (Yap et al., 2013).

In studies of reproductive outcomes, Hu et al. (2015) observed an increased risk of gestational diabetes in Florida for mothers in rural areas. Meanwhile, in a nationwide study of infant births in Canada, Stieb et al. (2015) observed no substantial evidence of modification by maternal residential status. However, the authors observed small increases in rural births at risk for small for gestational age, as well as a decline in term birthweight.

12.5.5.2 Residential Proximity to Traffic

Traffic-related air pollution is a complex mixture typically consisting of both particulate and gaseous pollutants. Elevated near-road concentrations of UFP have been observed, although measured $PM_{2.5}$ concentrations are generally not elevated near the road (Karner et al., 2010), given that most $PM_{2.5}$ is produced via atmospheric chemistry. Both traffic-related air and noise pollution have been hypothesized to be associated with detrimental health effects; however, few studies have examined if

residential traffic proximity modifies existing associations between short- and long-term $PM_{2.5}$ exposure and health effects. No studies examined residential proximity to traffic in the 2009 PM ISA, though one study did suggest urban areas of low SES were disproportionately exposed to traffic-related pollutants (Yanosky et al., 2008).

Recent epidemiologic studies provide limited evidence that those living close to major roadways may be at greater risk for $PM_{2.5}$ associated cardiovascular or respiratory effects compared to those living farther from major roadways. In a study of short-term $PM_{2.5}$ exposure using data from the multicity MESA cohort, Auchincloss et al. (2008) observed stronger positive associations with pulse pressure and systolic blood pressure among those living within 300 meters of highways compared to those living further from highways, as well as positive associations for those in areas of higher road density. Smaller studies also observed stronger associations with $PM_{2.5}$ among residents living close to major roadways; however, the evaluated distance from roadways varied. In Atlanta, Georgia Sinclair et al. (2014) observed higher risk for $PM_{2.5}$-related asthma pediatric primary care visits among residents within 150 meters of major roadways, though not at 300 meters. Among stroke hospitalizations in southern Israel, Yitshak Sade et al. (2015) observed an increased risk of ischemic stroke for those living within 75 meters from main roads (OR: 1.42, 95% CI: 1.06, 1.87) compared to those further than 75 meters away (OR: 1.06, 95% CI: 0.89, 1.27).

A limited number of animal toxicology studies also support the importance of proximity to PM source. In Los Angeles, the enhancement of allergic responses was greater in allergic BALB/c mice exposed to $PM_{2.5}$ CAPs (multiday, 400 $\mu g/m^3$) 50 m from a busy roadway compared to those at a distance of 150 m (Kleinman et al., 2005). Additionally, a single acute exposure to aerosolized diesel exhaust particles resulted in increased BALF IL-4 levels in OVA-sensitized/challenged mice at exposures of 2000 $\mu g/m^3$, but not 870 $\mu g/m^3$ (Farraj et al., 2006a, b).

Summary

Overall, there is inadequate evidence to determine if residential location, either close proximity to a roadway or in a rural or urban area, increases risk for $PM_{2.5}$-related health effects. There is evidence that degree of urbanicity may modify the risk of $PM_{2.5}$-related health effects, particularly from large nationwide studies of mortality and long-term $PM_{2.5}$ exposure; however, in contrast to studies of mortality, several cardiovascular, respiratory, reproductive, and developmental studies observed limited evidence of increased risk in rural areas compared to urban areas. There may also be differences between metro areas of different sizes, though interpreting these trends is limited by the varying definition of urbanicity across studies. Furthermore, despite recent developments in methods to estimate ambient $PM_{2.5}$ concentrations, the limited availability of monitored data in smaller metropolitan and rural locations to validate modeled ambient $PM_{2.5}$ remains an important limitation (Sections 3.3.2, 3.3.3, 3.4.2.4). A limited number of epidemiologic studies also provide some evidence of stronger $PM_{2.5}$ related effects for those living closer to major roadways for asthma, stroke, and elevated

blood pressure compared to those living further from roadways. The available animal toxicology studies also suggest elevated immune responses among mice exposed to traffic-related exhaust. However, there is insufficient information available to determine how far these effects may extend from roadways, and if the relevant distances vary by health outcome, or other factors, such as levels of noise pollution.

12.6 Behavioral and Other Factors

12.6.1 Smoking

Overview

- It is unclear whether smoking exacerbates health effects associated with air pollutant exposures, including PM, and the potential for this was not evaluated in the 2009 PM ISA.
- Recent evidence does not indicate that smoking modifies the effect of long-term $PM_{2.5}$ exposures on cardiovascular disease or mortality; evidence evaluating differential effects by smoking status is limited for short-term $PM_{2.5}$ exposures.
- **Overall, the evidence is inadequate to determine whether individuals who smoke are at increased risk of $PM_{2.5}$-related health effects compared to those that do not smoke.**

Smoking is a common behavior as indicated by the 2016 National Health Interview Survey which estimated that within the U.S. adult population approximately 15.5% of individuals report being current smokers and 21.5% report being a former smoker (Blackwell and Villarroel, 2018). Smoking is a well-documented risk factor for many diseases, but it is unclear whether smoking exacerbates health effects associated with air pollutant exposures, including PM.

A number of studies have evaluated whether smoking status modifies the relationship between $PM_{2.5}$ exposure and health effects. The majority of these studies examined the relationship between long-term $PM_{2.5}$ exposure and mortality or cardiovascular morbidity. Generally, little difference is observed in the relationship between long-term exposure to $PM_{2.5}$ and mortality or cardiovascular morbidity when examined by smoking status. When differences in the relationship do occur, there is no consistent pattern or trend that support current, former, or ever smokers (i.e., both current and former smokers) being at increased or decreased risk than never smokers for these health outcomes. In a reanalysis of the ACS cohort, Turner et al. (2017) evaluated the interaction between $PM_{2.5}$ exposure and smoking, stratifying $PM_{2.5}$ exposure into low (<10.59 $\mu g/m^3$) and high (>14.44 $\mu g/m^3$) categories. These authors observed positive associations between higher $PM_{2.5}$ exposures and both total and CVD mortality; the interaction between current smoking and high $PM_{2.5}$ exposure increased the risk by 10%. In addition to the mortality and cardiovascular effects, several studies examined the ability of smoking status to modify the relationship between long-term $PM_{2.5}$ exposure and changes in blood pressure (Chan et al.,

2015; Mu et al., 2014; Fuks et al., 2011; Auchincloss et al., 2008) and indicators of atherosclerosis (Bauer et al., 2010; Lenters et al., 2010) and observed no consistent pattern among any smoking strata.

A smaller number of studies examined smoking status as a potential modifier of the effect of short-term $PM_{2.5}$ exposure on health outcomes (Supplemental Table S12-14) (U.S. EPA, 2018). A multicity analysis of mortality observed higher effects of $PM_{2.5}$ in counties where the prevalence of smoking was higher, but lacked individual-level smoking data (Dai et al., 2014). O'Donnell et al. (2011) examined whether the relationship between short-term $PM_{2.5}$ exposure and ischemic stroke differed by smoking status of participants and observed no evidence that smoking modified this relationship.

Overall, the inconsistent evidence is inadequate to determine whether individuals who smoke are at increased risk of $PM_{2.5}$-related health effects compared to those that do not smoke. A number of long-term exposure studies observed a mix of positive or nearly null associations for mortality and cardiovascular morbidity endpoints, but no clear or consistent trend is apparent among current, former, or ever smokers when compared to never smokers. Fewer studies evaluated smoking as an effect modifier of the relationship between short-term $PM_{2.5}$ exposure and health outcomes, and one study observed a stronger $PM_{2.5}$-mortality relationship in counties with a higher prevalence of smoking, but no individual-level data were available. Additionally, the varied metrics used to define smoking across studies (e.g., current, former, quantity) is a particular uncertainty in this evidence base.

12.6.2 Diet

Overview

- Dietary habits are well-established risk factors for metabolic/cardiovascular conditions that may be associated with $PM_{2.5}$ exposure; diet is an important source of anti-inflammatory and antioxidant compounds that may alter early biological responses to $PM_{2.5}$.
- Limited stratified epidemiologic analyses of alcohol or fruit and vegetable consumption do not indicate differences in mortality and $PM_{2.5}$ exposure.
- Limited evidence from controlled human exposure studies in the current and previous ISA demonstrates reduced cardiovascular and inflammatory responses among those taking B vitamin supplements
- **Overall, the evidence is inadequate to determine whether dietary patterns modify $PM_{2.5}$-related health effects.**

Dietary habits are well established risk factors for a variety of health outcomes, in particular, the development of metabolic-related conditions that may simultaneously be associated with PM exposure (Cardiovascular Effects, Section 6.2.1 and Section 6.3.1; Metabolic Effects, Section 7.2.1). It is possible that as dietary habits influence the development of chronic disease, there are increased risks of other $PM_{2.5}$-health effects for those with cardiovascular disease (Section 12.3.1), diabetes (Section 12.3.2), and

obesity (Section 12.3.3). Dietary tendencies also differ across the U.S. population, for example, low socioeconomic status (SES) individuals may have limited access to fresh foods (Larson et al., 2009). Limited access to fresh foods may lead to reduced intake of anti-inflammatory compounds and antioxidant polyunsaturated fatty acids and vitamins, which has been hypothesized to increase a population's risk of developing a PM-related health effect (Romieu et al., 2005).

The 2009 PM ISA concluded that nutritional status, among other surrogates of SES, may modify the association between PM and various health outcomes. Evidence for this conclusion was largely based a single study that examined $PM_{2.5}$ exposure and heart-rate variability (HRV) by nutritional status among those with genetic predisposition for cardiovascular disease (Baccarelli et al., 2008). The authors found that when individuals with genetic polymorphisms increased their consumption of B vitamins or methionine, they no longer observed an association between $PM_{2.5}$ and HRV. More recently, several studies have evaluated the ability of alcohol, fruit and vegetable consumption, and fatty acid supplementation to modify associations between $PM_{2.5}$ exposure and health outcomes in populations beyond those with specific genetic polymorphisms, primarily for long-term $PM_{2.5}$ exposure and mortality. While some studies observed differential effects, there is little consistency across studies, and effect estimates were often imprecise (i.e., wide 95% confidence intervals) (Supplemental Table S12-15) (U.S. EPA, 2018).

A limited number of epidemiologic studies evaluated effect measure modification by alcohol consumption. In a study of the Canadian Community Health Survey cohort, Pinault et al. (2016) examined associations between mortality and long-term $PM_{2.5}$ exposure and observed little evidence of differences based on regular drinking status for all-cause, cardiovascular, or respiratory mortality. In a study of long-term $PM_{2.5}$ exposure and systemic inflammation among mid-life women, Ostro et al. (2014) also observed little difference in C-reactive protein changes between abstainers and occasional consumers of alcohol. However, in a subanalysis examining the probability of a clinically relevant level of CRP (3 mg/l), the authors observed a positive association in older women who abstained from alcohol compared to a null association among older women who were occasional drinkers.

Several epidemiologic studies that examined the association between mortality and long-term $PM_{2.5}$ exposure evaluated potential modification by fruit and/or vegetable consumption patterns. Overall, few differences in mortality were observed when results were stratified by dietary patterns, and there is no consistent pattern to support greater fruit and vegetable consumptions leads to differential risk compared to lower fruit and vegetable consumption. U.S. based studies of cardiovascular mortality (Pope et al., 2014) and lung cancer mortality (Turner et al., 2011) did not observe a consistent pattern of differential risk by diet. Results stratified by quartile of fat consumption showed a similar pattern as when stratifying by fruit and vegetable consumption (Pope et al., 2014). Using data from the Canadian Community Health Survey cohort, Pinault et al. (2016) observed similar inconsistencies by mortality type, where the risk of $PM_{2.5}$ associated mortality slightly increased, or decreased depending on mortality categorization for the group consuming at least five or more servings of vegetables and fruit per day. Likewise, in a pooled

analysis of mortality and long-term $PM_{2.5}$ exposure across European cohorts (ESCAPE), no consistent pattern was observed between groups based on estimated grams of fruit consumed per day for all-cause, cardiovascular mortality, or respiratory mortality (Beelen et al., 2014a; Beelen et al., 2014b; Dimakopoulou et al., 2014).

The 2009 PM ISA examined a single study on nutritional status, which observed B vitamin supplementation attenuated the association between $PM_{2.5}$ and HRV among individuals with specific genetic polymorphisms that are associated with increased cardiovascular risk (Baccarelli et al., 2008). A recent pilot crossover study using 2 hour CAPS exposures examined B vitamin supplementation in a more general population and continues to provide limited evidence that B vitamins may protect against subclinical cardiovascular and inflammatory responses. Zhong et al. (2017a) observed attenuation in effects for measure of HRV and inflammatory blood markers, while using the same study population Zhong et al. (2017b) observed attenuated effects for DNA methylation and mitochondrial DNA content following vitamin B supplementation.

Controlled human exposure studies among the elderly have also examined the role of fish and olive oil supplementation and provide limited evidence that these oils may protect against certain subclinical responses to short-term $PM_{2.5}$ CAPs exposure. A series of CAPs studies in Chapel Hill, North Carolina provided olive oil (OO) or fish oil (FO) supplements to participants for four weeks, and then examined cardiovascular responses after two hours of CAPs exposure (Section 6.2.6, Table 6-12 and Section 6.2.4, Table 6-9). Tong et al. (2015) observed larger changes in endothelial function (i.e., decreased flow-mediated dilation) in the FO and nonsupplemented groups compared to the OO group, as well as increased vasoconstrictor concentrations (i.e., endothelin-1) for the nonsupplemented group. Results of fibrinolysis were less consistent, with increased tissue plasminogen activator, but decreases D-dimer levels after 20 hours in the OO group, but not FO or nonsupplemented group. In examining electrophysiological responses, Tong et al. (2012) did not include a nonoil supplement group, though the authors observed decreased responses to CAP exposure for heart rate variability, QT repolarization, and some blood lipids, such as VLDL and triglycerides, among those using FO compared to those using OO.

Overall, there is inadequate evidence to determine whether dietary patterns modify $PM_{2.5}$-associated health effects. Based on the limited number of epidemiologic studies, there is little evidence of differences in the relationship between mortality and $PM_{2.5}$ based on either alcohol or fruit and vegetable consumption. However, controlled human exposure studies of B vitamin, fish, and olive oil supplementation suggest potential protective effects against short-term exposure to concentrated ambient particles. Among epidemiologic studies, the reliance on long-term mortality studies is an important limitation, as self-reporting biases may still be problematic in accurate collection of dietary habits.

12.7 Conclusions

This chapter characterized the evidence for factors that may result in populations and lifestages being at increased risk for $PM_{2.5}$-related health effects (Table 12-3). The evaluation of each factor focused on the consistency, coherence, and biological plausibility of evidence integrated across a range of scientific disciplines informing whether a specific population or lifestage might be at increased risk of a PM-related health effect using the systematic framework detailed in Table 12-1. In the evaluation and characterization of the evidence consideration was given to exposure, dosimetry, biological plausibility, and/or the relationships of PM exposure with health effects as evaluated in Chapters 5-11 of this ISA. As noted in the introduction to this chapter, the 2009 PM ISA focused broadly on the extent to which evidence indicated that certain populations or lifestages were "susceptible" to PM-related health effects, but more recent ISAs have applied the systematic framework so the evaluation and conclusions in this ISA are more nuanced. Table 12-3 presents a summary of the conclusions and evidence evaluated and integrated in this chapter for each factor potentially resulting in an increase in risk for a $PM_{2.5}$-related health effect.

Of the factors considered, race and lifestage (children) were the only factors for which evidence was adequate to indicate an increase in risk for $PM_{2.5}$-related health effects (Section 12.5.4 and Section 12.5.1.1). In particular, evidence for both health effects, primarily mortality, and exposure demonstrate that nonwhite populations are at increased risk compared to whites. Several high-quality studies indicate that nonwhite populations across different geographical regions are exposed to higher concentrations of $PM_{2.5}$. In addition, a number of high-quality epidemiologic studies demonstrate stronger associations in nonwhite populations for $PM_{2.5}$-associated mortality. Increased risk for nonwhites compared to whites has also been demonstrated for other health outcomes including respiratory and cardiovascular effects and birth outcomes, but there is less confidence in the evidence for these outcomes.

There is strong evidence from studies examining health endpoints specific to children indicating that children are at increased risk to the effects of $PM_{2.5}$ exposure. Specifically, epidemiologic studies of long-term $PM_{2.5}$ exposure demonstrate associations with impaired lung function growth (Section 5.2.2.1.1), decrements in lung function (Section 5.2.2.2.1), and increased incidence of asthma development in children (Section 5.2.3.1). The evidence from stratified analyses provides limited direct evidence that children are at increased risk of $PM_{2.5}$-related health effects compared to adults. In addition, there is some evidence indicating that children can have higher $PM_{2.5}$ exposures than adults and that there are dosimetric differences in children compared to adults that can contribute to higher doses.

There is suggestive evidence that populations with pre-existing cardiovascular or respiratory disease (Section 12.3.1 and Section 12.3.5), populations that are overweight or obese (Section 12.3.3), populations that have particular genetic variants (Section 12.4), or populations that are of low SES (Section 12.5.3) are at increased-risk for $PM_{2.5}$-related health effects compared to respective reference populations. While stratified analyses for pre-existing cardiovascular disease do not consistently indicate

differential risk, there is some evidence that those with hypertension may be at increased risk compared to those without hypertension. In addition, there is strong evidence supporting a causal relationship between exposure to $PM_{2.5}$ and cardiovascular health effects, particularly mortality and ischemic heart disease (Chapter 6), and those with underlying cardiovascular conditions related to these serious outcomes may be at increased risk based on pathophysiological considerations compared to those without these conditions. Similarly, for pre-existing respiratory disease, evidence is limited that directly informs differential risk between those with and without pre-existing respiratory disease. However, Chapter 5 concluded that there is likely to be a causal relationship between short-term $PM_{2.5}$ exposure and respiratory effects, based primarily on evidence for exacerbation of asthma and COPD. Those with pre-existing obesity may also be at increased risk compared to those of healthy weight, based on evidence indicating greater risk for mortality associated with long-term exposures to $PM_{2.5}$ in individuals who are obese or overweight compared to those who are normal weight. In considering the evidence for genetic background, a variety of gene variants have been studied. There is a consistent trend for increased risk for respiratory and cardiovascular effects associated with $PM_{2.5}$ across gene variants involved in the glutathione pathway and oxidant metabolism, which is consistent with biological plausibility indicating that oxidative stress is an early biological response to $PM_{2.5}$ exposure. Evidence for other genetic variants is very limited. Finally, evidence indicates that those that are of low SES are more likely to have higher $PM_{2.5}$ exposures and that low SES, as measured by metrics for income, may increase risk for $PM_{2.5}$-associated mortality compared to higher SES categories, though there is some inconsistency in the evidence and heterogeneity in the metrics used.

There is inadequate evidence to determine whether pre-existing diabetes (Section 12.3.2), elevated cholesterol (Section 12.3.4), lifestage: older adults (Section 12.5.1.2), residential location (including proximity to source and urban residence [Section 12.5.5], sex [Section 12.5.2], or diet [Section 12.6.2]) modify risk for $PM_{2.5}$-associated health effects. For lifestage related to older adults (Section 12.5.1.2) there is limited evidence indicating that older adults are at increased risk for $PM_{2.5}$-related health effects; however, epidemiologic panel studies and controlled human exposure studies of older adults provide some evidence that subclinical cardiovascular outcomes are associated with short-term exposure to $PM_{2.5}$ for this lifestage. Evidence for other factors is inadequate due to limited evidence (residential patterns, diet) or inconsistency across the available evidence (diabetes and sex).

Table 12-3 Summary of evidence for populations potentially at increased risk of $PM_{2.5}$-related health effects.

Evidence Classification	Factor Evaluated	Population/Lifestage Potentially at Increased Risk	Factor-specific Evidence	Evidence Informing an Increase in Risk
Adequate Evidence	Race (Section 12.5.4)	Nonwhite populations		Evidence from multiple high-quality studies demonstrating higher $PM_{2.5}$ exposure in nonwhite populations. Consistent evidence from high quality studies demonstrating increased risk for mortality and cardiovascular/respiratory morbidity.
	Lifestage	Children (Section 12.5.1.1)	Strong evidence demonstrating health effects in children, particularly from epidemiologic studies of long-term $PM_{2.5}$ exposure and impaired lung function growth, decrements in lung function, and asthma development.	Limited evidence from stratified analyses to inform increased risk in children compared to adults. However, evidence from studies of pediatric asthma and impaired lung development provide strong and consistent evidence that effects are observed in children.
Suggestive Evidence	Pre-existing Disease	Pre-existing Cardiovascular Disease (Section 12.3.1)	Causal relationship for $PM_{2.5}$ exposure and cardiovascular effects based on CV mortality and morbidities that are plausibly more prevalent in those with pre-existing CV disease/conditions.	Generally supportive evidence from epidemiologic studies demonstrating differential effects for those with hypertension. Limited and inconsistent evidence for other pre-existing cardiovascular diseases.
		Pre-existing Respiratory Disease (Section 12.3.5)	Likely to be causal relationship for short-term $PM_{2.5}$ exposure and respiratory effects based primarily on evidence for asthma and COPD exacerbation. Evaluated outcomes are often specific to those with asthma or COPD and those without asthma or COPD are not included for comparison.	Limited evidence. Primarily cardiovascular outcomes in epidemiologic studies. Although asthma exacerbation is a key outcome for conclusions on respiratory effects, no informs an increase in risk for those with asthma compared to those without. There is very limited evidence for COPD.

Table 12-3 (Continued): Summary of evidence for potential increased risk of $PM_{2.5}$-related health effects

Evidence Classification	Factor Evaluated	Population/Lifestage Potentially at Increased Risk	Factor-specific Evidence	Evidence Informing an Increase in Risk
Suggestive Evidence (continued)	Pre-existing Disease (continued)	Obesity (Section 12.3.3)		Based primarily on evidence for increased risk for mortality with supporting evidence from studies of subclinical cardiovascular outcomes.
	Genetic background (Section 12.4)	Individuals with variant genotypes	Biological plausibility for $PM_{2.5}$-associated health effects is based on biological pathways including oxidative stress as early biological responses upon exposure to $PM_{2.5}$.	Generally consistent evidence for increased risk for respiratory and cardiovascular outcomes for genetic variants in the glutathione pathway, which has an important role in oxidative stress. Limited evidence for other genetic variants.
Suggestive Evidence (Continued)	Socioeconomic Status (Section 12.5.3)	Low socioeconomic status		Evidence demonstrates increased exposure and some evidence for stronger associations for mortality with low SES. Comparison across SES metrics are a limitation.
Inadequate Evidence	Pre-existing disease	Pre-existing diabetes		Inconsistent evidence across studies of mortality, cardiovascular morbidity, and inflammation.
	Lifestage	Older adults (Section 12.5.1.2)	Evidence demonstrating health effects in older adults, particularly from short- and long-term $PM_{2.5}$ exposure and cardiovascular or respiratory hospital admission, emergency department visits, or mortality.	Inconsistent evidence across a large body of studies with stratified analyses.
	Residential location (Section 12.5.5)	Near-road or urban residence		Some evidence demonstrates potential for urbanicity to modify $PM_{2.5}$-related health effects, but results are inconsistent across the broad range of metrics used.
	Sex (Section 12.5.2)	Males[a]	Males: Reproductive factors e.g., sperm motility. Females: Gestation and birth outcomes.	Inconsistent evidence across studies for mortality and cardiovascular and respiratory effects.

Table 12-3 (Continued): Summary of evidence for potential increased risk of $PM_{2.5}$-related health effects

Evidence Classification	Factor Evaluated	Population/Lifestage Potentially at Increased Risk	Factor-specific Evidence	Evidence Informing an Increase in Risk
Inadequate Evidence (continued)	Smoking (Section 12.6.1)	Current smoking		Inconsistent evidence for modification of associations between $PM_{2.5}$ and mortality, cardiovascular, reproductive, metabolic, and reproductive outcomes.
Inadequate Evidence (Continued)	Diet (Section 12.6.2)	Individuals with reduced fruit/vegetable intake, alcohol consumption, or elevated cholesterol		Inconsistent evidence across a limited evidence base.
Evidence of no effect	None			

ISA = Integrated Science Assessment.

Males selected as potential at-risk group due to shorter life-span. The use of males or females as the reference/comparison group does not change the evaluation of evidence in determining differential risk.

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CHAPTER 13 WELFARE EFFECTS

Summary of Causality Determinations for Particulate Matter (PM) and Welfare Effects

This chapter characterizes the scientific evidence that supports causality determinations for PM exposure and nonecological welfare effects. The types of studies evaluated within this chapter are consistent with the overall scope of the ISA as detailed in the Preface (see Section P.3.1). More details on the causal framework used to reach these conclusions are included in the Preamble to the ISA (U.S. EPA, 2015).

Effect	Causality Determination
Visibility	Causal
Climate	Causal
Materials	Causal

13.1 Introduction

This chapter serves as the scientific foundation for the review of the secondary (welfare-based) National Ambient Air Quality Standards (NAAQS) for PM. The Clean Air Act definition of welfare effects includes, but is not limited to, effects on soils, water, wildlife, vegetation, visibility, weather, and climate, as well as effects on man-made materials, economic values, and personal comfort and well-being (CAA, 2005). In this review of the PM secondary NAAQS, welfare effects to be considered include PM-related visibility (Section 13.2), climate effects (Section 13.3) and materials damage and soiling (Section 13.4). As noted in the Preface, in the case of materials effects, the impacts of gaseous and particulate N and S wet deposition cannot be clearly distinguished, so both are considered in this review. The ecological effects associated with the deposition of oxides of nitrogen, oxides of sulfur and PM are being addressed in a separate review [i.e., the Integrated Science Assessment (ISA) for Oxides of Nitrogen, Oxides of Sulfur, and Particulate Matter-Ecological Criteria-(U.S. EPA, 2018)]. These PM-related ecological effects include nutrient enrichment, acidification, and sulfur enrichment associated with particle deposition, and the direct and indirect effects of PM on vegetation, soils, and biota.

The 2009 Integrated Science Assessment for Particulate Matter (2009 PM ISA) concluded that a causal relationship exists between PM and visibility impairment. Recent research provides additional evidence evaluated in the 2009 PM ISA, and confirms that a causal relationship exists between PM and visibility impairment. New research provides a better understanding of the relationship between PM composition and atmospheric visibility during a period of changing PM composition due to reduced

emissions of PM precursors. New research also indicates long-term visibility improvements throughout the U.S. There continues to be considerable uncertainty around quantifying acceptable visibility. Overall, the evidence is sufficient to conclude that a causal relationship exists between PM and visibility impairment.

The 2009 ISA concluded that a causal relationship exists between PM and climate effects—specifically on the radiative forcing of the climate system, including both direct effects of PM on radiative forcing and indirect effects involving cloud processes. Recent research reinforces and strengthens the evidence evaluated in the 2009 PM ISA, and reaffirms that a causal relationship exists between PM and climate effects. This causality determination provides greater specificity about the details of these radiative forcing effects and increased understanding of additional climate impacts driven by PM radiative effects. The IPCC AR states that "Climate-relevant aerosol processes are better understood, and climate-relevant aerosol properties better observed, than at the time of AR4 [released in 2007]" (Boucher, 2013). Research since the 2009 PM ISA has also improved characterization of the key sources of uncertainty in estimating PM climate effects, particularly with respect to PM-cloud interactions. Substantial uncertainties, however, still remain with respect to key processes linking PM and climate, both because of the small scale of PM-relevant cloud microphysical processes compared to the resolution of state-of-the-art models, and because of the complex cascade of indirect impacts and feedbacks in the climate system that result from a given initial radiative perturbation caused by PM. These uncertainties continue to limit the precision with which these effects can be quantified. Despite these remaining uncertainties, though, overall the evidence is sufficient to conclude that a causal relationship exists between PM and climate effects.

The 2009 PM ISA (U.S. EPA, 2009) concluded a causal relationship between PM and effects on materials. For most topics related to materials damage, the fundamental understanding of mechanisms of soiling and corrosion has not changed; rather, additional studies lend further support to the findings from the previous ISA and effects on some materials have been further characterized. There is new information for glass and metals including modeling of glass soiling and identifying which pollutants are most influential in metal corrosion in a multipollutant environment, and how that varies between metals. Development of quantitative dose-response relationships and damage functions for materials besides stone has also progressed, with new dose-response curves published for glass, and a new summary of available materials damage functions. Since the 2009 ISA there is a growing body of research, including quantitative assessment, of PM impacts on the energy yield from photovoltaic systems.

13.2 Effects on Visibility

13.2.1 Introduction

The 2009 PM ISA concluded that "a causal relationship exists between PM and visibility impairment" based on strong and consistent evidence that PM is the overwhelming source of visibility impairment in both urban and remote areas (U.S. EPA, 2009). Visibility refers to the visual quality of the view, or scene, with respect to color rendition and contrast definition. It is the ability to perceive landscape form, colors, and textures. Visibility involves optical and physical processes of light interacting with scenic elements and the atmosphere, as well as psychophysical processes involving human perception, judgment, and interpretation. On very clear days, near objects have bright, crisp colors and textures while objects over 200 km away may still be visible. Even when there are no distant objects, a clear day produces vibrant blue skies and bright white clouds with sharp edges. Removal and addition of visible light to an observer's sight path reduces both the contrast of near objects and the ability to see distant objects. Light between the observer and the object can be scattered into or out of the sight path and absorbed by PM or gases in the sight path. The sum of scattering and absorption of visible light due to PM and gases is referred to as light extinction, b_{ext}.

In polluted environments, light extinction by gases is usually small compared to PM (Malm, 2016; U.S. EPA, 2009). Light absorbing carbon (e.g., soot and smoke), incorporating and often referred to as elemental, black, and brown carbon (Andreae and Gelencsér, 2006), and some crustal minerals (Moosmueller et al., 2012) are the only commonly occurring PM components that absorb light. However, all particles scatter light, and scattering by particles is usually greater than absorption by particles or than scattering or absorption by gases (Hand et al., 2011). Particulate scattering is dependent on particle shape, refractive index, and size. Provided these properties are known, light scattering can be accurately calculated for a distribution of particles.

The linkage between PM and human perception of haze[84] involves a number of physical/chemical/optical and psychophysical processes. These processes can be divided into three broad categories, around which the discussion of the evidence is largely organized: 1) the impairment of visibility by haze; 2) the spatial, temporal, and compositional distributions of PM and their optical properties causing the haze; and 3) human perception of and response to the haze.

Evidence in the 2009 PM ISA (U.S. EPA, 2009) supported that PM was the overwhelming source of visibility impairment in both urban and remote areas, and light scattering by gases contributed

[84]In Sections 13.2 and 13.3, the term haze is used as a qualitative description of the blockage of sunlight by dust, smoke, and pollution. This usage is widespread in the scientific literature on visibility and in discussion of the Regional Haze Rule (U.S. EPA, 2003). This contrasts with the use of the term haze in Section 13.4, where it is used as defined in the scientific literature on soiling of glass, i.e., the ratio of diffuse transmitted light to direct transmitted light (Lombardo et al., 2010).

substantially only under pristine conditions. Elemental carbon (EC) and some crustal minerals are the only common PM components that absorb light, and that light scattering is greatest for particles in the size range from 0.3 to 1.0 μm (U.S. EPA, 2009). The 2009 PM ISA (U.S. EPA, 2009) also described methods for estimating contributions of PM components to light extinction as well as direct optical measurements for light scattering, absorption, and total extinction (U.S. EPA, 2009). Particulate sulfate was found to be the dominant source (>40% of PM light extinction) of regional haze in the Eastern U.S. and an important contributor (>20% of PM extinction) elsewhere in the U.S. EC and organic carbon (OC) were found to be responsible for 10−40% the haze in the U.S., with the greatest contribution in the Northwest, although per unit mass sulfate had a greater impact on visibility because of its hygroscopicity. Particulate nitrate was found to be a substantial contributor in the Midwest and California and crustal material was an important contributor in the Southwest (U.S. EPA, 2009). Human perception of visibility impairment was also reviewed in the 2009 PM ISA (U.S. EPA, 2009) based on estimates of median acceptable values from existing visibility preference studies.

The discussion of PM visibility impairment opens with reviews of metrics and monitoring methods and approaches used for evaluating visual air quality and advances in their development (Section 13.2.2). The relationship between PM and visibility impairment, including the central role of mass scattering efficiencies and advances in their use to estimate atmospheric light extinction from network PM data are then described (Section 13.2.3). Next, recent PM network data are examined to provide an up to date summary of spatial and temporal visibility patterns (Section 13.2.4). Finally, reviews of new approaches to evaluating human perception and preferences concerning atmospheric visibility and its value are provided (Section 13.2.5).

13.2.2 Visibility Impairment

13.2.2.1 Visibility Metrics

Two fundamental characteristics of atmospheric visibility impairment are 1) a reduction in *visual range*, the greatest distance through the atmosphere at which a prominent object can be identified, and 2) a reduction in *contrast*, the sharpness with which an object can be distinguished from another object or background (Malm, 2016). Both of these concepts can be understood in terms of an *atmospheric extinction coefficient* that relates the distance of an observed object to atmospheric light extinction following the Beer-Lambert Law (Finlayson-Pitts and Pitts, 2000).

The atmospheric extinction coefficient (b_{ext}) is a measure of the alteration of radiant energy as it passes through the atmosphere. b_{ext} can be expressed as the sum of light scattering by particles (b_{sp}), scattering by gases, known as Rayleigh scattering (b_{sg}), absorption by particles (b_{ap}), and absorption by gases (b_{ag}):

$$b_{ext} = b_{sp} + b_{sg} + b_{ap} + b_{ag}$$

Equation 13-1

b_{ext} varies with concentration and composition of scattering and absorbing substances in the atmosphere, and is especially useful for relating visual properties of distant objects theoretically to known concentrations and characteristics of atmospheric species (Malm, 2016). According to Malm (2016). Consequently, as described in Section 13.2.1, light extinction by gases is usually small compared to PM, and b_{sp} and b_{ap} are the main contributors to b_{ext}.

Contrast and visual range can both be conceptualized in terms of b_{ext}. The contrast can be between a haze layer and its background or between two different elements within a landscape feature, referred to as contiguous contrast. Contrast can be expressed in terms of a single color or as a color contrast. *Threshold contrast* is the reduction of contrast between two features to a point where it can just be seen (Malm, 2016). A *suprathreshold* value is a contrast change that is just noticeable when a landscape feature is clearly visible (Malm, 2016). If the background is the sky and light is uniform then contrast follows the Koschmieder relationship $C_r = C_o T_r$, (Middleton, 1968; Koschmieder, 1924), where T_r is the transmittance over path length r (Malm, 2016). The uniform sky light conditions necessary for the Koschmieder relationship to be valid do not always hold, but are most likely to be met under hazy conditions (Malm, 2016). If uniform light conditions are met, the Koschmieder relationship works well for perceptibility of isolated scenic elements, but uncertainty increases as light conditions become less uniform. Also, contrast is a scene-dependent metric based on the perception of a single object, and may not be representative of responses to visual characteristics of the scenic view as a whole (Malm, 2016). This limits its use for comparing visual impairment between different scenes or locations. Still, the Koschmieder relationship is widely used for assessing atmospheric visibility impairment, including the explanation of visual range.

If a just visible black object is viewed against the sky and the sky radiances at the observer and landscape feature are equal, then the Koschmeider relationship can be used to define the visual range as

$$V_r = \frac{-ln(\varepsilon)}{\bar{b}_{ext}}$$

Equation 13-2

where ε is the threshold contrast (a contrast level that can just be detected). If $\bar{b}_{ext} = b_{ext}$ and the threshold contrast ε is taken to be 0.02 based on historical observations (Malm, 2016), visual range can be calculated from b_{ext}:

$$V_r = \frac{3.912}{b_{ext}}$$

Equation 13-3

If b_{ext} is constructed such that Rayleigh scattering, i.e., b_{sg}, is set equal to 10 Mm^{-1}, then V_r is known as the standard visual range (SVR), which by Equation 13-3 is 391 km.

Visual range and extinction coefficient are metrics that can be consistently measured and used to assess visual air quality and track its changes and responses to emissions and PM. A third widely used metric the deciview haze index is a log transformation of light extinction (Pitchford and Malm, 1994):

$$dv = 10\left(ln\frac{b_{ext}}{0.01\ km^{-1}}\right)$$

Equation 13-4

The deciview is similar to the decibel for acoustic measurements. A one deciview (dv) change is about a 10% change in light extinction, which is a small change that is detectable for sensitive viewing situations. The haze index in deciview units is an appropriate metric for expressing the extent of haze changes where the perceptibility of the change is an issue. The Regional Haze Rule has adopted the deciview haze index as the metric for tracking long-term haze trends of visibility-protected federal lands (U.S. EPA, 2001).

Due to the dependence of the perception of haze by the human observer, scenic elements, and atmospheric optics, a number of different visibility metrics have been proposed over the years. They tend to fall into two broad categories: those metrics that are scene dependent, incorporating landscape characteristics and possibly human responses to the changes and those metrics that are independent of the scene but depend only on optical characteristics of the atmosphere, also called universal metrics.

Atmospheric extinction coefficient, visual range, and deciview are all universal, or scene independent metrics. There are also scene-dependent metrics, which incorporate changes in the radiance from landscape features and possibly human responses due to haze and depend on the landscape features, haze, illumination, and possibly the observer. Although these metrics are dependent on multiple scene features, it is also useful to have metrics that can directly relate human judgments of the visual air quality of a scene under varying haze conditions to a basic atmospheric variable such as light extinction. Contrast is a scene dependent metric. Numerous other universal and scene dependent metrics have been developed, but are not included in this assessment because they have not been used in studies reviewed here and were thoroughly reviewed recently (Malm, 2016).

13.2.2.2 Monitoring of Visibility Impairment

Direct PM light extinction, scattering, and absorption measurements are considered more accurate estimates derived from PM mass measurements because they do not depend on assumptions about particle characteristics (e.g., size, shape, density, component mixture, etc.). They can also be made with high time resolution, allowing characterization of subdaily temporal patterns of visibility impairment. Methods for measurement of light extinction, scattering, and absorption were reviewed in the 2009 PM ISA, which

included discussion of transmissometers for measurement of path-averaged light extinction and integrating nephelometers for measurement of light scattering. The use of integrating nephelometers for investigating effects of ambient PM size and water growth characteristics on light scattering was also described. The discussion also included measurement of PM light absorption by transmittance through filters on which PM has been collected as well as with aethelometers and photoacoustic instruments (U.S. EPA, 2009). Not reviewed in the 2009 PM ISA were methods for measuring scene-dependent visibility metrics that quantify the appearance of the view, accounting for the effects of particle and lighting conditions on the appearance of the scene. These include teleradiometers and telephotometers as well as photography and photographic modeling, which were described in the 2004 PM AQCD (U.S. EPA, 2004) and recently updated by Malm (2016). The discussion here is focused on strengths, limitations, and new developments of methods that were also discussed in the 2009 PM ISA (U.S. EPA, 2009), but includes recent research results that confirm or add to this body of knowledge. The convention for visibility monitoring is to make measurements at or near 550 nm, which is the wavelength of maximum eye response.

The integrating nephelometer was described in the 2009 PM ISA (U.S. EPA, 2009). It is characterized by high sensitivity and good sample control options and has been a widely used scattering instrument for air-quality-related visibility and PM monitoring purposes (Charlson et al., 1974). Integrating nephelometers significantly underestimate large particle scattering (Mueller et al., 2011b; Massoli et al., 2009; Mueller et al., 2009; Quirantes et al., 2008; Anderson and Ogren, 1998). Thus, they are better suited to measure scattering from fine PM than total or coarse PM. Historically, nephelometer chambers have been heated by radiation from their lamps and nearby electronics, drying out hygroscopic particles such as sulfates and nitrates underestimating ambient scattering. Current nephelometers generally use LED light sources, substantially reducing heating and its effects (Mueller et al., 2011b). Polar nephelometers measure the scattering as a function of scattering angle and thus can define the scattering phase function for a given aerosol (Dolgos and Martins, 2014; McCrowey et al., 2013). This can be important for visibility impairment assessments, since the path function will vary as a function of sun, landscape features, and observer geometry.

Forward and backscatter monitors measure light scattering in a prespecified solid angle (Heintzenberg, 1978). Open-air, forward scattering instruments are robust instruments and are extensively used by the National Weather Service (NWS) Automated Surface Observing System (ASOS) for characterizing visibility, principally for transportation safety purposes (NOAA, 1998; Richards et al., 1996). These instruments are also increasingly being used in Asian air quality and visibility studies, e.g., Shahzad et al. (2013) and Wang et al. (2014b).

Light absorption by PM is typically due mostly to black carbon (BC), with some contribution from organic matter also possible (Petzold et al., 2013). Soil or dust particles in the atmosphere also contribute to potentially significant amounts of atmospheric absorption (Fialho et al., 2014). Aerosol absorption measurements are made from a loaded filter based on the reflectance and transmittance of light

through the filter (Moosmüller et al., 2009; Bond et al., 1999) or in situ using a variety of methods including photoacoustic absorption spectrometry (Moosmüller et al., 2009).

All filter-based measurements require adjustments to the optical measurements to account for filter and sampled particle light-scattering effects associated with particles concentrated on and within the matrix of the filters (U.S. EPA, 2009; Bond et al., 1999). In a recent intercomparison of filter based absorption measurements, Mueller et al. (2011a) found a large variation in response from the different instruments and concluded that current correction functions for these measurements are not adequate. Quartz or glass fiber filters are the most widely used substrates in filter based absorption measurements. Organic gases are known to adsorb onto these filter media biasing organic carbon measurements, and these can be pyrolyzed to form artifact BC during the analysis, producing substantial biases in filter-based absorption measurement (Vecchi et al., 2014).

In situ measured absorption was also described in the 2009 PM ISA (U.S. EPA, 2009), and does not suffer from filter-based artifacts. Two first principle methods are absorption measured by extinction-minus-scattering and photoacoustic absorption spectrometry. The extinction-minus-scattering method suffers from potentially large subtraction errors for aerosols with high single scattering albedo and systematic errors such as the truncation errors in nephelometer scattering measurement for large particles (Singh et al., 2014; Moosmüller et al., 2009). Photoacoustic spectrometry operates by measuring the changes in pressure waves resulting from the heating and cooling of absorbing aerosols from a pulsed source of electromagnetic energy, typically a laser (Arnott et al., 2005; Arnott et al., 1999). These methods have been found to have low errors (Moosmüller et al., 2009). New developments include the combination of photoacoustic absorption measurements with integrating nephelometer in the same instrument package. For example, Sharma et al. (2013) developed a new multiwavelength, photoacoustic nephelometer spectrometer that measures scattering and absorption at wavelengths of 417, 475, 542, 607, and 675 nm.

Transmissometers measure the change in light intensity over a known distance from which b_{ext} can be derived. Long-path transmissometers were with path lengths up to 10 km were described in the 2009 PM ISA, and were concluded to suffer from a number of interferences that can cause large errors and difficulty in data interpretation (U.S. EPA, 2009; Debell et al., 2006). Cavity ring-down transmissometers do not suffer from these interferences. In this configuration, a beam of light, typically with wavelengths between 500 and 600 nm, is reflected back and forth between mirrors through an air sample, and the decay in the beam intensity over time is measured (Singh et al., 2014; Fiddler et al., 2009; Moosmuller et al., 2005; Wheeler et al., 1998). A disadvantage of the cavity ring-down configuration is that it is a point measurement and does not account for changes in b_{ext} over a sight path.

For scene-dependent visibility metrics, digital cameras have become used in much the same way as teleradiometers, recording signals proportional to radiance from all landscape features in the view. Digital or photographic cameras can be used to collect two-dimensional arrays, referred to as pixels, of film densities or digitized voltages in three color channels that are proportional to the image radiance

field, and if calibrated properly, provide quantitative radiance levels over the scene (Malm, 2016; Du et al., 2013). Advances have also been made in the application of photography in a less polluted environment. Most studies of visibility impairment have been carried out under fairly hazy conditions in urban environments, where fairly uniform lighting conditions correspond closely to conditions of the Koschmieder relationship. Furthermore, urban scenes tend to be gray, devoid of color associated with vegetation or brightly colored cliffs or terrain faces, such as those viewed in many of our national parks and wilderness areas. Bright edges of cloud formations are typically far enough from the observer to be obscured by heavy haze levels. Malm et al. (2015) investigated the ability to extract useful visibility metrics from routine webcams located in low-haze environments, specifically at the Grand Canyon National Park, Arizona, and Great Smoky Mountains National Park, Tennessee. This task is made more challenging by the effects of greater changes in lighting conditions that occur in low-haze conditions. Nonetheless, it was shown that meaningful relationships between metrics derived from the webcam images and atmospheric optical variables could be obtained as long as the indices were averaged over sufficient time to average out the effects of changing lighting.

13.2.3 Relationship between Particulate Matter and Visibility Impairment

Our understanding of the relationship between light extinction and PM mass has changed little since the 2009 PM ISA (U.S. EPA, 2009). Briefly, the impact of PM on light scattering depends on particle size and composition as well as relative humidity. All particles scatter light as described by Mie theory, which relates light scattering to particle size, shape, and index of refraction (Van de Hulst, 1981; Mie, 1908). Hygroscopic particles like ammonium sulfate, ammonium nitrate, and sea salt exhibit substantial growth as relative humidity increases, leading to increased light scattering (U.S. EPA, 2009). For externally mixed particles, a linear relationship between the b_{ext} is the sum of the mass concentration of each PM species multiplied by its specific mass extinction efficiency can be derived from Mie theory (Ouimette and Flagan, 1982):

$$b_{ext} = \sum_{j} a_j \, f_j(RH) M_j$$

Equation 13-5

where the species (j) mass concentration is given by M_j ($\mu g/m^3$); its extinction efficiency is given by α_j ($m^2 g^{-1}$); and its hygroscopic scattering growth factor given by $f_j(RH)$. The particle species j can be for a single compound or class of compound, such as particulate organic matter or even $PM_{2.5}$.

Equation 13-5 not only describes the theoretical relationship between light extinction and PM characteristics, but also provides the basis for practical use of mass scattering efficiencies in combination with ambient PM concentration data to estimate light extinction. This approach was previously described in the 2009 PM ISA (U.S. EPA, 2009), but is included here because it was used to estimate the extinction data used to examine seasonal and spatial patterns of visibility impairment in Section 13.2.4.

Equation 13-5 strictly applies to external mixtures of PM, i.e., PM is composed of a mixture of species, but each single particle is composed of only one of species. Although ambient PM is usually a complex and unknown combination of both internal and external mixtures of PM components, differences in calculated light extinction using various external and internal mixture assumptions were generally less than about 10%. As a result, the form of Equation 13-5 has been accepted as a reasonable approach to apportioning light extinction to PM components (U.S. EPA, 2009).

Applying Equation 13-5 to major PM species generates Equation 13-6, which was developed specifically for use with PM monitoring data (Section 13.2.4) (U.S. EPA, 2009; Malm et al., 1994):

$$b_{ext} \cong 3f(RH)([AS] + [AN]) + 4[OM] + 10[EC] + 1[FS] + 0.6[CM] + 10$$

Equation 13-6

Light extinction (b_{ext}) is in units of Mm^{-1}; [AS], [AN], [OM], [EC], [FS], [CM] are the concentrations in $\mu g/m^3$ of ammonium sulfate, ammonium nitrate, organic matter, elemental carbon, fine soil, and coarse mass, respectively; f(RH) is the relative-humidity-dependent water growth function, and the various coefficients are empirically derived mass scattering and absorption coefficients originally proposed by (Malm et al., 1994). Particulate organic matter concentration [OM] is derived from measured organic carbon concentration [OC] by multiplying by a factor of 1.4, [OM] = 1.4 [OC]. Equation 13-6 is widely referred to as the *original IMPROVE algorithm* to distinguish it from subsequent variations developed later. Although considerable research has focused on evaluating mass extinction coefficients, assessing the linearity of the relationship, and investigating the need for additional terms, a modification of Equation 13-6 (Hand et al., 2011) remains widely used for relating light extinction to PM components, including this document. Three major modifications were made to the Equation 13-6 for use in the most recent IMPROVE network report (Hand et al., 2011):

- A sea salt term was added.
- The factor used to compute particulate organic matter concentration from organic carbon concentration was increased from [OM] = 1.4[OC] to [OM] = 1.8[OC].
- A site-specific term based on elevation and mean temperature was used for Rayleigh scattering (gas scattering) instead of the constant value of 10 Mm^{-1} used in the original equation for all sites.

The resulting equation has been referred to as the *modified original IMPROVE algorithm* to distinguish it other, more extensive revisions:

$$b_{ext} \cong 3f(RH)([AS] + [AN]) + 4[OM] + 10[EC] + 1[FS] + 1.7f(RH)[SS]$$

Equation 13-7

where [SS] is sea salt concentration. All estimates of light extinction from $PM_{2.5}$ species in this document were made with Equation 13-7.

13.2.3.1 Estimated Mass Extinction

Mass scattering efficiencies, α_{sp}, can be calculated for single particle components or composites of different particle types, e.g., $PM_{2.5}$. The three main methods for calculating mass scattering efficiencies, α_{sp}, are 1) as a simple ratio of measured mass concentrations to measured light scattering coefficients, 2) by multilinear regression with b_{ext} as the independent variable and the measured PM mass concentrations for each species as the dependent variables, and 3) from Mie theory (see Section 13.2.3.1) if PM distribution, chemical composition, and optical properties are known (Malm, 2016; U.S. EPA, 2009; Hand and Malm, 2007). Average dry mass scattering efficiencies estimated by various methods from ground-based measurements in a survey of 60 studies since 1990 by Hand and Malm (2007). Results were briefly discussed in the 2009 PM ISA (U.S. EPA, 2009) and are more fully presented in Table 13-1. The results for individual species were considered generally consistent with the coefficients of Equation 13-6 or Equation 13-7 (U.S. EPA, 2009).

Table 13-1 Mass scattering efficiencies for urban, remote, and ocean regions.

Species/Mode[a]	Urban (m^2/g)	Remote/Rural Continental (m^2/g)	Ocean/Marine (m^2/g)	All Methods (m^2/g)
Fine mixed	3.2 ± 1.3 (32)	3.1 ± 1.4 (24)	4.1 ± 0.8 (42)	3.6 ± 1.2 (98)
Coarse mixed	0.6 ± 0.3 (6)	0.7 ± 0.4 (24)	1.6 ± 1.0 (21)	1.0 ± 0.9 (51)
Total mixed	1.7 ± 1.0 (14)		2.5 ± 1.0 (6)	1.9 ± 1.1 (20)
Fine sulfate	2.6 ± 0.7 (9)	2.7 ± 0.5 (56)	2.0 ± 0.7 (28)	2.5 ± 0.6 (93)
Fine nitrate	2.2 ± 0.5 (6)	2.8 ± 0.5 (42)		2.7 ± 0.5 (48)
Fine POM	2.5 (1)	3.1 ± 0.8 (38)	5.6 ± 1.5 (19)	3.9 ± 1.5 (58)
Coarse POM			2.6 ± 1.1 (19)	2.6 ± 1.1 (19)
Total POM			3.5 ± 0.9 (8)	3.5 ± 1.0 (8)
Fine dust		2.6 ± 0.4 (4)	3.4 ± 0.5 (19)	3.3 ± 0.6 (23)
Coarse dust		0.5 ± 0.2 (3)	0.7 ± 0.2 (19)	0.7 ± 0.2 (22)
Total dust		0.71 (1)	1.1 ± 0.4 (11)	1.1 ± 0.4 (12)
Fine sea salt		1.8 (1)	4.6 ± 0.7 (24)	4.5 ± 0.9 (25)
Coarse sea salt			0.96 ± 0.18 (21)	1.0 ± 0.2 (21)
Total sea salt			2.1 ± 0.5 (10)	2.1 ± 0.5 (10)

[a]Mode is listed in the table as fine or coarse rather than $PM_{2.5}$ and $PM_{10-2.5}$ because the variety of sampling and estimation methods used may not have always been based on $PM_{2.5}$ or $PM_{10-2.5}$ sampling methods.

Source: Permission pending, Malm and Hand (2007).

There is a broad range in scattering efficiencies across both regions and species in Table 13-1. Part of this variability is due to the different methods and their varying biases and uncertainties used in each study. Therefore, the true variances in mass scattering efficiencies due to microphysical differences in the particles are likely smaller. Based on their review, Hand and Malm (2007) made a series of recommendations for the dry mass scattering efficiencies for the visible wavelengths listed in Table 13-2.

Table 13-2 Mass scattering efficiency recommendations.

Species	Recommendation (m^2/g)	Comment
$PM_{2.5}$ ammonium sulfate	2.5	2 m^2/g in dry, clean environments 3 m^2/g in more polluted environments
$PM_{2.5}$ ammonium nitrate	2.7	
$PM_{2.5}$ organic matter	3.9	assuming carbon multiplier of 1.8
$PM_{2.5}$ soil	3.3	assuming perfect 2.5 μm cut point ~1 m^2/g for IMPROVE, CSN samplers
$PM_{2.5}$ sea salt	4.5	assuming perfect 2.5 μm cut point 1−1.3 m^2/g for more realistic samplers
Mixed $PM_{10-2.5}$ mass	1	large variability depending on RH, PM composition, PM size distribution
Mixed $PM_{2.5}$ mass	3.6	large variability depending on RH, PM composition, PM size distribution

Source: Permission pending, Hand and Malm (2007).

Mass scattering efficiencies from a number of studies in urban and rural environments were reported since the publication of these recommendations (Cheng et al., 2015; Pandolfi et al., 2014; Tao et al., 2014; Titos et al., 2012; Wang et al., 2012; Malm et al., 2009; Wagner et al., 2009; Andreae et al., 2008; Cheng et al., 2008). Overall, within a given species or mix of PM, there is wide variation in results, with over a factor of 2 or more difference between average results across the studies. However, these values are within the range of the study results reviewed by Hand and Malm (2007). In addition, Malm et al. (2011) showed that the organic mass scattering efficiency in Equation 13-7 is also sensitive to changes in the organic composition.

In addition to mass scattering efficiencies required for all major PM species, a full accounting for light extinction also requires mass absorption efficiencies for species that absorb light. Light absorption by PM is due mostly to black carbon (BC), although some contribution from organic matter is also possible (Petzold et al., 2013). Soil or dust particles in the atmosphere also contribute to potentially substantial amounts of atmospheric absorption (Fialho et al., 2014; Moosmueller et al., 2012). While light absorption by elemental carbon is included as a term in Equation 13-7, several estimates of mass absorption efficiencies for light absorbing carbon (LAC) were published before publication of the 2009 PM ISA, but were not included in the document. To fill this gap, those earlier studies are included for the first time in this ISA along with more recent observations.

Bond and Bergstrom (2006), attempted to understand and reconcile the wide range of reported LAC absorption efficiencies and recommended a mass absorption efficiency of 7.5 ± 1.2 m^2/g for LAC. This recommendation is consistent with results of Andreae et al. (2008), who estimated the LAC absorption efficiency to be 8.5 m^2/g. When organics and LAC were incorporated into a multilinear regression analysis, the LAC absorption efficiency reduced to 7.7 m^2/g. In Fresno, California, Chow et al. (2009) derived a LAC absorption efficiency of 7.9 ± 1.5 m^2/g. The large range of values for light absorbing carbon (LAC) mass absorption efficiencies is due in large part to LAC mass concentration measurements being method dependent, as well as to dependence of the absorption efficiency on wavelength and size distribution.

Absorption is often assumed to be due to particulate black carbon that absorbs in all visible wavelengths. However, there is increasing evidence that organic carbon compounds such as organonitrates absorb light in the near-ultraviolet–blue wavelengths (Lack et al., 2013; Claeys et al., 2012; Kitanovski et al., 2012). This absorption can be significant, with organic mass absorption efficiencies at ~400 nm in a smoke plume varying between 0.25 m^2/g and 2.9 m^2/g (Lack et al., 2013; Yang et al., 2009; Hoffer et al., 2006; Kirchstetter et al., 2004)). It is also missed by measurement methods that focus on green wavelengths, i.e., $\lambda \sim 550$ nm. The absorption of brown carbon in the blue wavelengths is important from a radiation balance standpoint. However, since brown carbon has little absorption in the green and red wavelengths, this should have only a small effect on visibility.

13.2.3.2 Hygroscopic Growth

The relative humidity growth functions in Equation 13-7 are the same for both sulfate and nitrate and are based on experimental growth curves for ammonium sulfate in their most hydrated state (Pitchford et al., 2007; Malm et al., 1994). The growth curves used are supported by a number of recent field studies (Lowenthal et al. (2015); (Chen et al., 2014; Liu et al., 2013; Liu et al., 2012; Stock et al., 2011; Achtert et al., 2009).Numerous laboratory studies have also shown that organic coatings on inorganic particles induce a lower deliquescence point compared to that of the pure inorganic compounds (Li et al., 2014; Peckhaus et al., 2012; Smith et al., 2012; Wu et al., 2011; Pope et al., 2010), and mixed-salt particles generally deliquesce at lower relative humidity than the single-salt particles (Freney et al., 2009). Consequently, outside of very dry environments, even ambient, fully neutralized inorganic salts would generally exhibit smooth growth with relative humidity.

Water uptake by particulate organic matter is not well understood, and in Equation 13-7 the size of organic particles is assumed to be independent of relative humidity, based on the observed the relationship between relative humidity and PM mass with high organic content (Reid et al., 2005; Malm et al., 2003). More recent studies suggest that organic mass is at least slightly hygroscopic, with observations of wet particle diameter/dry particle diameter of water soluble organic PM and humic-like substances from urban, rural, and biomass burning samples ranging from 1.08 to 1.10 at RH of 80%

(Lowenthal et al., 2015; Hallar et al., 2013), 1.13 to 1.19 at RH of 90% (Lowenthal et al., 2015; Kristensen et al., 2012), and 1.25 at RH of 95% (Kristensen et al., 2012) Organics are a significant contributor to urban $PM_{2.5}$ (see Chapter 2) and the exclusion of an f(RH) term for organics in Equation 13-6 likely results in an underestimation of the urban reconstructed b_{ext}.

13.2.3.3 Reconstructing b_{ext} from PM Speciation Data

In addition to the slight modification to develop Equation 13-7 from Equation 13-6, other revisions or rearrangements have been developed as attempts to improve performance or convenience, and results to these changes have been evaluated recently. Equation 13-6 tended to underestimate the highest light scattering values and overestimate the lowest values at IMPROVE monitors throughout the U.S. (Malm and Hand, 2007; Ryan et al., 2005; Lowenthal and Kumar, 2004), in the polluted Pearl River Delta region, and in Shanghai, China using 24-hour $PM_{2.5}$ filter samples (Deng et al., 2013) or $PM_{2.5}$ speciation data from semicontinuous monitors with higher time resolution (Cheng et al., 2015; Zhang et al., 2013b). Limited field studies suggested that particle size distributions and associated mass scattering coefficients may increase with concentrations (Lowenthal and Kumar, 2004; Malm et al., 2003). Although little research has been carried out on urban areas in the U.S., a similar shift of particle size distribution to larger sizes with increasing concentrations in rural and urban settings has been consistently observed in more recent studies in Europe and China (Cheng et al., 2015; Tian et al., 2014; Wang et al., 2014a; Wang et al., 2012; Yang et al., 2012; Calvo et al., 2010; Yue et al., 2009; Baeumer et al., 2008).

To resolve these biases, *a revised IMPROVE equation* was developed (Pitchford et al., 2007) that divides PM components into small and large particle sizes with separate mass scattering efficiencies and hygroscopic growth functions for each size. The revised IMPROVE *equation* was described in detail in the 2009 PM ISA (U.S. EPA, 2009), and it both reduced bias at the lowest and highest scattering values and improved the accuracy of the reconstructed $b_{ext.}$ However, poorer precision was observed with the revised IMPROVE equation compared to the original IMPROVE equation, indicating that the revised equation introduced new random errors. The differences resulting from the two equations in identifying the best and worst haze conditions and the apportionment of the various PM components were small (U.S. EPA, 2009).

Lowenthal and Kumar (2016) recently tested assumptions and evaluated the performance of the revised IMPROVE equation in National Parks and suggested further modifications were needed. They observed that the ration of [OM]/[OC] was closer to 2.1 than the currently used value of 1.8. They also observed that water soluble organic matter absorbs water as a function of RH, which is not accounted for in either the original or revised IMPROVE equations. They further reported that sulfate was not always completely neutralized, as assumed by both the original and the revised IMPROVE equation. Their results suggested that light scattering by sulfate was overestimated and light scattering by organic matter was underestimated by the revised IMPROVE equation. They concluded that the revised IMPROVE equation

did not resolve the biases it was intended to address, and that it should be re-examined (Lowenthal and Kumar, 2016).

Equation 13-6 has also been rearranged for convenient use with hourly measured RH, $PM_{2.5}$, and NO_2, and historical monthly averaged particulate composition (So et al., 2015). Overall, r^2 for all study sites, including those without site-specific speciation data, ranged from 0.72 to 0.77, and absolute normalized mean bias and normalized mean error were generally less than 5% and 25%, respectively, at all sites. Although NO_2 extinction was included in the study, it was mainly used to determine how much of the total extinction was due to $PM_{2.5}$, and conclusions were limited to $PM_{2.5}$ extinction.

In Equation 13-6 and Equation 13-7 it is assumed that the particle species are externally mixed, but this is generally not the case (Degheidy et al., 2015). Although previous studies have indicated that differences among the calculated light extinction values using external and various internal mixture assumptions are generally less than about 10% (U.S. EPA, 2009), newer work suggests potential nonlinearities in the resulting refractive indices of mixed particles. Freedman et al. (2009) found that the refractive indices of internal mixtures of ammonium sulfate and succinic acid were higher than for either pure compound alone at high organic mass fractions and that for mixtures of oxalic or adipic acid with ammonium sulfate, the refractive indices of the mixtures were about the same as ammonium sulfate for all organic mass fractions. Freedman et al. (2009) also calculated that a distribution of mixed particles containing 25% ammonium sulfate and 75% succinic acid resulted in 40% more scattering than would be estimated using volume-weighted, average refractive indices.

13.2.4 Seasonal and Spatial Patterns of Visibility Impairment

In this section light extinction is apportioned to PM species using data from the from the IMPROVE and CSN monitoring networks described in Chapter 2 (Section 2.4). Concentrations for all reconstructed particulate components used for estimating b_{ext} are determined using calculations listed in Table 13-3, which are based on the analyses and procedures laid out in the IMPROVE Report V (Hand et al., 2011) and related publications (Hand et al., 2014b; Hand et al., 2014a; Hand et al., 2013; Hand et al., 2012a; Hand et al., 2012b; Hand et al., 2012c). For example, the mass of ammonium sulfate (AS) is used in Equation 13-7 along with masses of other $PM_{2.5}$ species in the first column of Table 13-3 to estimate light extinction. However, the species actually measured in the CSN and IMPROVE networks is sulfate SO_4^{2-} rather than AS, which is NH_4^+ added to SO_4^{2-} and has a greater mass. Column 2 shows that the concentration of ammonium sulfate [AS] is calculated from the concentration of sulfate [SO_4^{2-}] by multiplying [SO_4^{2-}] by 1.375, which is the ratio of the equivalent mass of [AS] to the equivalent mass of [SO_4^{2-}], i.e., adding ammonium to sulfate increases its mass by a factor of 1.375.

Table 13-3 Composite PM components.

$PM_{2.5}$ Species[a]	Calculation[b]	Assumptions
Ammonium sulfate AS = $(NH_4)_2(SO_4)$	$1.375[SO_4^{2-}]$	Sulfate is assumed to be fully neutralized for both IMPROVE and CSN data.
Ammonium nitrate AN = NH_4NO_3	$1.29[NO_3^-]$	Nitrate is assumed to be ammonium nitrate for both IMPROVE and CSN data.
Particulate organic matter (POM)	1.8[OC]	Derived from organic carbon (OC), assuming an average organic molecule is 55% carbon.
Light absorbing carbon (LAC)	LAC	
Fine particulate soil	2.2[Al] + 2.49[Si] + 1.63[Ca] + 2.42[Fe] + 1.94[Ti]	Fine soil is composed of common metal oxides; FeO and Fe_2O_3 are equally abundant; soil potassium = 0.6[Fe]; a factor of 1.16 is used to account for other compounds such as MgO, Na_2O, CO_3. Same assumption for both IMPROVE and CSN data.
Sea salt (SS)	$1.8[Cl^-]$ or 1.8[Cl]	Sea salt is 55% chloride by weight. IMPROVE sea salt is computed from chloride ion data, while CSN is computed from chlorine concentrations, since Cl^- is not available.
Dry reconstructed fine mass (RCFM)	[AS] + [AN] + [POM] + [LAC] + [Soil] + [SS]	
Coarse mass	$[PM_{10}] - [PM_{2.5}]$	

[a]Species used in Equation 13-7.

[b]The species measured in IMPROVE and CSN network is not exactly the same as the species used in Equation 13-7. The calculation column lists the factor multiplied by the measured species to give the calculated species concentration actually used in Equation 13-7. For example, sulfate is measured in the IMPROVE and CSN networks, but available mass scattering efficiencies are for ammonium sulfate. Therefore, the measured sulfate concentrations must be converted to ammonium sulfate by calculating the corresponding ammonium sulfate mass from the measured sulfate mass.

Sources: Hand et al. (2014b); Hand et al. (2014a); Hand et al. (2013); Hand et al. (2012a); Hand et al. (2012b); Hand et al. (2012c); Hand et al. (2011)

$PM_{2.5}$ mass reconstruction methods were recently reviewed, uncertainties in $PM_{2.5}$ mass concentration, and reconstructed PM components in the IMPROVE and CSN networks using multiple linear regression methods (Chow et al., 2015; Malm et al., 2011). In addition, several field studies in rural environments tested some of the assumptions in Table 13-3, concluding that ammonium sulfate was fully neutralized and particle size with increasing RH followed a smooth growth curve (Lowenthal et al., 2015; Lowenthal et al., 2009). $PM_{2.5}$ concentrations are directly measured in the IMPROVE network. Particulate sulfate is assumed to be fully neutralized ammonium sulfate and estimated from the sulfate ion

measurement. Particulate nitrate is assumed to be in the form of ammonium nitrate from the reaction of nitric acid and ammonia gas. Organic mass is estimated by scaling the OC from the thermal optical reflectance analysis to particulate organic mass (POM) where the scale factor accounts for oxygen, hydrogen, and other noncarbon molecules. It was assumed that the ratio of POM divided by OC mass (ROC) was 1.8, or 55% of POM was carbon. This value was based on a regression analysis of the major PM composite components against measured $PM_{2.5}$ concentrations in the IMPROVE network (Malm and Hand, 2007).

LAC is the EC concentration reported from the thermal optical analysis of organic carbon (OC) and elemental carbon (EC) (Watson et al., 2005). Soil mass concentrations are estimated by a general method that sums the oxides of elements that are typically associated with soil (Al_2O_3, SiO_2, CaO, K_2O, FeO, Fe_2O_3, TiO_2). To account for other compounds such as MgO, Na_2O, and carbonates, the sum is multiplied by a factor of 1.16 (Malm et al., 1994). Molar concentrations of iron are assumed to be equally abundant in the forms of FeO and Fe_2O_3, and soil potassium is estimated by using Fe as a surrogate, or [K] = 0.6[Fe], because unlike Fe and other soil elements, the K in $PM_{2.5}$ is also contributed in abundance by another source, biomass burning (Malm et al., 1994). Sea salt concentrations are typically computed from sea salt markers, with the most common being sodium (Na). The Na ion is not routinely measured in the IMPROVE program, and elemental Na is poorly detected by IMPROVE's routine X-ray fluorescence analysis (White, 2008), so the chloride ion is used instead (Table 13-3).

The chloride ion has been shown to be a good predictor of conserved sea salt mass near coastal areas (White, 2008) but can be lost during atmospheric aging due to reactions with nitric acid, which produces particulate sodium nitrate and gaseous hydrochloric acid. The use of the chloride ion likely results in an underestimation of sea salt's contribution to $PM_{2.5}$ farther away from coastal areas, but sea salt concentrations are generally reduced by dispersion and removal processes, leading to smaller contributions to $PM_{2.5}$. Elemental chlorine concentrations are used to estimate sea salt for CSN data, because the chloride ion is not analyzed by the CSN. Comparisons of sea salt concentrations between 25 collocated CSN and IMPROVE sites located throughout the U.S. observed that IMPROVE concentrations were up to three times higher on average compared to CSN, with a relative bias of 63%, or large enough for the data to be considered semiquantitative (Hand et al., 2011). Difficulties in measuring sea salt in the IMPROVE and CSN networks including the lack of Na^+ measurements as a check and depletion of Cl^- due to displacement by NO_3^- are discussed by Hand et al. (2011).

13.2.4.1 Seasonal and Spatial Light Extinction $PM_{2.5}$ Species Contributions

Approximately every five years the IMPROVE program releases a report summarizing the spatial and temporal patterns of $PM_{2.5}$ composition and its contribution to light extinction from IMPROVE and CSN monitoring sites, which are mostly urban and rural, respectively. The latest report, IMPROVE Report V, was published in 2011 (Hand et al., 2011) and included a summary of the seasonal and

geographic distributions of species contributions to $PM_{2.5}$ and light extinction for IMPROVE and CSN monitoring sites averaged over the years 2005–2008. The b_{ext} associated with $PM_{2.5}$ components was calculated using Equation 13-7 and the same monthly climatological f(RH) curves used in the Regional Haze Rule guidance document (U.S. EPA, 2003). These data can be used to identify differences between urban and rural light extinction species contributions by region and season. This contrasts with most visibility data, including data presented in the 2009 PM ISA (U.S. EPA, 2009), which have historically been based mainly on rural and remote measurements.

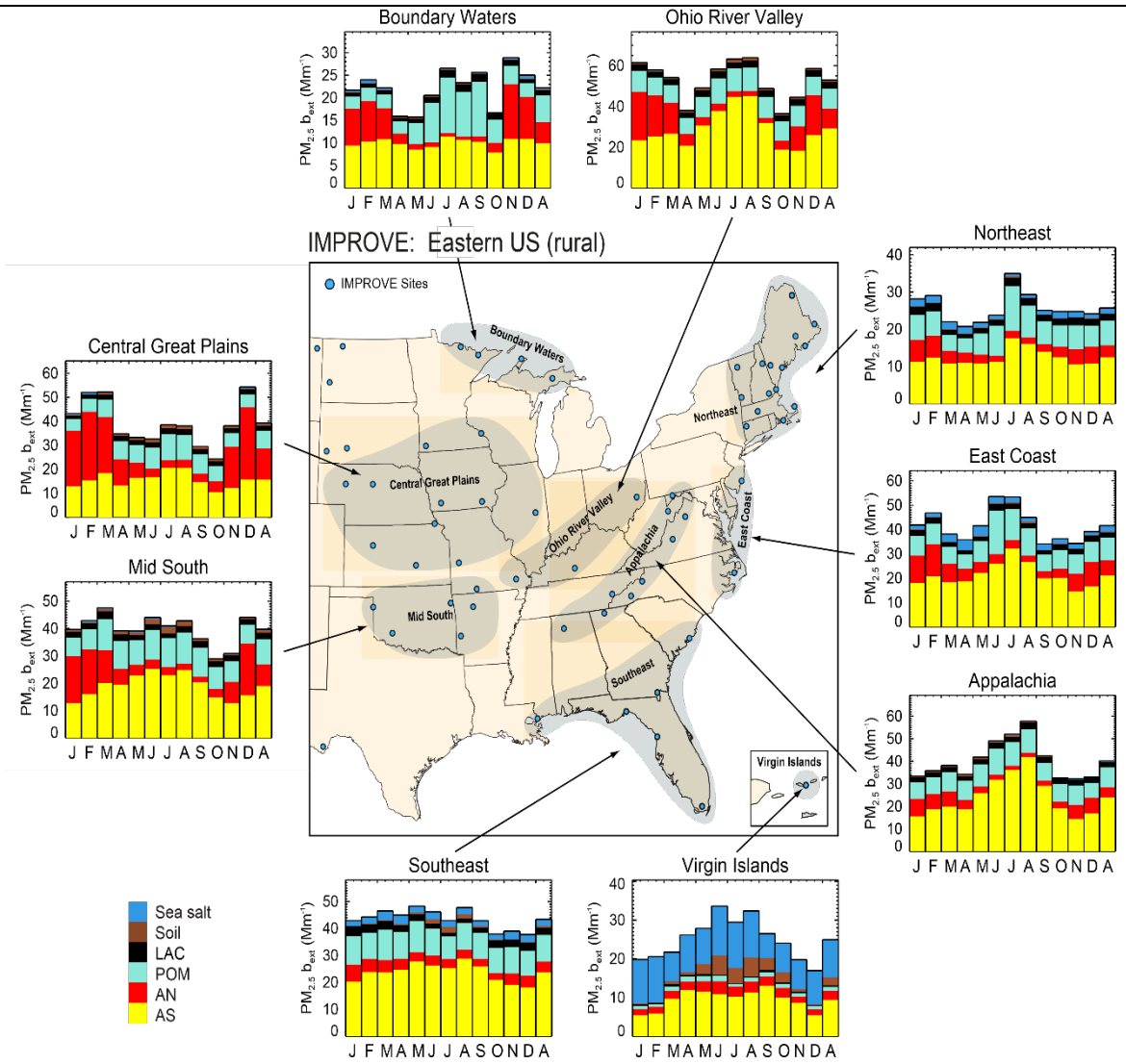
Twenty-eight IMPROVE regions were empirically defined based on-site location and magnitudes and seasonal distribution of PM concentrations for major species. Elevation was not explicitly taken into account in these groupings. Thirty-one CSN regions were defined based on seasonal distributions of PM concentrations and site locations. For comparison purposes and where possible, CSN regions were defined similarly to those for the IMPROVE network (Hand et al., 2011). Although the ability to leverage the sampling networks to provide extinction estimates provides valuable insight, these mass-based estimates are less accurate than calculations that use particle size and composition information.

Hand et al. (2012c) published the finding for the seasonal $PM_{2.5}$ species concentrations for the IMPROVE and CSN regions using PM species listed in Table 13-3, averaged over the years 2005−2008. The data were aggregated over regions or groupings of IMPROVE or CSN monitoring sites. Twenty-eight IMPROVE regions were empirically defined based on-site location and magnitudes and seasonal distribution of aerosol concentrations for major species. Elevation was not explicitly taken into account in these groupings. Thirty-one CSN regions were defined based on seasonal distributions of aerosol concentrations and site locations. Of the thirty-one CSN regions, eight had only one site per region because seasonal distributions were unique in comparison to the nearest other monitors, and these regions are identified by individual cities. Where possible, CSN regions were defined similarly to those for the IMPROVE network for comparison purposes.

Following is a summary of the $PM_{2.5}$ b_{ext} species contribution estimates from Hand et al. (2011). The b_{ext} species contributions differ from the $PM_{2.5}$ mass contributions in that the relative contribution of fine soil scattering is reduced due to its comparatively low scattering efficiency, and the relative contributions of ammonium sulfate and nitrate are increased due to the f(RH) factors. The results are presented as monthly stacked bar charts for each region in Figure 13-1, Figure 13-2, Figure 13-3, Figure 13-4, Figure 13-5, Figure 13-6, Figure 13-7, Figure 13-8, Figure 13-9, Figure 13-10, Figure 13-11, and Figure 13-12. The figures are arranged in pairs, with odd-numbered figures showing data for 2011−2014 and even-numbered figures for the same region and monitors showing data for 2005−2008. The most recent data are presented first because the discussion focuses mainly on the 2011−2014 data shown in the odd-numbered figures, but earlier data for 2005−2008 are shown for comparison. Figure 13-1, Figure 13-2, Figure 13-3, Figure 13-4, Figure 13-5, and Figure 13-6 summarize the IMPROVE b_{ext} species contributions, while Figure 13-7, Figure 13-8, Figure 13-9, Figure 13-10,

Figure 13-11, Figure 13-12, Figure 13-13, and Figure 13-14 summarize the CSN b_{ext} species contributions.

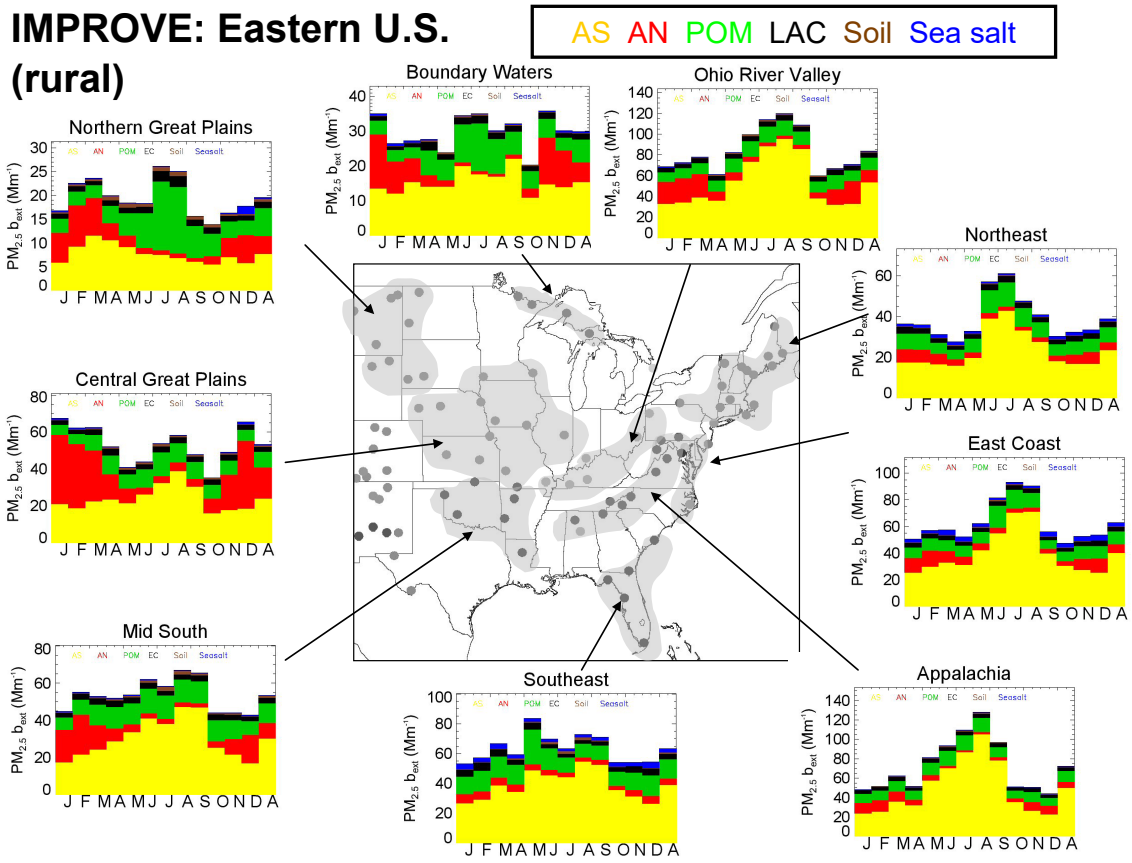
Figure 13-13 and Figure 13-14 show b_{ext} budgets for Alaska, Hawaii, and the Virgin Islands for 2005−2008 from the IMPROVE and CSN networks, respectively. These were presented separately in the original publication by Hand et al. (2011), but are included if available with other regions in the updated figures from 2011−2014 (Figure 13-3, Figure 13-5, and Figure 13-9).



Note: The letters on the x-axis correspond to the month and "A" corresponds to "annual" mean. Ammonium sulfate (AS) in yellow, ammonium nitrate (AN) in red, particulate organic matter (POM) in green, light absorbing carbon (LAC) in black, soil in brown, and sea salt in blue. The shaded area corresponds to the regions that comprise the sites used in the analysis, shown as dots. Extinction coefficients were determined from Equation 13-7 (see text). Wavelength corresponds to 550 nm.

Source: Permission pending, Update of Hand et al. (2011).

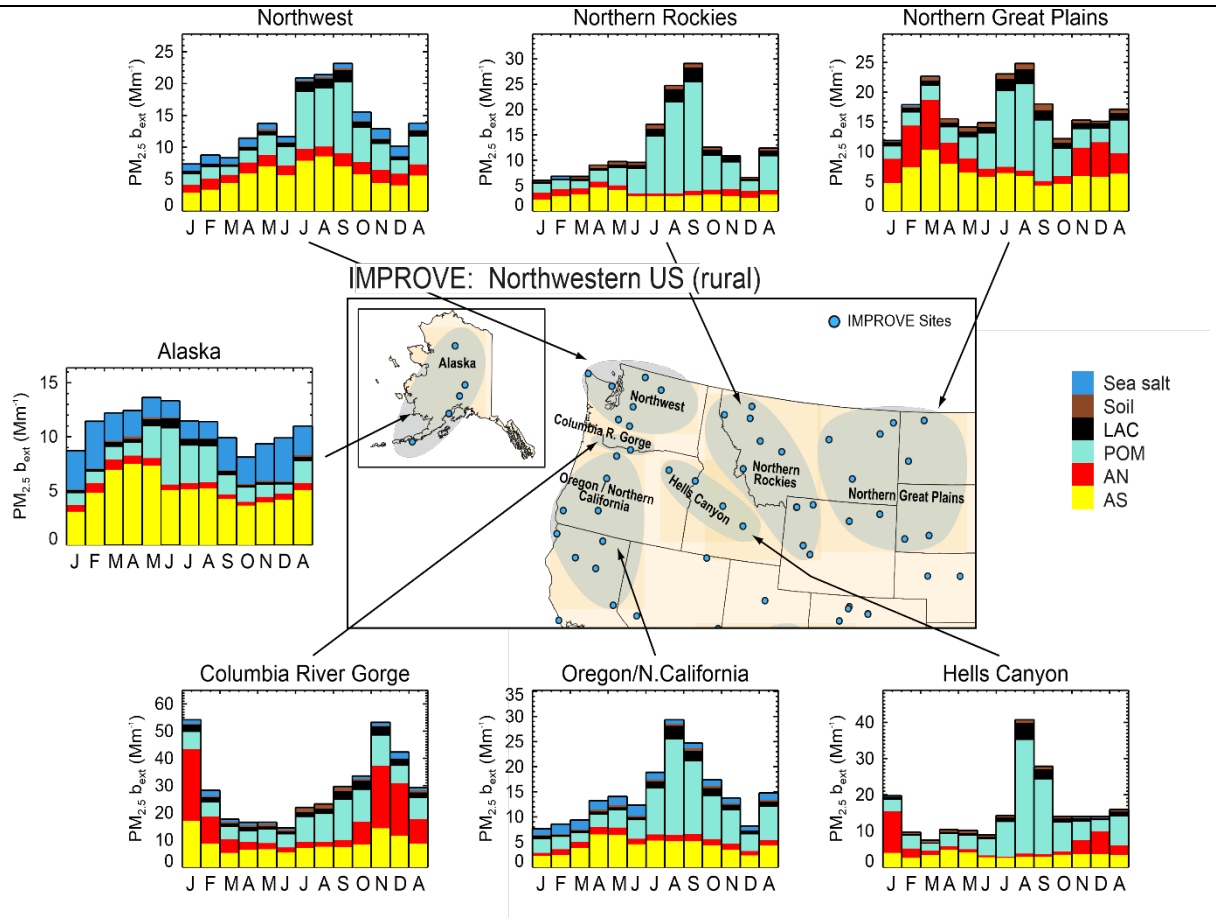
Figure 13-1 IMPROVE 2011–2014 regional monthly mean $PM_{2.5}$ reconstructed light extinction coefficients (b_{ext}, Mm^{-1}) for the Eastern U.S.



Note: The letters on the x-axis correspond to the month and "A" corresponds to "annual" mean. Ammonium sulfate (AS) in yellow, ammonium nitrate (AN) in red, particulate organic matter (POM) in green, light absorbing carbon (LAC) in black, soil in brown, and sea salt in blue. The shaded area corresponds to the regions that comprise the sites used in the analysis, shown as dots. Extinction coefficients were determined from Equation 13-7 (see text). Wavelength corresponds to 550 nm.

Source: Permission pending Hand et al. (2011).

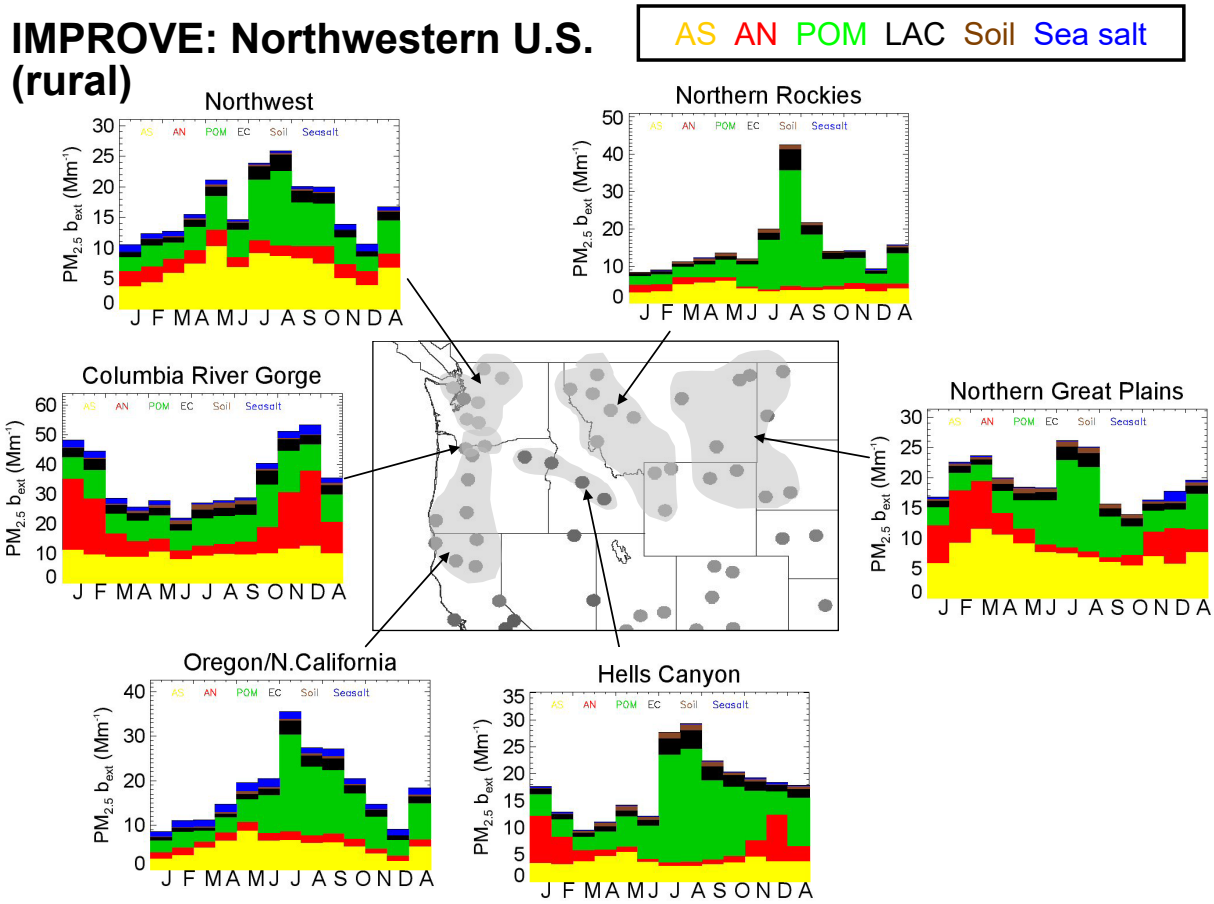
Figure 13-2 IMPROVE 2005–2008 regional monthly mean $PM_{2.5}$ reconstructed light extinction coefficients (b_{ext}, Mm^{-1}) for the Eastern U.S.



Note: The letters on the x-axis correspond to the month and "A" corresponds to "annual" mean. Ammonium sulfate (AS) in yellow, ammonium nitrate (AN) in red, particulate organic matter (POM) in green, light absorbing carbon (LAC) in black, soil in brown, and sea salt in blue. The shaded area corresponds to the regions that comprise the sites used in the analysis, shown as dots. Extinction coefficients were determined from Equation 13-7 (see text). Wavelength corresponds to 550 nm.

Source: Permission pending, Update of Hand et al. (2011).

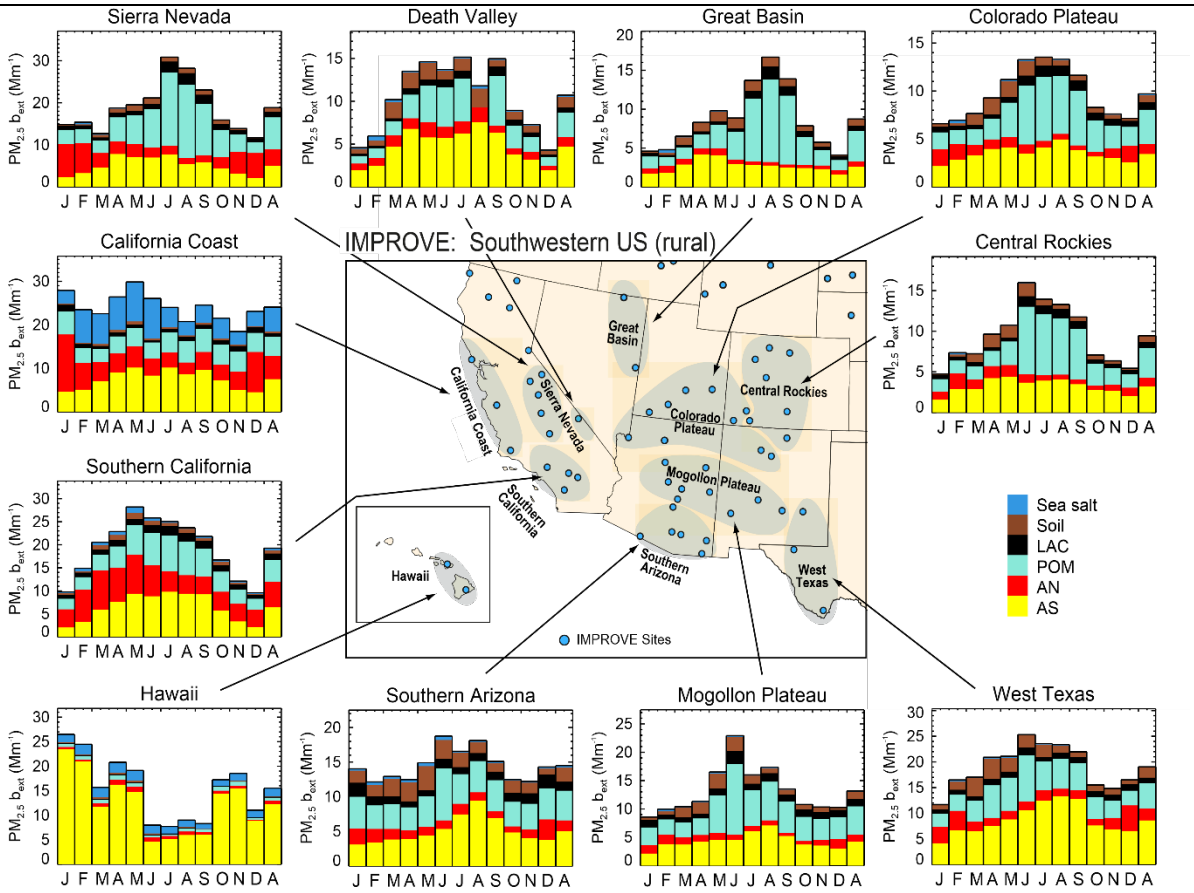
Figure 13-3 IMPROVE 2011–2014 regional monthly mean $PM_{2.5}$ reconstructed light extinction coefficients (b_{ext}, Mm^{-1}) for the Northwestern U.S.



Note: The letters on the x-axis correspond to the month and "A" corresponds to "annual" mean. Ammonium sulfate (AS) in yellow, ammonium nitrate (AN) in red, particulate organic matter (POM) in green, light absorbing carbon (LAC) in black, soil in brown, and sea salt in blue. The shaded area corresponds to the regions that comprise the sites used in the analysis, shown as dots. Extinction coefficients were determined from Equation 13-7 (see text). Wavelength corresponds to 550 nm.

Source: Permission pending, Hand et al. (2011).

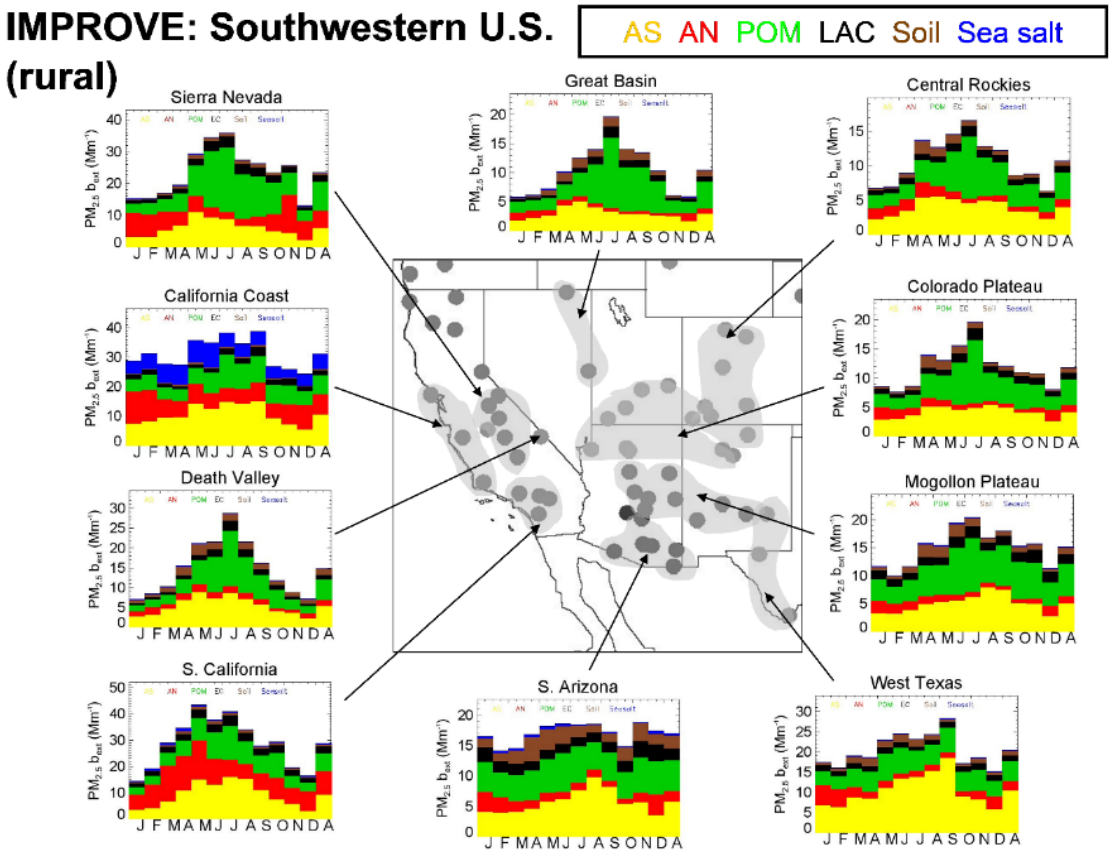
Figure 13-4 IMPROVE 2005–2008 regional monthly mean $PM_{2.5}$ reconstructed light extinction coefficients (b_{ext}, Mm^{-1}) for the Northwestern U.S.



Note: The letters on the x-axis correspond to the month and "A" corresponds to "annual" mean. Ammonium sulfate (AS) in yellow, ammonium nitrate (AN) in red, particulate organic matter (POM) in green, light absorbing carbon (LAC) in black, soil in brown, and sea salt in blue. The shaded area corresponds to the regions that comprise the sites used in the analysis, shown as dots. Extinction coefficients were determined from Equation 13-7 (see text). Wavelength corresponds to 550 nm.

Source: Permission pending, Update of Hand et al. (2011).

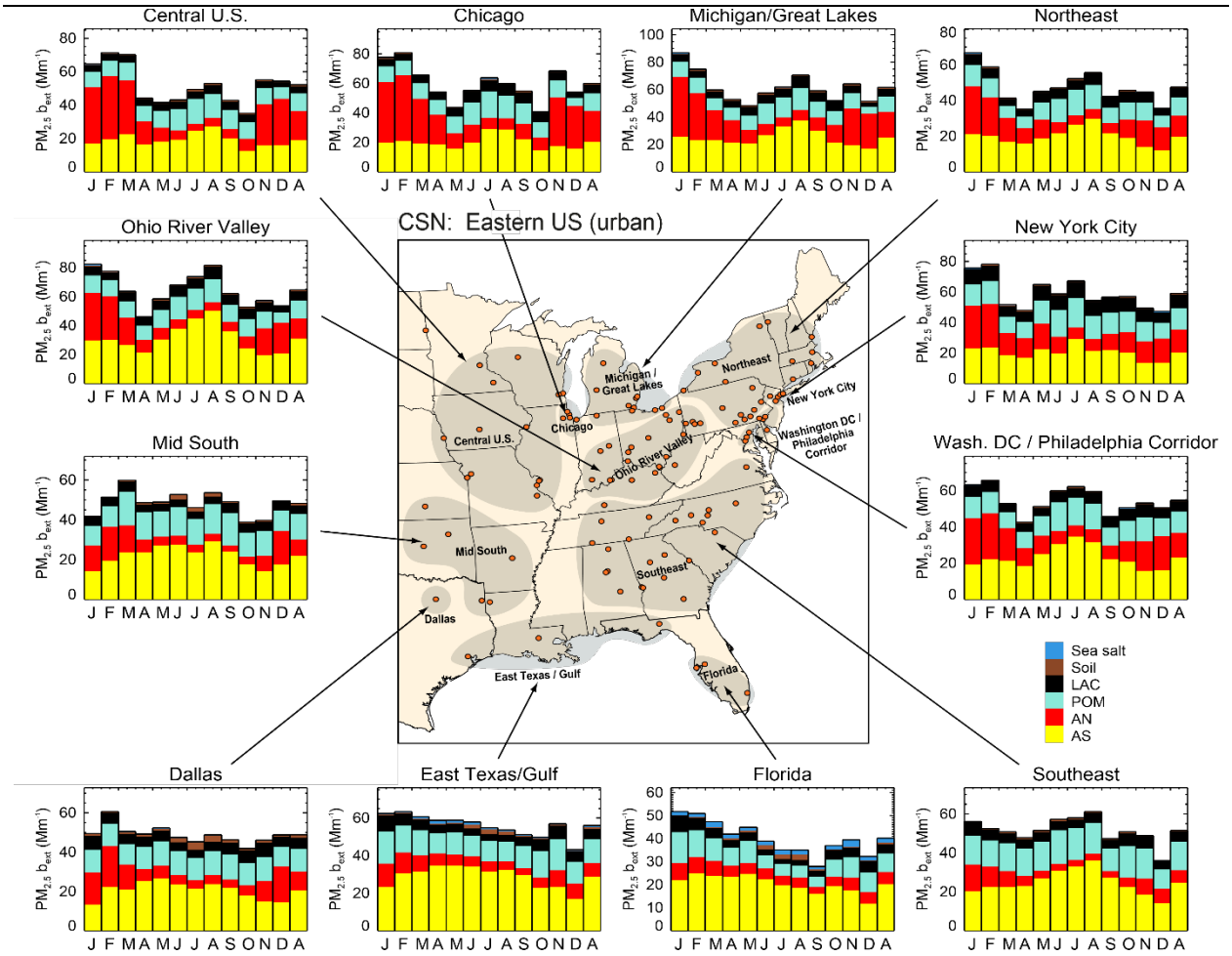
Figure 13-5 IMPROVE 2011–2014 regional monthly mean $PM_{2.5}$ reconstructed light extinction coefficients (b_{ext}, Mm^{-1}) for the Northwestern U.S.



Note: The letters on the x-axis correspond to the month and "A" corresponds to "annual" mean. Ammonium sulfate (AS) in yellow, ammonium nitrate (AN) in red, particulate organic matter (POM) in green, light absorbing carbon (LAC) in black, soil in brown, and sea salt in blue. The shaded area corresponds to the regions that comprise the sites used in the analysis, shown as dots. Extinction coefficients were determined from Equation 13-7 (see text). Wavelength corresponds to 550 nm.

Source: Permission pending, Hand et al. (2011).

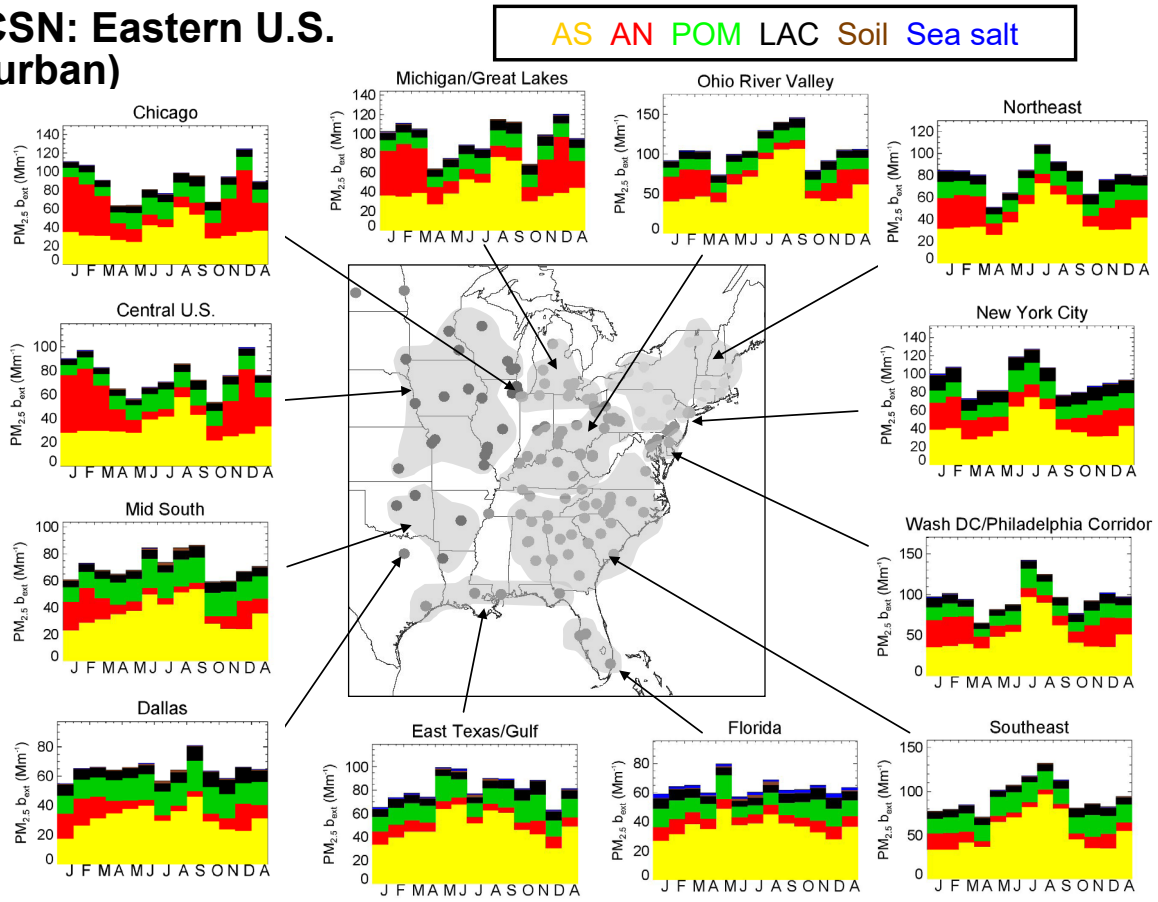
Figure 13-6 IMPROVE 2005–2008 regional monthly mean $PM_{2.5}$ reconstructed light extinction coefficients (b_{ext}, Mm^{-1}) for the Southwestern U.S.



Note: The letters on the x-axis correspond to the month and "A" corresponds to "annual" mean. Ammonium sulfate (AS) in yellow, ammonium nitrate (AN) in red, particulate organic matter (POM) in green, light absorbing carbon (LAC) in black, soil in brown, and sea salt in blue. The shaded area corresponds to the regions that comprise the sites used in the analysis, shown as dots. Extinction coefficients were determined from Equation 13-7 (see text). Wavelength corresponds to 550 nm.

Source: Permission pending, Update of Hand et al. (2011).

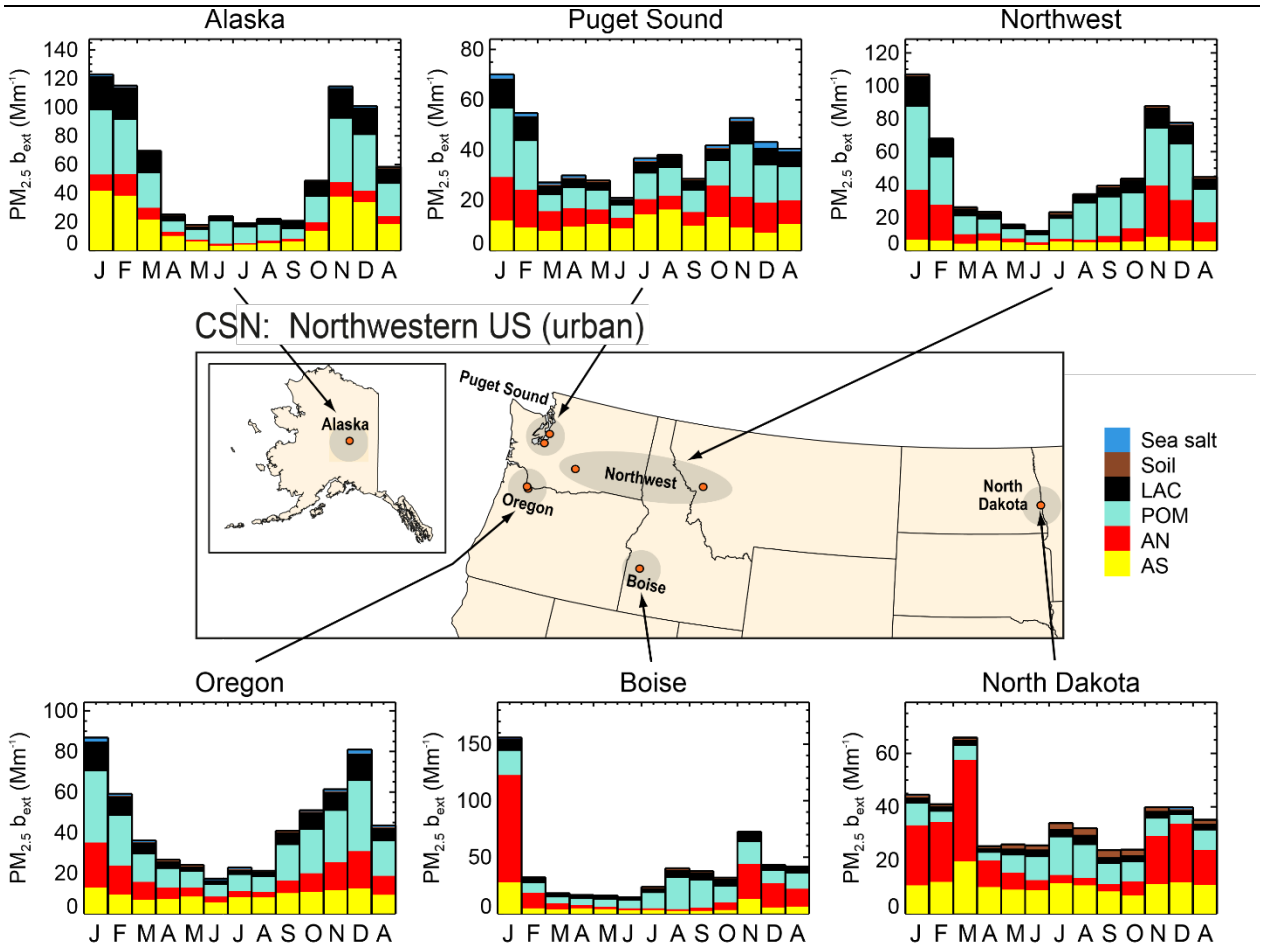
Figure 13-7 Chemical Speciation Network 2011–2014 regional monthly mean $PM_{2.5}$ reconstructed light extinction coefficients (b_{ext}, Mm^{-1}) for the Eastern U.S.



Note: The letters on the x-axis correspond to the month and "A" corresponds to "annual" mean. Ammonium sulfate (AS) in yellow, ammonium nitrate (AN) in red, particulate organic matter (POM) in green, light absorbing carbon (LAC) in black, soil in brown, and sea salt in blue. The shaded area corresponds to the regions that comprise the sites used in the analysis, shown as dots. Extinction coefficients were determined from Equation 13-7 (see text). Wavelength corresponds to 550 nm.

Source: Permission pending, Hand et al. (2011).

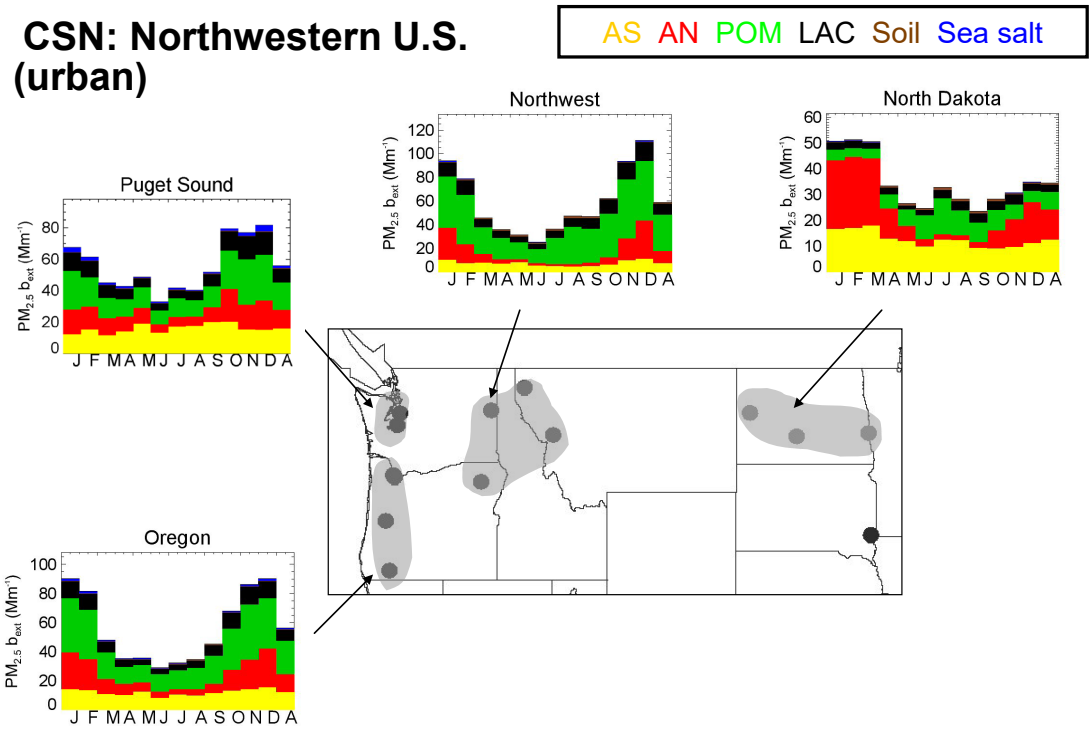
Figure 13-8 Chemical Speciation Network 2005–2008 regional monthly mean $PM_{2.5}$ reconstructed light extinction coefficients (b_{ext}, Mm^{-1}) for the Eastern U.S.



Note: The letters on the x-axis correspond to the month and "A" corresponds to "annual" mean. Ammonium sulfate (AS) in yellow, ammonium nitrate (AN) in red, particulate organic matter (POM) in green, light absorbing carbon (LAC) in black, soil in brown, and sea salt in blue. The shaded area corresponds to the regions that comprise the sites used in the analysis, shown as dots. Extinction coefficients were determined from Equation 13-7 (see text). Wavelength corresponds to 550 nm.

Source: Permission pending, Hand et al. (2011).

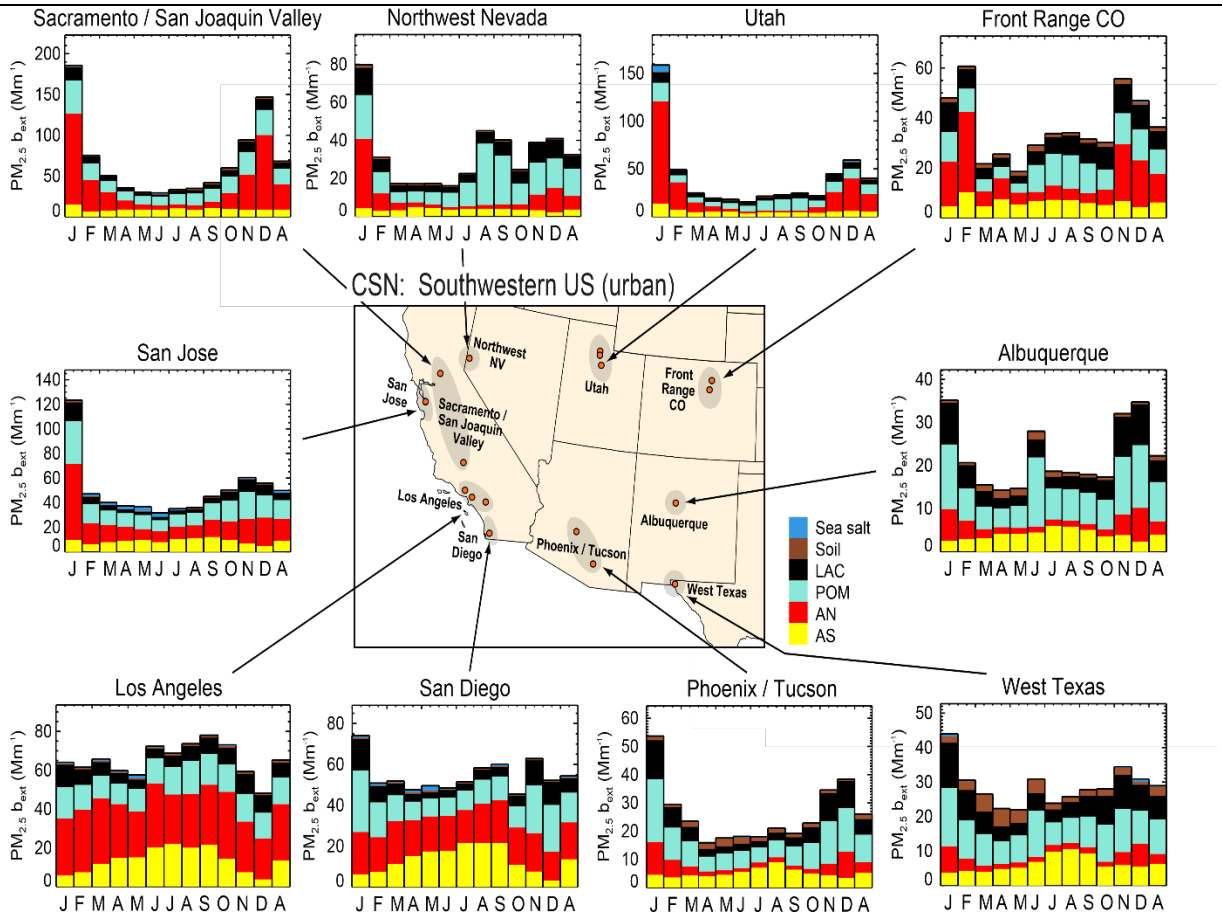
Figure 13-9 Chemical Speciation Network 2011–2014 regional monthly mean $PM_{2.5}$ reconstructed light extinction coefficients (b_{ext}, Mm^{-1}) for the Northwestern U.S.



Note: The letters on the x-axis correspond to the month and "A" corresponds to "annual" mean. Ammonium sulfate (AS) in yellow, ammonium nitrate (AN) in red, particulate organic matter (POM) in green, light absorbing carbon (LAC) in black, soil in brown, and sea salt in blue. The shaded area corresponds to the regions that comprise the sites used in the analysis, shown as dots. Extinction coefficients were determined from Equation 13-7 (see text). Wavelength corresponds to 550 nm.

Source: Permission pending, Update of Hand et al. (2011).

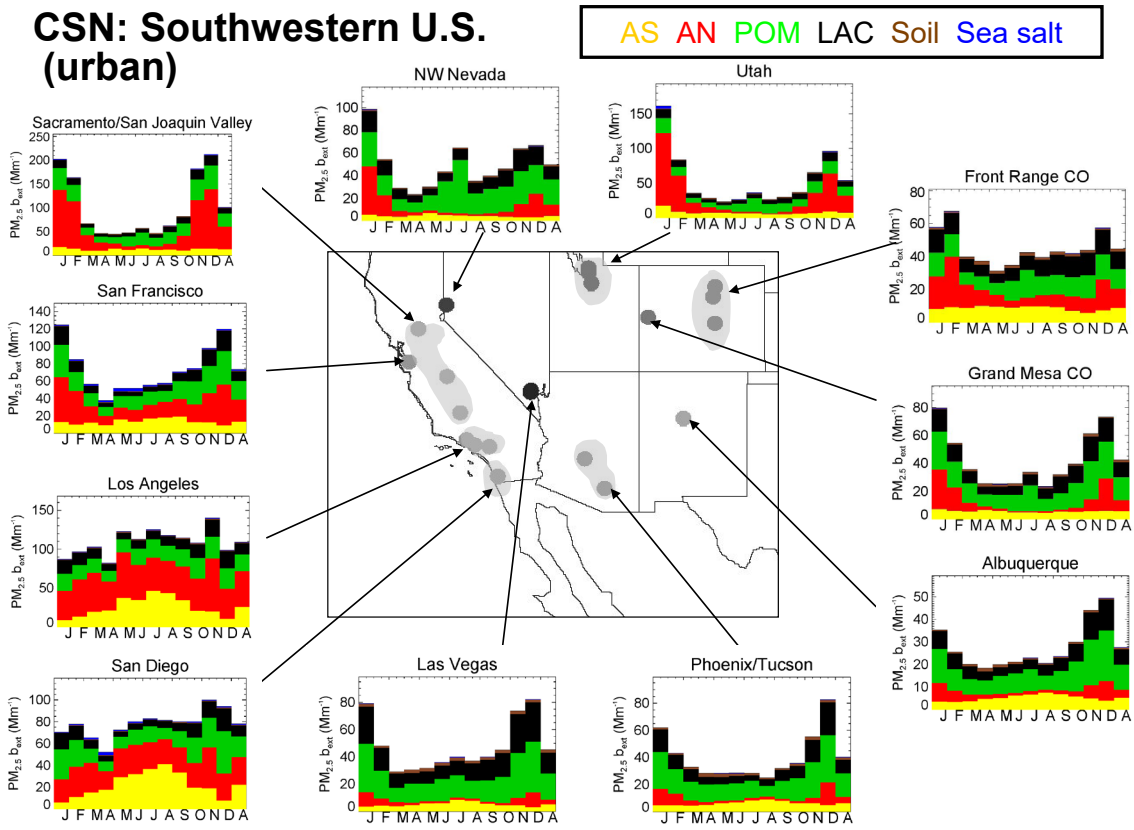
Figure 13-10 Chemical Speciation Network 2005–2008 regional monthly mean $PM_{2.5}$ reconstructed light extinction coefficients (b_{ext}, Mm^{-1}) for the Northwestern U.S.



Note: The letters on the x-axis correspond to the month and "A" corresponds to "annual" mean. Ammonium sulfate (AS) in yellow, ammonium nitrate (AN) in red, particulate organic matter (POM) in green, light absorbing carbon (LAC) in black, soil in brown, and sea salt in blue. The shaded area corresponds to the regions that comprise the sites used in the analysis, shown as dots. Extinction coefficients were determined from Equation 13-7 (see text). Wavelength corresponds to 550 nm.

Source: Permission pending, Hand et al. (2011).

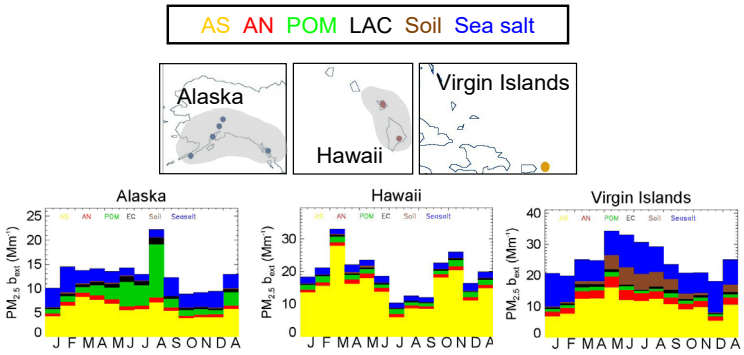
Figure 13-11 Chemical Speciation Network 2011–2014 regional monthly mean $PM_{2.5}$ reconstructed light extinction coefficients (b_{ext}, Mm^{-1}) for the Southwestern U.S.



Note: The letters on the x-axis correspond to the month and "A" corresponds to "annual" mean. Ammonium sulfate (AS) in yellow, ammonium nitrate (AN) in red, particulate organic matter (POM) in green, light absorbing carbon (LAC) in black, soil in brown, and sea salt in blue. The shaded area corresponds to the regions that comprise the sites used in the analysis, shown as dots. Extinction coefficients were determined from Equation 13-7 (see text). Wavelength corresponds to 550 nm.

Source: Permission pending, Update of Hand et al. (2011).

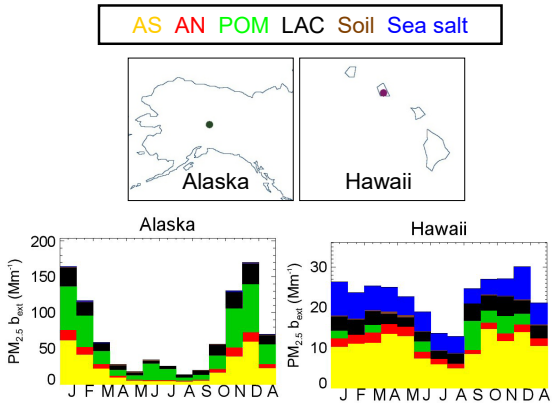
Figure 13-12 Chemical Speciation Network 2005–2008 regional monthly mean $PM_{2.5}$ reconstructed light extinction coefficients (b_{ext}, Mm^{-1}) for the Southwestern U.S.



Note: The letters on the x-axis correspond to the month and "A" corresponds to "annual" mean. Ammonium sulfate (AS) in yellow, ammonium nitrate (AN) in red, particulate organic matter (POM) in green, light absorbing carbon (LAC) in black, soil in brown, and sea salt in blue. The shaded area corresponds to the regions that comprise the sites used in the analysis, shown as dots. Extinction coefficients were determined from Equation 13-7 (see text). Wavelength corresponds to 550 nm.

Source: Permission pending, Hand et al. (2011).

Figure 13-13 IMPROVE 2005–2008 regional monthly mean $PM_{2.5}$ reconstructed light extinction coefficients (b_{ext}, Mm^{-1}) for Hawaii, Alaska, and the Virgin Islands.



Note: The letters on the x-axis correspond to the month and "A" corresponds to "annual" mean. Ammonium sulfate (AS) in yellow, ammonium nitrate (AN) in red, particulate organic matter (POM) in green, light absorbing carbon (LAC) in black, soil in brown, and sea salt in blue. The shaded area corresponds to the regions that comprise the sites used in the analysis, shown as dots. Extinction coefficients were determined from Equation 13-7 (see text). Wavelength corresponds to 550 nm.

Source: Permission pending, Hand et al. (2011).

Figure 13-14 Chemical Speciation Network 2005–2008 regional monthly mean $PM_{2.5}$ reconstructed light extinction coefficients (b_{ext}, Mm^{-1}) for Alaska and Hawaii.

Several major differences among the various regions are apparent from the 2011−2014 data. Annual average reconstructed b_{ext} is considerably higher in the East and Midwest than in the Southwest. Based on IMPROVE data, the highest annual average b_{ext} was greater than 50 Mm^{-1} in the Ohio River Valley, and annual average b_{ext} and was greater than 40 Mm^{-1} in the Southeast, East Coast, Mid-South, Central Great Plains, and Appalachian regions (Figure 13-1). In contrast, annual average b_{ext} was less than 40 Mm^{-1} for all Western IMPROVE regions (Figure 13-3 and Figure 13-5), but in the eastern half of the U.S. b_{ext} was less than 40 Mm^{-1} only for the Boundary Waters, Northeast, and Virgin Islands regions. (Figure 13-1). For perspective, a b_{ext} value of 40 Mm^{-1} corresponds to a visual range of about 100 km from Equation 13-3. Annual average b_{ext} values are also generally higher in Eastern than in Western CSN regions, although the highest annual average b_{ext} in the CSN regions are in the Sacramento/San Joaquin Valley and Los Angeles regions, and annual average b_{ext} in Alaska and other California regions are comparable to Eastern CSN regions.

Ammonium sulfate accounted for 34−60% of the annual average b_{ext}, in these Eastern regions with greatest contributions to extinction usually in the summer. Particulate organic matter (POM) was the next largest contributor, ranging from 19−32% of annual average b_{ext} with less seasonal variation. Ammonium nitrate was also important in most regions, accounting for 9−34%, with generally much higher concentrations winter than in summer (see Section 2.5).

In the Northwest (Figure 13-10 and Figure 13-13), POM was the largest contributor in most urban and rural regions, accounting for up to 69% of annual average b_{ext} and usually making its greatest contribution to b_{ext} in the fall, possibly due to wildfires. Exceptions were Boise and North Dakota, where ammonium nitrate was the greatest contributor, and the Alaska IMPROVE region, where ammonium sulfate was the greatest contributor to annual average b_{ext}.

In the Southwest IMPROVE regions (Figure 13-11), b_{ext} ammonium sulfate or POM were usually the greatest contributors to annual average b_{ext}, with close to equivalent contributions from each in several regions. In the Southwest CSN regions (Figure 13-14), ammonium nitrate was often the greatest contributor to annual average $b_{ext,}$ contributor, with especially high $b_{ext,}$ contributions in winter. Mass scattering from $PM_{10-2.5}$ was relatively small at less than 10% of the fine mass scattering in the eastern and northwestern U.S. However, in the Southwest it can be large, contributing more than 30% of the fine mass scattering in southern Arizona and New Mexico and more than 20% throughout the southwestern U.S. In the southwestern U.S., coarse mass is composed of primarily soil.

A number of differences between the urban CSN (Figure 13-12, Figure 13-13, and Figure 13-14) and mainly rural IMPROVE (Figure 13-9, Figure 13-10, and Figure 13-11) data also stand out. Light extinction is generally higher in CSN regions than geographically corresponding IMPROVE regions. Annual average total reconstructed b_{ext} exceeded 50 Mm^{-1} in 11 CSN regions, compared to only 1 IMPROVE region, and was higher than 20 Mm^{-1} in all CSN regions, but slightly more than half of IMPROVE regions. Light absorbing carbon was not among the three greatest contributors to light extinction in any IMPROVE regions, but was a substantial contributor in several Western regions,

accounting for more than 20% of annual average $PM_{2.5}$ b_{ext} in the West Texas, Albuquerque, Phoenix/Tucson, and Front Range CSN regions of the Southwest (Figure 13-11). Ammonium nitrate also accounted for more light extinction in the CSN than IMPROVE regions. It was the single greatest contributor in all of the CSN California regions as well as the Boise, Utah, North Dakota, and Chicago CSN regions. In contrast, ammonium nitrate accounted for the most extinction among all species only in the Columbia Gorge IMPROVE region.

In Equation 13-5 and Equation 13-6, b_{ext} is directly proportional mass. As a consequence, estimates of metrics like visual range, which is inversely proportional to b_{ext} (Equation 13-3), and deciview, which is a logarithmic function of b_{ext} (Equation 13-4), become less sensitive to changes in b_{ext} as PM mass increases. As a result, the same incremental increase in PM mass in a relatively clean area is predicted to have a greater impact on visual range and deciview than in a more polluted area. Because PM concentrations are generally lower in Western and rural areas than in Eastern and urban areas, these areas are likely to experience a greater incremental impact of a change in PM concentration.

Noticeable differences are also apparent when the 2011−2014 data (Figure 13-9, Figure 13-10, Figure 13-11, Figure 13-12, Figure 13-13, and Figure 13-14) are compared to data from 2005−2008 (Figure 13-1, Figure 13-2, Figure 13-3, Figure 13-4, Figure 13-5, Figure 13-6, Figure 13-7, and Figure 13-8). In 2005−2008 annual average b_{ext} exceeded 80 Mm^{-1} in most CSN regions in the Eastern U.S. (Figure 13-5), but in 2011−2014 annual average b_{ext} was less than 60 Mm^{-1} in all CSN regions (Figure 13-12). Based on Equation 13-3, this corresponds to an improvement in average visual range in most Eastern U.S. regions from less than 50 km in 2004−2008 to more than 65 km in 2011−2014. A more long-term comparison can be carried out with IMPROVE data, which extends as far back as 1988. As Figure 13-9 shows, annual average $PM_{2.5}$ b_{ext} estimates are under 50 mM^{-1} in all IMPROVE regions except the Ohio River Valley (between 55−60 mM^{-1}). This compares to estimates greater than 90 mM−1 for a wide area of the Eastern U.S. encompassing the East Coast, Appalachia, and Ohio River Valley regions of Figure 13-9 reported for 1988−1991 IMPROVE data (Malm et al., 1994).

A second major difference between the 2011−2014 data and 2005−2008 data concerns the fraction of b_{ext} accounted for by ammonium sulfate. As detailed in Section 2.5, atmospheric sulfate concentration has decreased by −2.7% per year from 1992 to 2010 and −4.6% per year from 2001−2010 at rural sites, and by −6.2% per year from 2001−2010 at urban sites due to a sharp decline in SO_2 emissions. From Equation 13-6, ammonium sulfate also makes a greater contribution to light extinction than an equivalent mass of most other species (Malm et al., 1994). The impact of decreased sulfate on visibility impairment is clearly evident at the most strongly impacted Eastern U.S. CSN regions of the Ohio River Valley, Michigan/Great Lakes, Chicago, and New York City when monthly extinction patterns are compared between 2011−2014 (Figure 13-12) and 2005−2008 (Figure 13-5). The fraction of total b_{ext} accounted for by ammonium sulfate is less in 2011−2014 than in 2005−2008, and monthly ammonium sulfate b_{ext} show less difference between summer months and monthly b_{ext} estimates from other times of year.

13.2.4.2 Long-Term Trends

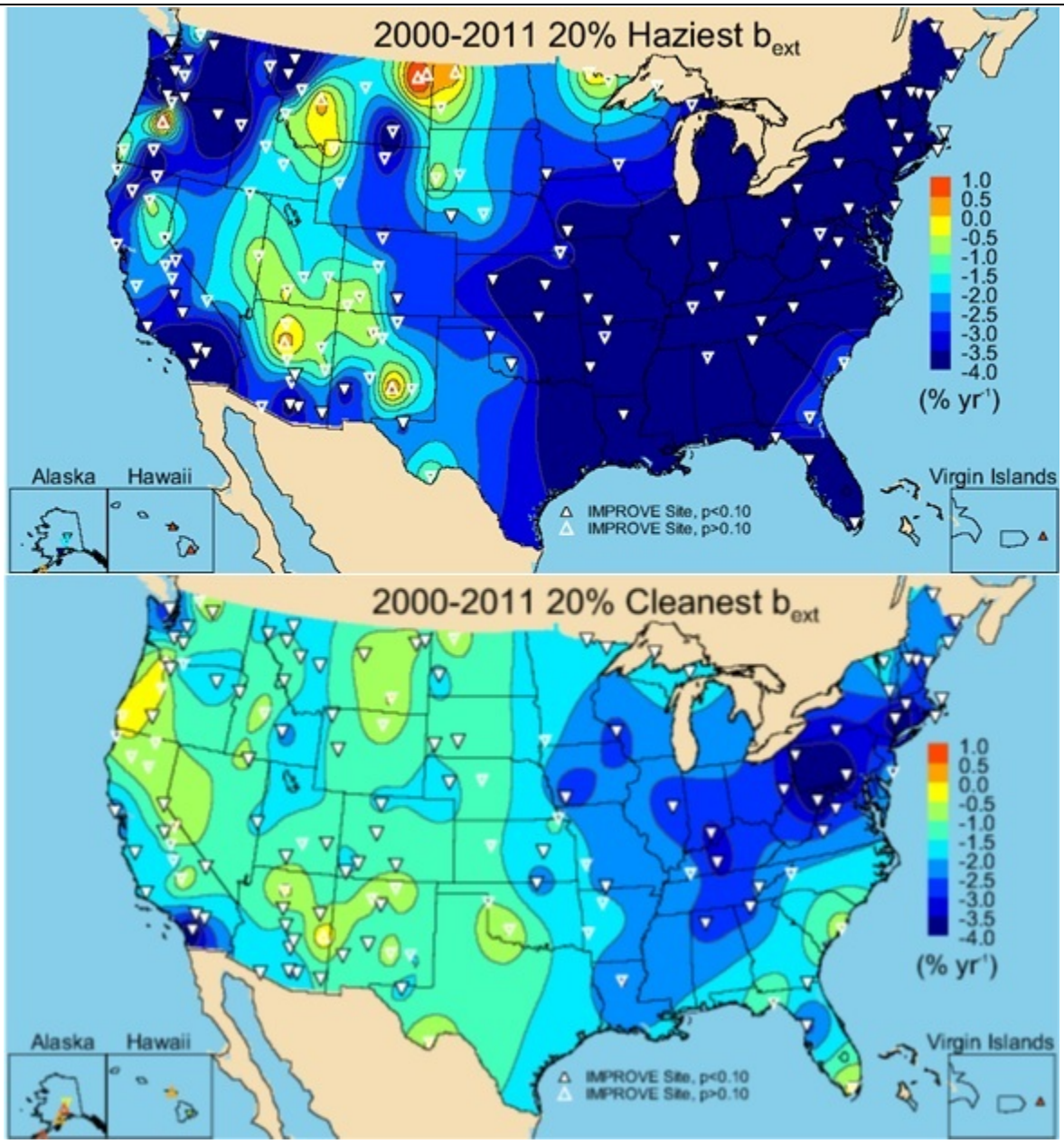
Long-term trends in atmospheric concentrations and visibility reduction since implementation of the IMPROVE network were reviewed in the 2009 PM ISA (U.S. EPA, 2009). Since that time there have been significant changes in the composition of atmospheric particulate matter in the U.S., described in detail in Chapter 2. On average, particulate ammonium sulfate (Hand et al., 2012b; Sickles and Shadwick, 2008), organic matter (Hand et al., 2013), light absorbing carbon (Murphy et al., 2011), and ammonium nitrate (Hand et al., 2011; Sickles and Shadwick, 2008) have decreased over the U.S. for both the IMPROVE and CSN monitoring data, resulting in decreasing $PM_{2.5}$ (Murphy et al., 2011) and haze (Attwood et al., 2014; Hand et al., 2014a).

The current Regional Haze Rule guidance documents require the tracking of haze in deciviews for the 20% worst and 20% clearest haze days (U.S. EPA, 2003, 2001). The trends in these haze metrics for 139 IMPROVE sites is presented in Figure 13-15 (Hand et al., 2014a). As shown, across the country, the 20% clearest days are less hazy (Hand et al., 2014a). Of the 139 sites, only three have upward trends compared to 136 downward trending sites. The largest downward trends were in the eastern U.S., where haze decreased by more than 3.5% per year in Pennsylvania and West Virginia. At the western sites, haze on the clearest days generally decreased 0.5–2%/year (Hand et al., 2014a).

The trends in the 20% worst haze days are somewhat different from those for the clearest days (Figure 13-15). As shown, in the eastern U.S., there have been steep declines in haze. All 54 sites east of −100-degree longitude had decreasing trends, and on average, eastern haze decreased 5%/year, or over 50% from 2000 to 2011. This large decrease was driven primarily by the reduction in ammonium sulfate (Hand et al., 2014a; Hand et al., 2012b). As illustrated in Figure 13-16 these reductions resulted in noticeably improved visibility at places like Great Smoky Mountains National Park and Washington, D.C. Improvements in visibility are also evident at many sites in the Pacific Coast states. This is not the case in the Intermountain and Southwest regions. These regions had 55 monitoring sites, and while a number of sites had increasing haze trends, none were significant. Fourteen of the 55 sites had significantly decreasing haze trends. These regions are subject to summertime wildfires, which have increased in the past decade. These wildfire events create high PM loadings and haze and often fall into the 20% haziest days (Hand et al., 2011). In northwestern North Dakota, wildfire is not a significant contributor to the worst haze days, and instead the increasing trends may be due to the rapid expansion of oil and gas extraction and the associated population growth (Prenni et al., 2015; Hand et al., 2012a). The range in annual b_{ext} values varies by about a factor of 10, with values above 70 Mm^{-1} in the Ohio River Valley region and less than 10 Mm^{-1} in the Southwest (Hand et al., 2011).

A recent revision to the Regional Haze Rule in 2017 clarified that haze should be tracked on the 20% most anthropogenically impaired days rather than the 20% haziest days to remove the influence of natural events like wildfire smoke and dust storms. Although a guidance document describing the method for determining anthropogenic impairment has not yet been finalized, a 2016 draft guidance recommended a metric which results in similar trend to Figure 13-15 for the Eastern U.S. but a decrease

in b_{ext} for the Intermountain and Southwest regions. The 2017 Regional Haze Rule revision did not change method of tracking haze for the 20% clearest days.



Note: Triangles correspond to IMPROVE sites; upward-pointing triangles correspond to increased b_{ext} and downward-pointing triangles correspond to decreased b_{ext}.

Source: Permission pending, Hand et al. (2011).

Figure 13-15 IMPROVE 2000–2011 trends (% yr^{-1}) in the reconstructed mean 20% haziest (top) and clearest (bottom) ambient light extinction coefficient (b_{ext} at 550 nm).

Source: Permission pending, Hand et al. (2014a).

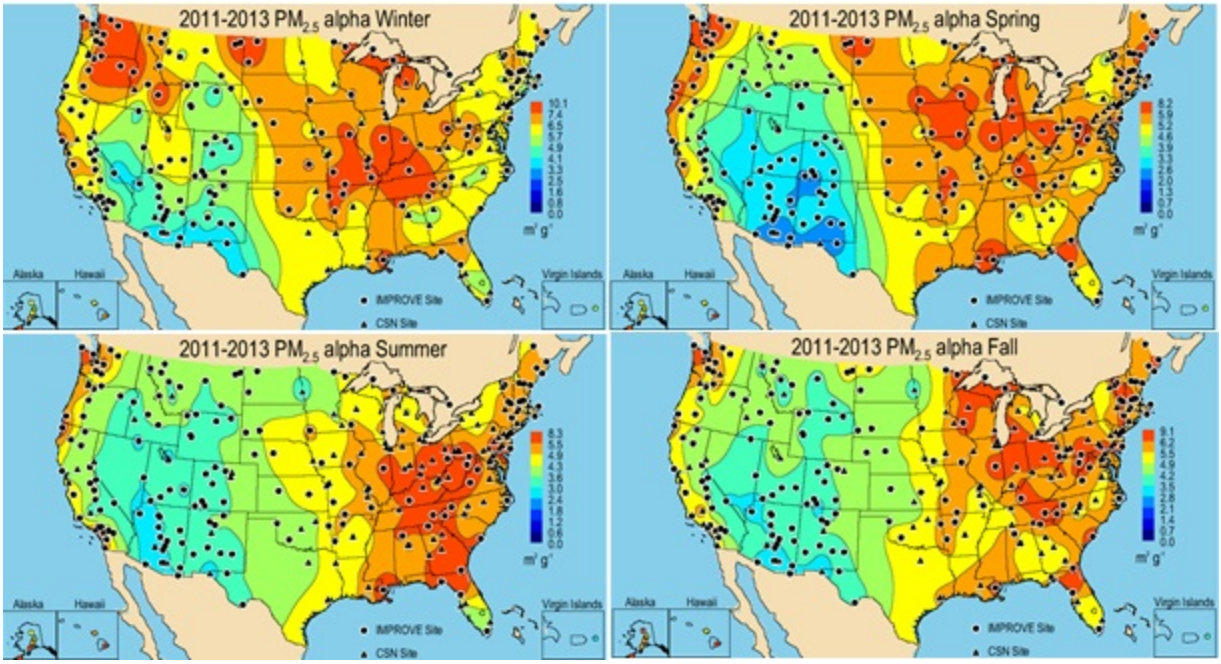
Figure 13-16 Simulations of the view at Great Smoky Mountains National Park, TN (top), and Washington, DC (bottom), corresponding to the mean 20% haziest b_{ext} in 1990 (left side of image) and 2012 (right side of image). Contributions from Rayleigh scattering are included.

13.2.4.3 Characteristic Fine Particulate Mass Light Scattering Efficiencies

The effective $PM_{2.5}$ mass extinction efficiencies, i.e., b_{ext} to $PM_{2.5}$ concentrations vary depending on the $PM_{2.5}$ composition and relative humidity. Based on Equation 13-7 and Section 13.2.3, the PM components can be divided into three groups: 1) soil and coarse mass (low scattering efficiency); 2) organic mass and sea salt and associated water (mid scattering efficiency); and 3) ammonium sulfate nitrate and associated water, and EC (high extinction efficiency).

As discussed in Section 2.5 and Section 13.2.4.2, these PM components vary regionally and seasonally, as well as by urban versus rural settings. The ratio of the sum of PM component concentrations to light extinction by season averaged over the years 2011–2013 is presented in Figure 13-17. These values were calculated using the same procedures as in Hand et al. (2012a); Hand et al. (2011) listed in Table 13-3 and Equation 13-7. In general, regardless of season $PM_{2.5}$ b_{ext} is largest in the eastern half of the U.S. including the Northeast, Southeast, and Midwest, and lowest in the Southwest and interior portions of the Western U.S. A relatively high b_{ext} in urban areas, such as in the Northwest, and in those urban centers near the higher elevation rural sites in the Appalachian Mountains, is evident.

The average annual $PM_{2.5}$ extinction efficiency and standard deviation across all sites is 5.1 ± 1.1 m^2/g and a factor of 2.8 between the lowest and highest values. There is some variation in the $PM_{2.5}$ extinction efficiencies seasonally but the overall average and standard deviation across the seasons are similar to the annual values at 5.2 ± 1.3 m^2/g. These values are somewhat higher than reported in the literature and summarized in Table 13-1 possibly because of RH effects.



Source: Permission pending, http://vista.cira.colostate.edu/IMPROVE/

Figure 13-17 The effective $PM_{2.5}$ light extinction efficiency calculated as the ratio of the annual average reconstructed $PM_{2.5}$ b_{ext} and $PM_{2.5}$ concentrations.

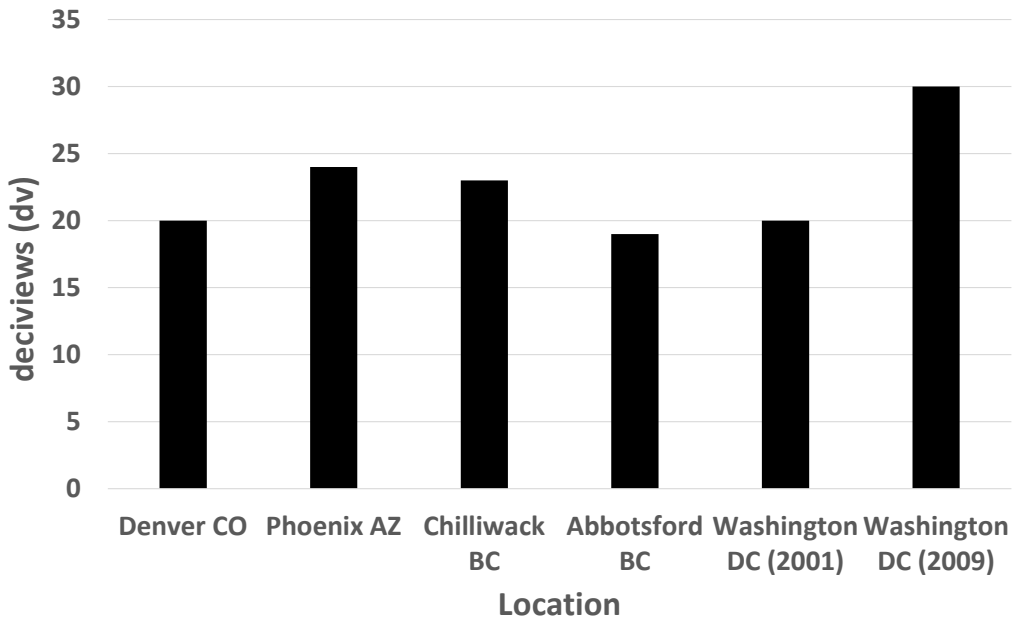
13.2.5 Human Perception of Haze and Landscape Features

The 2009 PM ISA (U.S. EPA, 2009) provided a detailed review of urban visibility preference studies from which haze and acceptability response curves were derived. Results indicated a wide range in the responses for a given deciview (dv) haze index (see Section 13.2.2.1) between urban areas, depending on their setting. Since then, no new visibility preference studies have been conducted in the U.S. Outside of the U.S., a visibility preference study was carried out in Beijing, China (Fajardo et al., 2013), but will not be further discussed because the high $PM_{2.5}$ concentrations in Beijing outside the range typically observed in the U.S.

As reported in the 2009 PM ISA (U.S. EPA, 2009), four North American urban visibility studies were conducted in Phoenix, Arizona (AZ-DEQ, 2003), two cities in British Columbia, Canada (Pryor, 1996), Denver, Colorado (Ely et al., 1991), and Washington, D.C. (Abt, 2001). The studies estimated the visibility preference, or level of visibility impairment judged acceptable, by respondents using a focus-group method with photographs of a single scene. A broad downtown area and hills or mountains making up the scene's backdrop were in each photograph. As described in U.S. EPA (2009), there was a large variance in the mean dv value for a preference of 50%, with 19 dv at Denver and 28 dv at Washington, D.C. The most distant landscape feature varied from 150 km away for the Denver scene to only 8 km away for the Washington, D.C., scene. The closer the landscape features are to the observer,

the more particulate matter, as represented by dv levels, it takes to cause the same level of perceived haziness. The deciview corresponding to 50% preference levels for each location is shown in Figure 13-18.

Figure 13-18 shows that considerably more haze was required to cause the Washington, D.C. scene to be judged unacceptable than the Denver scene. Between Washington, D.C. scene and the Denver scene there was a 9.2 dv difference in the amount of haze required for an unacceptable judgment at the 50% level, corresponding to about 30 μg/m^3 of particulate matter, assuming the particles are not hygroscopic. Consequently, it takes about 250% more particulate mass or b_{ext} to reach an unacceptable level of haze in the Washington, D.C. scene than in the Denver setting. In other scenes, the amount of haze required to be judged unacceptable was in between the amounts in Washington, D.C. and Denver.



Source: Permission pending, adapted from 2009 PM ISA U.S. EPA (2009).

Figure 13-18 Mean deciview (dv) values of 50% acceptability in 5 visibility preference studies (CO, AZ, BC, DC 2001, DC 2009).

These results clearly demonstrate a large range in dv or any transform of b_{ext} at a given level of acceptability, indicating these metrics are not universal indicators of visibility preference levels. For context, the 50% preference deciview range between 19 and 30 dv corresponds to a b_{ext} range of approximately 60 to 180 mM^{-1}, which can be compared to b_{ext} estimates by season and region in Figure 13-9, Figure 13-10, Figure 13-11, Figure 13-12, Figure 13-13, and Figure 13-14 in Section 13.2.4.3. Roughly half of the CSN regions evaluated in Section 13.2.4.3 had at least one monthly average b_{ext} estimate within that range in 2011−2014.

There is little new published information regarding preference levels in the U.S. The single new study by Smith (2013) was an investigation of "framing bias" in preference studies that can potentially occur because preference levels are chosen in part based on experimental variables such as number of photographs shown or range of the range of dv levels participants are shown when asked to state a preference about whether scenes in photographs are acceptable.

13.2.6 Summary and Causality Determination

Overall, visibility in most regions of the U.S. has improved since the 2009 PM ISA, as indicated by lower estimates of $PM_{2.5}$ mass extinction. The greatest improvements have occurred in the eastern half of the U.S., in regions with the poorest visibility. This has likely occurred because of a reduction in SO_2 emissions resulting in lower ammonium sulfate concentrations, because ammonium sulfate has historically accounted for a larger fraction of $PM_{2.5}$ mass than other $PM_{2.5}$ components, and also because ammonium sulfate is more effective than other $PM_{2.5}$ components at scattering light. The resulting decrease in $PM_{2.5}$ in the Eastern U.S. has resulted in better visibility.

Rural visibility impairment is greatest in Eastern U.S. regions, including the Southeast, East Coast, Mid-South, Central Great Plains, and Appalachian regions. In contrast, visibility is better on average in most regions of the Western U.S. Urban visibility is also generally better in the Western U.S. than in the Eastern U.S., with exceptions of urban areas in California and Alaska. In part, this reflects the difference in $PM_{2.5}$ composition between the East and West, with a greater fraction of ammonium sulfate in the Eastern U.S., and particulate organic matter in the Western U.S. The effectiveness of light extinction by $PM_{2.5}$ depends on composition and relative humidity, with low scattering efficiency from $PM_{10-2.5}$, moderate scattering efficiency by organic mass and sea salt, and high extinction efficiency by ammonium sulfate, ammonium nitrate, and light absorbing carbon. However, the difference in extinction between the Eastern U.S. and Western U.S. also reflects considerably higher $PM_{2.5}$ concentrations in the Eastern U.S. and California than in the rest of the Western U.S.

Altogether, new results and observations regarding atmospheric visibility provide evidence atmospheric visibility has improved as PM concentrations have decreased, that regional and seasonal differences in atmospheric visibility parallel regional and seasonal PM concentration patterns, and that regional differences in the relationship between PM and visibility are due to differences in PM

composition characteristics, rather than any factors beyond PM. These results confirm a well-established relationship between PM and visibility summarized in the 2009 PM ISA and earlier assessments. O**verall the evidence is sufficient to conclude that a causal relationship exists between PM and visibility impairment.**

13.3 Effects on Climate

13.3.1 Introduction

The 2009 PM ISA (U.S. EPA, 2009) concluded that there was sufficient evidence to determine a causal relationship between PM and climate effects—specifically on the radiative forcing of the climate system, and including both direct effects of PM on radiative forcing and indirect effects involving cloud processes. This section examines the role of anthropogenic PM in driving global and regional climate change, with a focus on the U.S. PM in the atmosphere significantly influences global and regional climate through interactions with incoming solar radiation and with clouds. For example, certain PM species reflect solar radiation back to space, leading to cooling at the Earth's surface. On the other hand, PM species that absorb solar radiation can heat the atmosphere and change the vertical temperature profile, with consequences for atmospheric stability, cloud formation, and convective rainfall. By providing cloud condensation or ice nuclei, PM can also influence cloud cover and affect the Earth's radiative balance, with additional impacts on the distribution and intensity of precipitation. Finally, because PM is not distributed evenly across the globe, spatial variation in these radiative and hydrologic impacts can also contribute to shifts in atmospheric circulation patterns over a range of space and time scales.

As the abundance of natural or anthropogenic PM changes over time, the effects on climate may be substantial. A key question for the scientific community is to what extent trends in anthropogenic PM have influenced climate through the 20th and early 21st centuries. Global trends in PM have varied by species. For example, U.S. emissions of SO_2, a precursor to sulfate PM, tripled from 1900 to 1980 (Smith et al., 2011), while black carbon (BC) emissions peaked in the early to mid-20th century (Bond et al., 2007). In more recent decades, as regulatory actions have been put in place to improve air quality, U.S. levels of sulfate and other PM species have declined rapidly (Keene et al., 2014; Murphy et al., 2011). The climate impacts of such trends are currently topics of intensive research (Fiore et al., 2015; Mickley et al., 2014; Bond et al., 2013; Boucher, 2013; Myhre, 2013).

Assessing the role of anthropogenic activity in past and future climate change is the mandate of the Intergovernmental Panel on Climate Change (IPCC), an initiative begun in 1988 by the World Meteorological Organization (WMO) and the United Nations Environmental Program. The IPCC supports the work of the Conference of Parties to the United Nations Framework Convention on Climate

Change (UNFCCC). New IPCC reports are issued every 5 to 7 years, and the climate discussion in the 2009 PM ISA (U.S. EPA, 2009) relied heavily on the Fourth IPCC Assessment Report (AR4), published in 2007. The Fifth IPCC Assessment Report (AR5) (IPCC, 2013) reports on the key scientific advances in understanding the climate effects of PM since AR4. This section thus accordingly draws substantially upon AR5 in summarizing these effects.

Section 13.3.2 provides an overview of the physics of climate as well as the metrics used to assess climate change (discussion of the models used to simulate climate, atmospheric chemistry, and the behavior of PM in the atmosphere is provided in Chapter 2). Section 13.3.3 describes the mechanisms of PM's influence on the Earth's energy budget. Sections 13.3.4 and Section 13.3.5 report the estimated radiative forcing for total PM and individual PM components, respectively. Section 13.3.6 describes the climate response to changing PM, including the feedbacks of climate onto PM abundance. Section 13.3.7 provides further details on the climate response to PM trends in specific U.S. regions, especially in the eastern half of the country, and Section 13.3.8 summarizes key uncertainties in gauging the role of PM in driving climate. Section 13.3.9 provides the final summary and causality determination. Note that, in the climate science community, PM is encompassed by what is typically referred to as aerosol (though the definitions do not completely overlap), but this section on the climate effects of PM uses the term PM throughout for consistency with the rest of this ISA. Exceptions to this practice include certain acronyms that are widely used by the climate community that include the term aerosol (e.g., aerosol optical depth, or AOD).

13.3.2 Overview of the Physics of Climate Change and Radiative Forcing

The Earth's climate is driven by energy from the sun. Radiant solar energy enters the atmosphere in a range of wavelengths, peaking strongly in the visible part of the spectrum. Approximately 70% of incoming solar energy is absorbed by the earth-atmosphere system, while the rest is reflected back to space, mainly by clouds and by snow- and ice-covered surfaces (Trenberth et al., 2009).

Atmospheric PM also interacts with incoming solar radiation. Many species of PM (e.g., sulfate and nitrate) are efficient scatterers of solar energy. By enhancing reflection of solar energy back to space, scattering PM exerts a cooling effect on the surface below. Certain species of PM such as BC, brown carbon (BrC), or dust can also absorb incoming sunlight. Whether absorbing PM warms or cools the underlying surface depends on several factors, including the altitude of the PM layer relative to cloud cover and the albedo of the surface (Ban-Weiss et al., 2014). PM also perturbs incoming solar energy by influencing cloud cover and cloud lifetime. For example, PM provides nuclei upon which water vapor condenses, forming cloud droplets. Finally, absorbing PM deposited on snow and ice can diminish surface albedo and lead to regional warming. More detailed information about these complex and sometimes competing effects of PM on climate is provided in Sections 13.3.3 and Section 13.3.4.

About two-thirds of the solar energy absorbed by the earth-atmosphere system is absorbed by the Earth's surface (Stephens et al., 2012; Trenberth et al., 2009). Much of that energy, in turn, is re-emitted at longer, infrared wavelengths, while some absorbed energy is also transformed into latent or sensible heat (Jung et al., 2011). Polyatomic gases such as water vapor, CO_2, methane, and ozone absorb and re-emit the infrared radiation upwelling from the Earth's surface, reducing the total amount of radiant energy that returns to space, keeping the surface and lower atmosphere substantially warmer than they would be in the absence of these gases. This heat trapping also contributes to further warming by increasing the concentration of water vapor, itself a strongly radiatively active gas, in the atmosphere, through increases in evaporation from the Earth's surface. In general, water vapor acts as an amplifier of the climate effects of other greenhouse gases; this process is one of the most important feedbacks in the climate system.

An important concept, used throughout this section, is "radiative forcing." Radiative forcing provides a simple way of characterizing and quantifying the net change in Earth's radiation budget resulting from a perturbation by one or more radiatively active atmospheric constituents, whether greenhouse gases, clouds, or PM species. Alternative definitions of radiative forcing (and related metrics), useful in different contexts, have been developed. The most relevant of these for the purposes of this ISA are defined below.

13.3.2.1 Observed Recent Climate Change: Detection and Attribution

Since the late 19th century, the global mean surface temperature of the Earth has warmed by ~0.85°C (Hartmann, 2013). The first decade of the 21st century represents the warmest decade in the instrumental record (Melillo et al., 2014), and 2016 was the warmest year globally (NOAA NCEI, 2017). Other indicators of climate change include a shrinking Arctic ice cap and a sharp decline in snow cover over North America, an increase in global-mean sea level by ~0.2 m since 1900, consistent with thermal expansion of ocean waters and diminishing glaciers in a warming climate, and an increase in average precipitation over the mid-latitude land areas of the northern hemisphere (Stocker, 2013). Detecting trends in climatological variables such as temperature, and attributing these trends to a given causal factor, such as increases in greenhouse gases or PM, first requires distinguishing them from natural climate system variability, and then evaluating the relative contributions of relevant causal factors to the trends, with appropriate measures of statistical confidence (Bindoff et al., 2013; Hegerl et al., 2010). Sensitivity studies using climate models have shown that the observed global temperature trends can be reproduced only when both natural and anthropogenic emissions of greenhouse gases, PM, and their precursors are taken into account (Jones et al., 2013). The IPCC concluded that, globally, anthropogenic forcings caused more than half of the warming for 1951−2010, with a likely contribution range of 0.6 to 0.7ºC (1.1ºF to 1.3ºF), compared with the observed warming of about 0.65ºC (1.2ºF) (Bindoff et al., 2013).

In general, detecting and attributing climate change—and projecting future change—is more difficult for regional scales compared to globally, for shorter time periods compared to longer ones, and for certain variables (e.g., precipitation) that are particularly "noisy" in space and time. This is because the natural variability over years and decades inherent in the climate system is relatively more important at these scales, compared to the forced signal of climate change, especially for some variables (Northrop and Chandler, 2014; Deser et al., 2012; Hawkins and Sutton, 2009). Nevertheless, it is possible to make some robust detection and attribution statements for North America and/or the U.S. For example, as with the globe as a whole, surface temperatures in the U.S. have also warmed, though with large spatial and temporal variation. Alaska has warmed most rapidly, by ~1.2°C since 1900 (Melillo et al., 2014). The continental U.S. warmed by about 0.9°C over this period, with most of the increase occurring after 1980 (Vose et al., 2012; Lawrimore et al., 2011). Over the time period 1930−1990, however, much of the Southeast experienced a net cooling of ~1°C, a trend that some studies have linked to changes in the concentration of anthropogenic PM (Yu et al., 2014; Leibensperger et al., 2012a, b), though others have suggested that internal climate system variability (Knutson et al., 2013; Meehl et al., 2012) or land-use change (Xu et al., 2015; Goldstein et al., 2009) was responsible. This cooling trend in the Southeast, which will be discussed in greater detail in Section 13.3.7, has since reversed to warming.

In addition to mean temperatures, heatwave frequency across the U.S. has also increased since the 1970s. For example, Meehl et al. (2009) found that the ratio of daily record high maximum temperatures to record low minimum temperatures in the U.S. is approximately two to one, a result confirmed in a more recent study (Meehl et al., 2016). With respect to precipitation, average annual precipitation over the U.S. has increased by roughly 5% since 1900, though with important regional differences (Melillo et al., 2014). Precipitation trends tend to be positive for the eastern and central states, with increases of as much as 10% since 1900 (McRoberts and Nielsen-Gammon, 2011). The western U.S., on the other hand, has recently experienced its most severe drought since the megadrought of 900−1300 A.D., although the connection to global climate change is uncertain (Griffin and Anchukaitis, 2014; Cook et al., 2010). The heaviest rainfall events, by contrast, have become heavier and more frequent across most of the U.S. For example, since 1991, the amount of rain falling in very heavy precipitation events has been significantly above average, with the greatest increases in the Northeast, Midwest, and upper Great Plains (Melillo et al., 2014).

13.3.2.2 Metrics of Climate Change, Including Radiative Forcing

Phenomena that perturb the Earth's energy system are known as climate forcing agents. When comparing the efficacy of one climate forcing agent against another it is useful to devise metrics to make such comparisons more systematically. While surface temperature change would seem to be an obvious choice for such a metric, the temperature response to a climate forcing agent is actually the net result of a cascade of feedback effects, both positive and negative, that can either amplify or diminish the initial temperature response to a given forcing (Myhre, 2013). The strengths of such feedbacks are not always

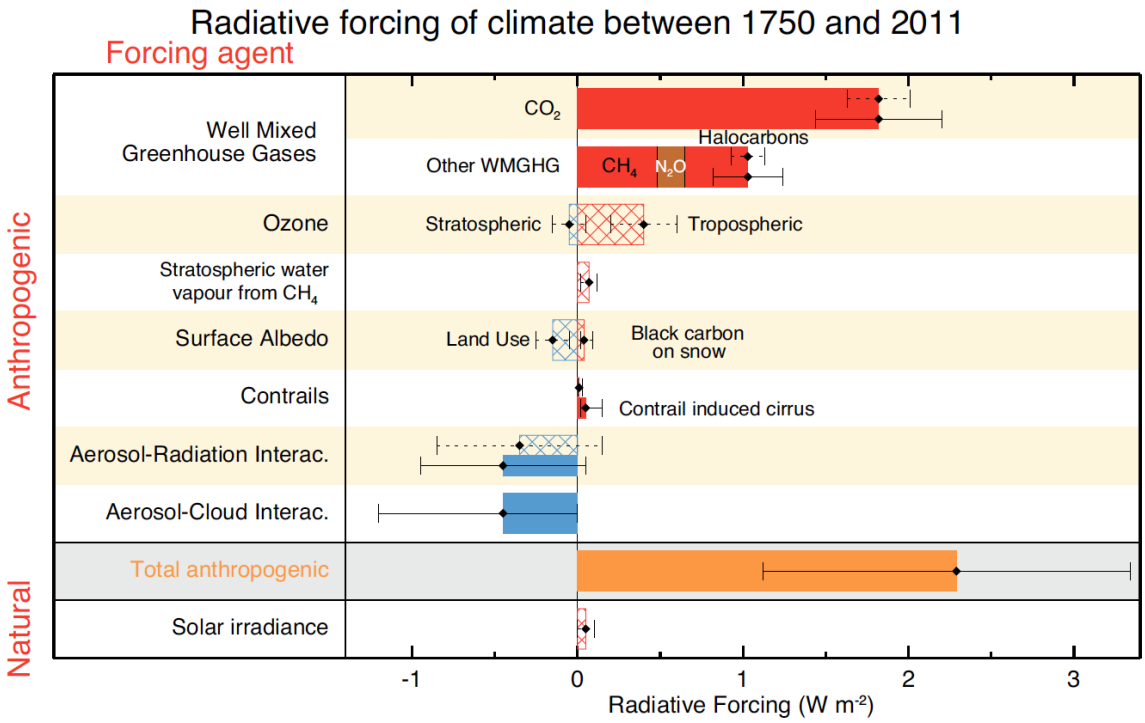
well constrained, making it challenging to use surface temperature as a metric of climate forcing agent efficacy, even with the use of climate models.

Four alternative metrics of climate change are identified below: radiative forcing (RF), effective radiative forcing (ERF), global warming potential (GWP), and global temperature potential (GTP). All four metrics are typically calculated with models; RF can also be estimated using a combination of models and satellite data. Of these metrics, RF and ERF provide the most direct descriptions of the radiative effects of PM in the climate system, and are therefore described in the most detail below (and will be focused on throughout the rest of this document). The definitions in this section draw heavily upon, and have been adapted from Myhre (2013) and Fiore et al. (2015).

Radiative forcing (RF) for a given atmospheric constituent is defined as the perturbation in net radiative flux, at the tropopause (or the top of the atmosphere), caused by that constituent, in Wm^{-2}, after allowing for temperatures in the stratosphere to adjust to the perturbation but holding all other climate responses constant, including surface and tropospheric temperatures (Fiore et al., 2015; Myhre, 2013). A positive forcing indicates net energy trapped in the Earth system and suggests warming of the Earth's surface, whereas a negative forcing indicates net loss of energy and suggests cooling. RF is typically classified according to wavelength, either shortwave (solar) or longwave (terrestrial). For PM, surface RF is also commonly reported, since haze events can significantly attenuate incoming solar energy, causing local "dimming."

For IPCC AR5, a new definition of RF was advocated, known as effective radiative forcing (ERF) (Myhre, 2013). ERF takes into account not just the instantaneous forcing but also a set of climate feedbacks, involving atmospheric temperature, cloud cover, and water vapor, that occur naturally in response to the initial radiative perturbation. These variables are allowed to adjust in the calculation of ERF. Climate system adjustments over longer timescales, e.g., involving sea surface temperatures and sea ice cover, are held constant in the calculation of ERF. An advantage of ERF for assessing the radiative forcing of PM is that, since it includes these rapid adjustments, the equilibrium change in global mean surface temperature scales more closely with ERF than with RF, making it more useful for analysis of the climate impacts of PM (Fiore et al., 2015; Myhre, 2013). A limitation of ERF is that quantifying it precisely depends on a robust understanding of all of the fast climate feedback processes. The response of clouds in particular to changing climate is, however, highly uncertain (Zhao et al., 2016; Soden and Vecchi, 2011), as will be discussed in more detail below.

The global mean values of RF and ERF are important indicators of the climate response to a given perturbation. Figure 13-19 shows the IPCC AR5 estimates of RF and ERF over the 1750−2011 timeframe for a range of anthropogenic climate forcers. For PM and other short-lived species, however, the temporal and spatial variation in such forcings can vary by orders of magnitude. For example, for a severe pollution event over the North China Plain in 2013, Che et al. (2014) reported large RFs from PM of as much as -60 Wm^{-2} at top of atmosphere (TOA) and $+200$ Wm^{-2} at the surface over several days (in comparison, for example, with the long-term, globally averaged values shown in Figure 13-19).



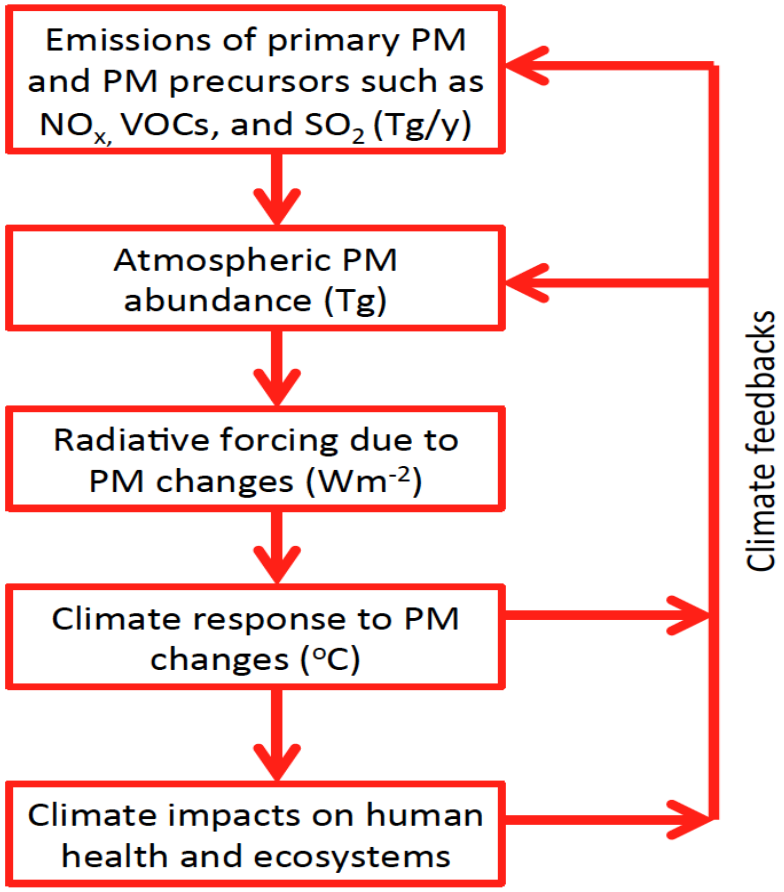
Note: Radiative forcings (RFs) are shown as hatched bars and effective radiative forcings (ERFs) are shown as solid bars. Uncertainties (5% to 95% confidence range) are indicated by dotted lines for RF and solid lines for ERF. Positive forcings denote warming of the Earth's surface, whereas negative forcings denote cooling. WMGHG refers to the well-mixed greenhouse gases, and aerosols refers to PM. The abbreviation "interac." means "interactions."

Source: Permission pending, Myhre (2013).

Figure 13-19 Global mean radiative forcing from anthropogenic activities from 1750 to 2011.

Two other metrics, GWP and GTP, are also sometimes used. Briefly, GWP is used to compare the climate impacts of a given atmospheric constituent to those of CO_2, taking into account not just the warming (or cooling) effects but also the constituent's atmospheric lifetime. GWP is defined as the integral over a specified time horizon (generally 20, 50, or 100 years) of the global mean RF arising from an emission pulse of a given constituent, normalized by the corresponding integral for an emission pulse of the same mass in CO_2 (Fiore et al., 2015; Myhre, 2013). GTP similarly assesses the effect of a climate forcing agent on surface temperature at a specific time horizon, but based on the surface temperature at the final timestep rather than as an integral. Both GWP and GTP have methodological or computational issues that make them less useful than RF or ERF for estimating the radiative impacts of PM.

The IPCC currently promotes the use of ERF over RF (Myhre, 2013), but not all published papers report ERF. The remainder of this section will therefore focus on RF and, when available, ERF of atmospheric particles. Figure 13-20 diagrams the links between PM sources, atmospheric abundance, radiative forcing, and the resulting climate response. Also illustrated in the figure are feedbacks between PM effects on climate and the ecosystem and PM sources and abundance. The nonuniform spatial and temporal distribution of PM and its constituent species compared to well-mixed greenhouse gases presents significant challenges for designing metrics able to capture the full range of global and regional climate forcing effects of PM. Some research on regional metrics [e.g., (Aamaas et al., 2016; Shindell, 2012)] and responses to regional forcings (Shindell et al., 2012; Shindell and Faluvegi, 2009) has been conducted to date, and additional research is currently ongoing.



Note: This figure depicts the relationships between PM sources, PM abundance, radiative forcing, climate response, and climate impacts. Units shown are those typical for each quantity illustrated. VOCs stands for volatile organic compounds. Feedbacks from both the climate response and climate impacts on ecosystems can affect both the emissions of PM sources and PM atmospheric abundance through multiple mechanisms.

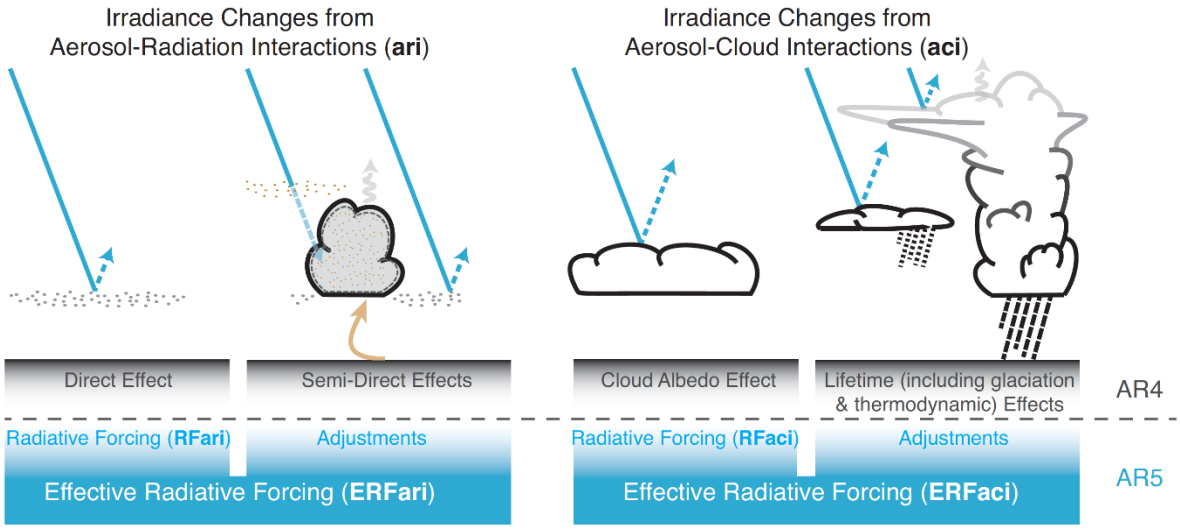
Figure 13-20 Schematic illustrating the effects of PM on climate.

13.3.3 Effects of PM on Radiative Forcing: Mechanisms

As introduced at the beginning of Section 13.3, PM radiative forcing, both through direct interactions with incoming solar radiation, and through interactions with clouds, affects surface and atmospheric temperatures, with subsequent impacts on precipitation and circulation patterns. This section describes the main mechanisms of PM impact on radiative forcing, including the influence of particle size on these mechanisms. The next two sections summarize quantitative estimates of PM radiative forcing globally for total PM, and by individual PM species, respectively. Later sections discuss the global and regional climate impacts of this PM radiative forcing, climate feedback mechanisms involving PM, and key sources of uncertainty in assessing these radiative and climate effects.

13.3.3.1 Interactions of PM with Radiation

Atmospheric PM interacts with solar radiation through scattering and absorption. These "aerosol-radiation interactions" (ARI) are also known as the "direct effects" of PM on climate, as opposed to the "indirect effects" that involve PM interactions with clouds (Section 13.3.2.2). The IPCC AR5 devised the acronym RFari to refer to radiative forcing due to ARI (Boucher, 2013). The fate of solar energy intercepted by PM, and thus the magnitude and sign of RFari, depends on the optical properties of the particles. Highly reflective PM such as sulfate scatter the incoming solar energy, with much of that energy returning to space. Highly absorbing PM such as BC convert solar energy to heat. A metric known as the single scattering albedo represents the ratio of the scattering cross section to the sum of scattering and absorbing cross sections for a given PM type and wavelength. The single scattering albedo for sulfate approaches 1.0. The water content and size distribution of PM can significantly also affect the scattering efficacy of PM. Figure 13-21 depicts the mechanisms of RFari, as well as the effective radiative forcing due to ARI (ERFari), which includes the fast meteorological responses to RFari (as described in Section 13.3.2.2 above).



Note: The blue arrows represent solar radiation, the gray arrows represent cloud longwave radiation, and the brown arrow symbolizes the coupling between the surface and the cloud layer that occur on rapid timescales. The left-hand panel depicts aerosol-radiation interactions (ari) and associated forcings: radiative forcing (RFari) for the direct effect and effective radiative forcing (ERFari) for the direct effect plus rapid meteorological adjustments. The right-hand panel shows aerosol-cloud interactions (aci) and associated forcings: radiative forcing (RFaci) for the cloud albedo effect and (ERFaci) for the cloud albedo effect plus rapid meteorological adjustments. Also shown are the equivalent terms for these effects and adjustments in IPCC AR4. See text for further details.

Source: Permission pending, Boucher (2013).

Figure 13-21 Schematic of mechanisms by which PM affects climate and the terminology used in the Intergovernmental Panel on Climate Change (IPCC) Fifth Assessment Report (AR5) to categorize PM radiative forcings.

Reflective PM, by sending a fraction of solar energy back to space, has an overall cooling effect on global climate. In contrast, absorbing PM has an overall warming effect on global climate, and the in situ warmth generated by solar absorption can be transported elsewhere in the atmosphere. Regardless of species type, PM generally cools the underlying surface through attenuation of solar radiation. Absorbing PM can also have complex and sometimes competing effects on regional hydrological cycles, with consequences for the Earth's energy budget. For example, in their model study, Koch and Del Genio (2010) found that BC particles embedded within clouds warm the local atmosphere and reduce cloud cover, while those located above clouds stabilize the atmosphere, enhancing stratocumulus clouds (semidirect effects). When all these effects are considered together, PM has a net cooling effect on global climate (Fiore et al., 2015; Myhre, 2013), as will be discussed in more detail below.

13.3.3.2 Interactions of PM with Clouds

By providing cloud condensation nuclei, PM increases cloud droplet number and thus cloud droplet surface area and albedo (Twomey, 1977). The climate effects of these perturbations are difficult to quantify but likely enhance the cooling influence of clouds by increasing cloud reflectivity (traditionally called the first indirect effect) and lengthening cloud lifetime (the second indirect effect). Such effects can be difficult to distinguish in the observational record, in part because they likely feed back onto one another (Rosenfeld et al., 2014). The IPCC AR5 defines the first indirect effect as "radiative forcing due to aerosol-cloud interactions" (RFaci), and includes the second indirect effect within "effective radiative forcing due to aerosol-cloud interactions" (ERFaci), which accounts for rapid adjustments in temperature, precipitation, and cloud lifetime. Figure 13-21 depicts the mechanisms of RFaci and ERFaci (Boucher, 2013).

Quantifying RFaci is challenging because it includes the impacts of a complex suite of meteorological and chemical variables (e.g., relative humidity, cloud updraft velocity, and mixing state) on microphysical cloud processes, most of which are not well captured in coarse-grid climate models (Ban-Weiss et al., 2014). Another difficulty involves establishing a baseline for RFaci in the natural atmosphere. For example, Schmidt et al. (2012) showed that the effect of volcanic PM on cloud albedo results in a -1.0 Wm^{-2} cooling in a pristine environment, but only half that value is achieved in the polluted present-day environment, when more PM are competing for the available water vapor. Still more complex to quantify is ERFaci, which includes the fast meteorological feedbacks to the interactions of PM with clouds. These uncertainties associated with aerosol-cloud interactions and feedbacks (discussed throughout the rest of this chapter section) present to the most significant obstacle to more precisely quantifying the effects of PM on climate.

13.3.3.3 Effects of Absorbing PM on Snow and Ice Albedo

Regions of high albedo, such as snow- and ice-covered surfaces, strongly reflect incoming solar radiation. The transport and subsequent deposition of absorbing PM such as BC to snow- and ice-covered regions can decrease the local surface albedo, leading to surface heating. The absorbed energy, in turn, can melt the snow and ice cover and further depress the albedo, resulting in a positive feedback loop (Bond et al., 2013; U.S. EPA, 2012). This feedback has been invoked to partly explain the rapid increase in temperatures over the Arctic relative to the increase over mid-latitudes [e.g., (Shindell and Faluvegi, 2009)]. BC deposition may also affect surface temperatures over glacial regions. For example, ice core records from the Tibetan plateau indicate at least a doubling in the deposition rates of absorbing species since preindustrial times, with the potential to contribute to increased future melting of the Tibetan glacier (Wang et al., 2015). Recent observations have also shown that dust particle deposition on mountain snowpack strongly controls snowmelt-driven runoff in the Upper Colorado River Basin (Painter et al., 2018).

13.3.3.4 Effect of Particle Size on the Interactions of PM with Climate

The size of particles influences how they interact with climate. Particles with diameters in the size range of 0.1−1.0 μm efficiently scatter solar radiation because they are within the same size range as the wavelength of solar energy. Thus $PM_{2.5}$, with diameter less than 2.5 μm, is more scattering and leads to greater surface cooling than the larger size fraction of $PM_{10–2.5}$. Most anthropogenic particles (e.g., sulfate and nitrate) fall within the $PM_{2.5}$ classification. Freshly emitted BC, BrC, and dust tend to be larger in size, though the smaller particles of these species have a disproportionately large radiative impact despite the total mass being dominated by the coarse mode (Boucher, 2013). Large particles have a relatively short lifetime and deposit quickly, leaving finer particles to travel further distances and extend their climate impact over a broader region. Large BC particles, however, can coagulate and then collapse into more compact and longer-lived structures (Raes et al., 2000). When exposed to high relative humidity, PM can take up water, deliquesce, and increase in size. As they age and acquire more hydrophilic coatings, even hydrophobic particles such as BC or dust can swell with water. Deliquesced particles tend to scatter more light than solid particles (Freney et al., 2010).

With regard to interactions of PM with clouds, laboratory experiments and model results show that particles with diameters in the range of 0.1−1.0 μm serve as efficient cloud condensation nuclei (Zhang et al., 2002). Thus $PM_{2.5}$ is a key contributor to such interactions. While UFP have traditionally been considered too small to influence cloud formation, they can rapidly grow into the size range required for cloud droplet activation, and so also play an important role in influencing cloud cover (Lee and Adams, 2012). In addition, there is now some evidence that UFP can themselves increase cloud condensation within tropical deep convective cloud systems (Fan et al., 2018). Coarse particles ($PM_{10–2.5}$), on the other hand, make a relatively small contribution to the number concentrations of cloud condensation nuclei, in part because key microphysical processes may occur over longer timescales than the typical residence time of such particles, and in part because $PM_{10–2.5}$ is less abundant (Raes et al., 2000). Mineral dust PM is a particularly important source of ice nuclei (IN) in cold clouds (Atkinson et al., 2013). Models attempting to capture the effects of PM on cloud cover and cloud lifetime often rely on cloud microphysical schemes with size-resolved particles (Pierce and Adams, 2007).

13.3.4 Estimates of Radiative Forcing from Total PM

This section discusses estimates of the forcing due to the sum of all PM species, including trends since the preindustrial era and since 1980. Table 13-4 summarizes this information.

Table 13-4 Estimates of global mean radiative forcings due to anthropogenic PM.

Reference	Forcing Agent and/or Time Period	Radiative Forcing RF, Wm^{-2}	Effective Radiative Forcing ERF, Wm^{-2}	Data Type
Forcing due to interactions between PM and radiation.				
Bellouin et al. (2011)	Anthropogenic PM	−0.65 Wm^{-2}		Satellite data
Quaas et al. (2008)	Anthropogenic PM	−0.9 ± 0.4Wm^{-2}		Satellite data and models
Koch et al. (2011)	1900−2000	−0.41 Wm^{-2}		GISS ModelE
Myhre et al. (2013)	1850−2000 or 2006 (all models); 1750−2000 (adjusted)	−0.27 (−0.58 to −0.02) Wm^{-2} (all models); −0.35 Wm^{-2} (adjusted)		AeroCom model ensemble
Shindell et al. (2013)	1850−2000	−0.26 (−0.49 to −0.06) Wm^{-2} (all models); −0.42 (−0.50 to −0.33) Wm^{-2} (filtered)		ACCMIP model ensemble
Boucher (2013)	1750−2000	−0.35 ± 0.5 Wm^{-2}	−0.45 ± 0.5 Wm^{-2}	IPCC AR5 best estimate
Forcing due to interactions of PM with clouds				
Quaas et al. (2009)	Anthropogenic PM	−0.7 ± 0.5 Wm^{-2}		Satellite data plus AeroCom
Boucher (2013)	1750−2000		−1.2 to 0 Wm^{-2}	90% confidence range across models.
Total forcing from interactions of PM with both clouds and radiation[a]				
Murphy et al. (2009)	1970−2000		−1.1 ±0.4 Wm^{-2}	Analysis of Earth's energy balance
Wang et al. (2011a)	Anthropogenic PM		−1.05 Wm^{-2}	Multiscale set of models
Shindell et al. (2013)	1850−2000 or 1850−2006		−1.17 (−0.71 to −1.44) Wm^{-2}	ACCMIP model ensemble

Table 13-4 (Continued): Estimates of global mean radiative forcings due to anthropogenic PM.

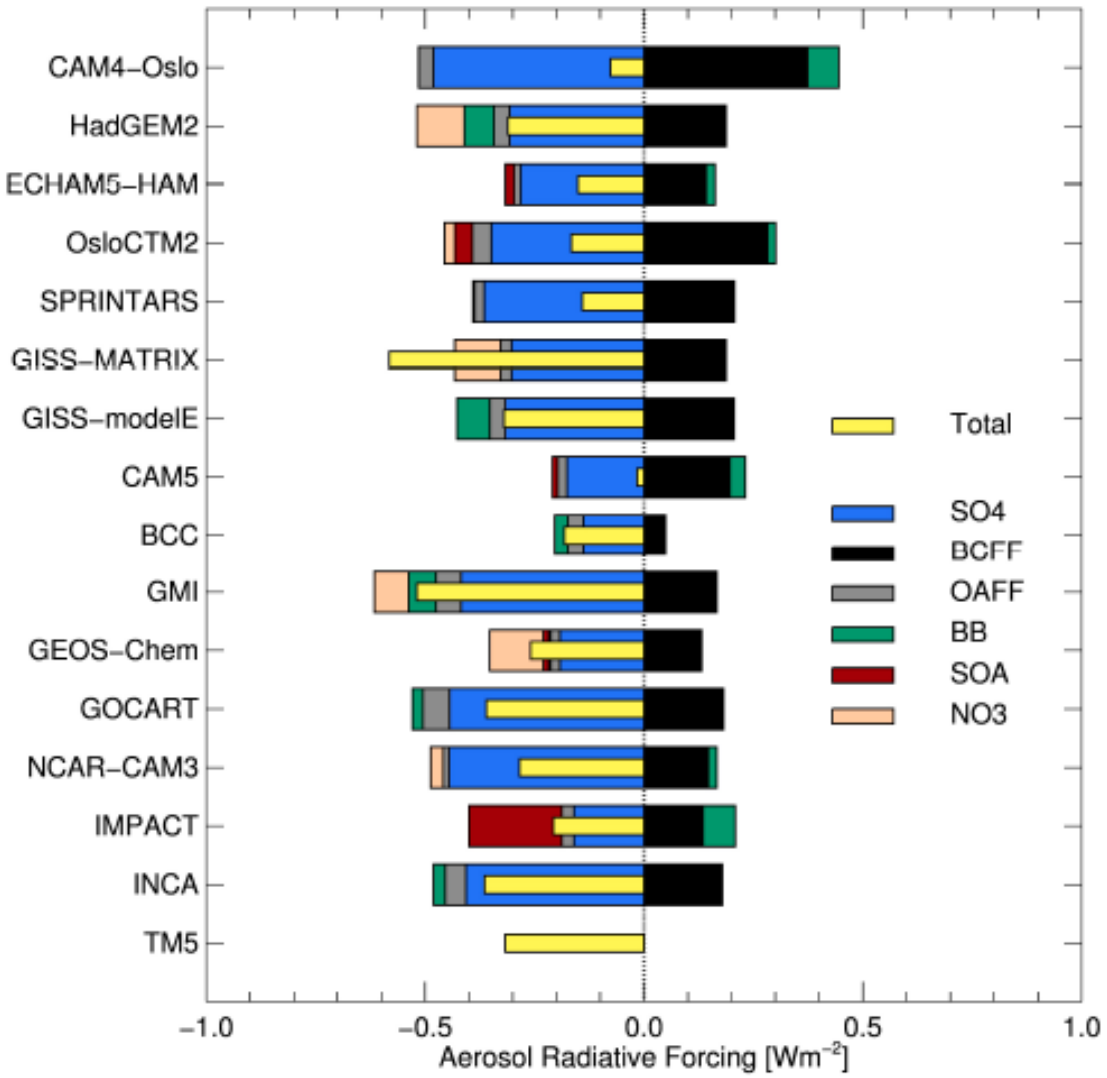
Reference	Forcing Agent and/or Time Period	Radiative Forcing RF, Wm^{-2}	Effective Radiative Forcing ERF, Wm^{-2}	Data Type
Boucher (2013)	1750–2000		−0.9 (−1.9 to 0.1) Wm^{-2}	IPCC AR5 best estimate[a]
Forcing due to the effects of absorbing PM on surface albedo				
Flanner et al. (2007)	Fossil fuel and biofuel BC on snow	+0.043 Wm^{-2}		Snow, Ice, and Aerosol Radiative (SNICAR) model
Skeie et al. (2011)	Anthropogenic BC on snow	+0.016 Wm^{-2}		Oslo chemical transport model
Bond et al. (2013)	Anthropogenic BC on snow	+0.034 (+0.007 to +0.074) Wm^{-2}		Best estimate across many model studies
Bond et al. (2013)	Anthropogenic BC on sea ice	+0.010 (+0.006 to +0.015) Wm^{-2}		Best estimate across many model studies
Lee et al. (2013)	1850–2000	+0.014 to +0.019 Wm^{-2}		ACCMIP model ensemble
Boucher (2013)	1750–2000	+0.04 (+0.02 to +0.09) Wm^{-2}		IPCC AR5 best estimate

[a]Excludes the effects of absorbing PM on surface albedo.

13.3.4.1 Forcing Due to Interactions of PM with Radiation

Historically, reflective PM have dominated absorbing PM in terms of forcing, leading to net global cooling and a negative RFari since the preindustrial era (Allen et al., 2013; Myhre, 2013). Koch et al. (2011) calculated a global mean value of −0.41 Wm^{-2} for the change in anthropogenic PM since 1900, while the AeroCom international model intercomparison study reports a value of −0.27 Wm^{-2} for the change since 1850, with values ranging from −0.58 to −0.02 Wm^{-2} across the ensemble of models considered (Myhre et al., 2013). Figure 13-22 shows the range of model estimates for total forcing and for individual species in the AeroCom ensemble. The large uncertainty in the AeroCom RFari arises in part from the neglect in some models of nitrate particles and SOA. Those models that do include SOA demonstrate a large range of forcing values for this particle type, and the range of positive forcings from fossil fuel BC is also large (Myhre et al., 2013). Adjustment of the AeroCom average to extend the time

horizon and to take into account species missing from some models yields a mean RFari of −0.35 Wm^{-2} over the period since 1750 (Myhre et al., 2013).

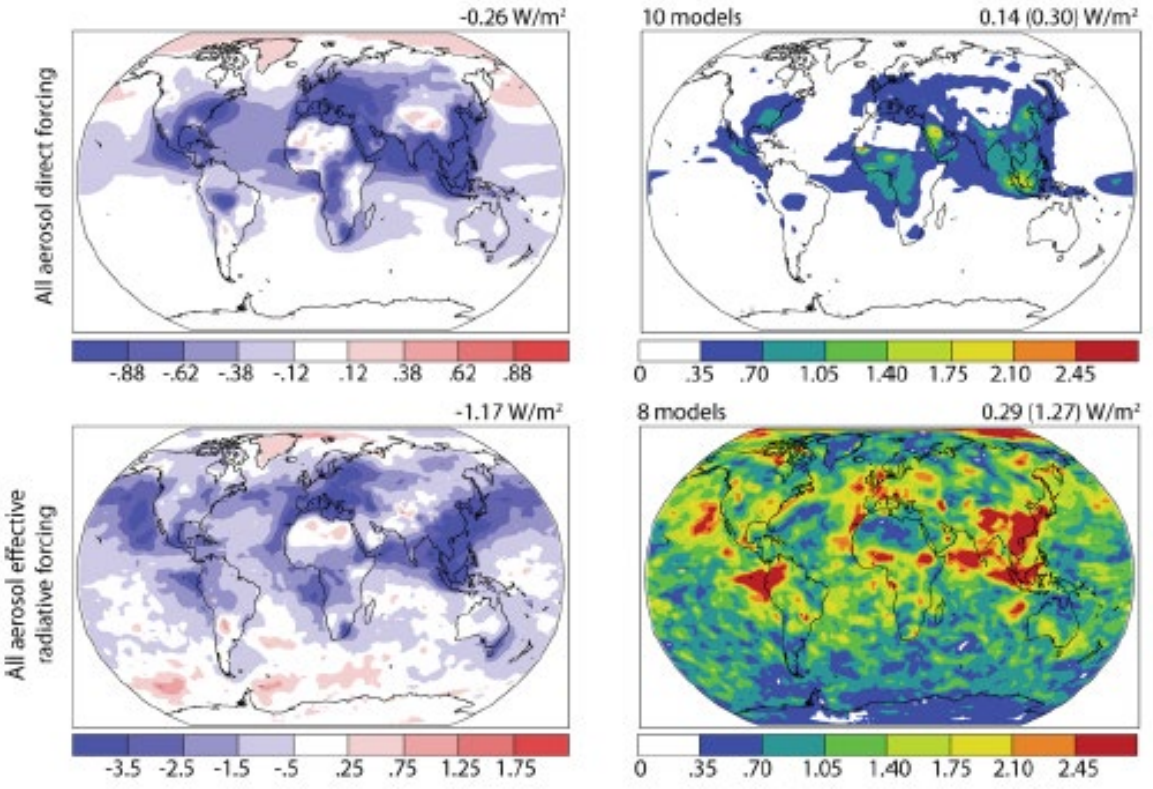


Note: The time period of the forcing is 1850 to 2000 or 2006, depending on the model, and the six components are sulfate (SO_4, blue), BC from fossil fuel (BCFF, black), organic particles from fossil fuel (OAFF, grey), biomass burning particles (BB, green), secondary organic particles (SOA, red), and nitrate (NO_3, brown).

Source: Permission pending, Myhre et al. (2013).

Figure 13-22 Radiative forcing from PM interactions with radiation (RFari) from six PM components in the AeroCom ensemble of models, overlain with total RFari for each model (yellow).

The ACCMIP model ensemble similarly shows a range of estimates for RFari, −0.26 (−0.06 Wm^{-2} to −0.49) Wm^{-2} (Shindell et al., 2013). Figure 13-23 shows the spatial distribution of the mean and standard deviation of RFari across the ACCMIP models. In general, RFari is greatest over regions of industrial activity—the eastern U.S., Europe, and Asia. As in the AeroCom study, the distribution of standard deviation in Figure 13-23 reveals the large disagreements among models in forcing magnitude.



Note: The top panels show the multimodel mean (left) and standard deviation (right) of forcing due to interactions of particles with radiation (RFari), also known as "direct forcing." The bottom panels show the multimodel mean (left) and standard deviation (right) of total effective radiative forcing due to interactions of PM with both radiation and clouds (ERFari+aci). ERF includes fast feedbacks involving clouds, atmospheric temperature, water vapor, and land albedo. Note the difference in color bars for RFari and ERFari+aci.

Source: Permission pending, Shindell et al. (2013).

Figure 13-23 Spatial distributions of radiative forcing due to changing PM from 1850 to 2000 in the Atmospheric Chemistry and Climate Model Intercomparison Project (ACCMIP) model ensemble.

Until recently satellite studies yielded more negative RFari forcings than did models, especially over land, for reasons that were not clear. For example, using remotely sensed data from the Moderate Resolution Imaging Spectroradiometer (MODIS), Bellouin et al. (2008) estimated a present-day RFari

from anthropogenic PM of −0.65 Wm^{-2}. Quaas et al. (2008) combined satellite data with model simulations to determine an even more negative RFari of −0.9 Wm^{-2}. This discrepancy was largely reconciled in Myhre (2009) by accounting for both direct radiative forcing missing from satellite retrievals and differences in aerosol optical properties between preindustrial and the present-day, bringing both the satellite- and model-based methods into agreement at the less negative values of RFari characteristic of model-based approaches.

Therefore, taking into account both model simulations and satellite observations, the IPCC AR5 reports an RFari from anthropogenic PM of −0.35 ± 0.5 Wm^{-2} (Boucher, 2013), which is slightly reduced in magnitude compared to AR4. Estimates of ERFari, which include the rapid feedback effects of temperature and cloud cover, rely mainly on model simulations, as this forcing is complex and difficult to observe. The IPCC AR5 best estimate for ERFari, −0.45 ± 0.5 Wm^{-2}, reflects this uncertainty (Boucher, 2013). Recall Figure 13-19, which shows the IPCC AR5 estimates of RFari and ERFari over the 1750−2011 timeframe, compared with other anthropogenic forcings.

13.3.4.2 Forcing Due to Interactions of PM with Clouds

Using data from a suite of satellite observations together with the AeroCom ensemble of models, Quaas et al. (2009) estimated RFaci at −0.7 ± 0.5 Wm, while climate models contributing to the IPCC AR5 yield a median value of −1.4 Wm^{-2} for anthropogenic RFaci (Boucher, 2013). ERFaci is difficult to quantify since it requires distinguishing between the feedbacks arising from interactions of PM with clouds and those arising from PM interactions with radiation. IPCC AR5 estimates ERFaci at −0.45 Wm^{-2}, with a 90% confidence interval of −1.2 to 0 Wm^{-2}.

13.3.4.3 Total Radiative Forcing Due to Interactions of PM with Clouds and Radiation

Using a cloud-resolving model embedded in a global climate model, Wang et al. (2011a) calculated an ERFaci+ari of −1.05 Wm^{-2}. Murphy et al. (2009) analyzed the Earth's energy balance and derived a similar value, −1.1 Wm^{-2}, while the ACCMIP ensemble of models yields an ERFari+aci of −1.17 (−1.44 to −0.71) Wm^{-2} (Shindell et al., 2013). Broadly consistent with these estimates, the IPCC AR5 reports a best estimate of ERFaci+ari of −0.90 (−1.9 to −0.1) Wm^{-2} (Boucher, 2013). As shown in Figure 13-19, which compares the IPCC AR5 estimates of ERFari and ERFaci over the 1750−2011 timeframe with other anthropogenic forcings, most of the uncertainty in total anthropogenic forcing since 1750 arises from uncertainties in the PM forcings. Figure 13-23 (bottom panels) shows the spatial distribution of ERFari+aci, with large forcings extending over oceans, where PM can strongly influence marine cloud cover downwind of source regions (Shindell et al., 2013).

13.3.4.4 Forcing Due to the Effects of Absorbing PM on Albedo

Recent estimates of the global mean RF from anthropogenic PM deposited on highly reflective surfaces such as snow and ice range from +0.01 to +0.04 Wm^{-2} (Bond et al., 2013; Lee et al., 2013; Skeie et al., 2011; Flanner et al., 2007). The IPCC AR5 reports a best estimate of RF from the albedo effect at the high end of this range, +0.04 Wm^{-2}, with an uncertainty range of +0.02 to +0.09 Wm^{-2} (Boucher, 2013). Table 13-1 contains a summary of these results, and Figure 13-23 (bottom right) shows the spatial distribution of this forcing from ACCMIP. As with other forcings, the uncertainty stems in part from uncertainties in emissions and in transport processes, including wet deposition (Doherty et al., 2010). The forcing is largest during March-May over the Arctic and boreal regions due to efficient winter-spring transport of pollution from Eurasia (Flanner et al., 2007).

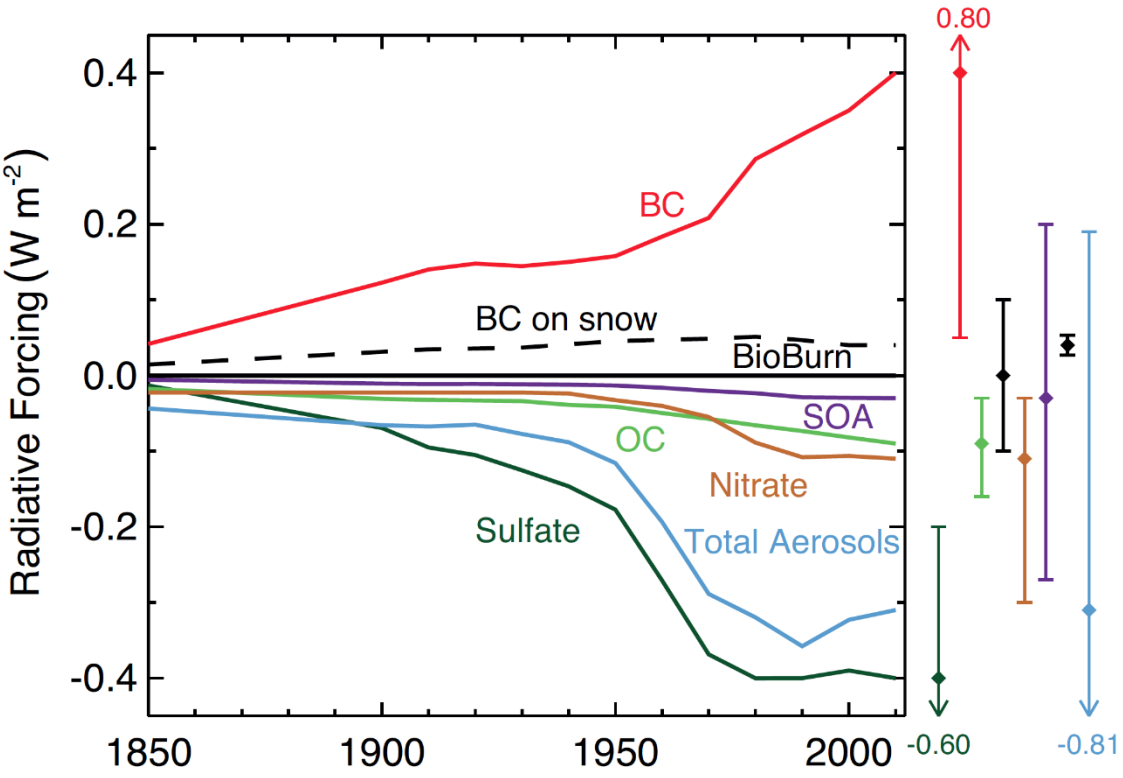
13.3.4.5 Recent Trends in PM Forcing

In response to air quality concerns, most developed countries have made significant cuts to emissions of PM or their precursors in recent decades, and this trend is revealed in the time series of forcing estimates for the 20th century. For example, in the ACCMIP ensemble of models, trends in global mean RFari for all PM species show maximum cooling around 1980, but with a large uncertainty range, from about −0.1 to −0.5 Wm^{-2} (Shindell et al., 2013). Smith and Bond (2014) estimate that the largest total impact of absorbing and scattering aerosols on climate occurred between 1950 and 1970, with a change in total aerosol forcing over this period ranging from −0.2 to −0.8 W m^{-2}. Major sources of uncertainty in these types of estimates of trends in aerosol radiative forcing include uncertainties in the temporal changes in emissions and in the mix of scattering versus absorbing aerosols (Xing et al., 2015; Smith and Bond, 2014).

Figure 13-24 shows the time evolution of RFari for a range of species from 1850 to 2010. In Figure 13-25 (top), the spatial distribution of the 1980−2000 forcing trend from the sum of all species reveals large heterogeneity. RFari is positive over North America and Europe due to declining sulfate loading in the time period. In contrast, RFari increases significantly over India and southeast Asia, where rising concentrations of reflective sulfate outpace those of the more absorbing BC. Over China, however, the increases in sulfate and BC loadings are more balanced, leading to an RFari close to zero for this time period. The positive RFari over Africa can be traced to increases in biomass burning and the subsequent rise in BC (Figure 13-25, bottom).

The forcings depicted in Figure 13-24 and Figure 13-25 are all TOA forcings. At the TOA, the effects of absorbing and scattering particles can cancel each other out, while at the surface, the effects of both types of particles combine to yield net cooling. For example, while China shows no TOA forcing over the 1980−2000 in Figure 13-25, another study suggests that increases in BC and sulfate particles

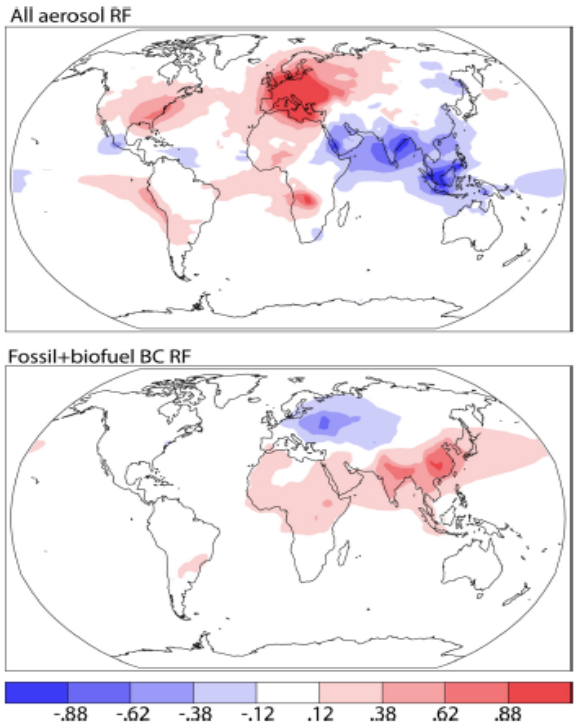
over this region have led to a cooling trend of -6 ± 2 Wm^{-2} per decade over the 1950–2000 time frame (Folini and Wild, 2015).



Note: The curves show the multimodel results for 1850, 1930, 1980, and 2000 from the ACCMIP ensemble for RFARI (Shindell et al., 2013) and the BC-albedo effect (Lee et al., 2013), combined with higher temporal-resolution results from two models in the ensemble. The blue curve represents the sum of all forcings shown. The 5% to 95% uncertainty ranges for 2010 are shown with vertical lines to the right of the graph. Values next to the uncertainty lines are for cases in which uncertainties go beyond the scale. All values have been scaled to the best estimates for 1750–2011 RFARI. SOA is for secondary organic particles, and "bioburn" represents the sum of RFARI of BC and primary organic particles from biomass burning. Estimates of forcings from mineral dust are not shown.

Source: Permission pending, Myhre (2013).

Figure 13-24 Time evolution of radiative forcing due to interactions of PM with radiation (RFARI) and the effects of black carbon (BC) on snow and ice albedo.



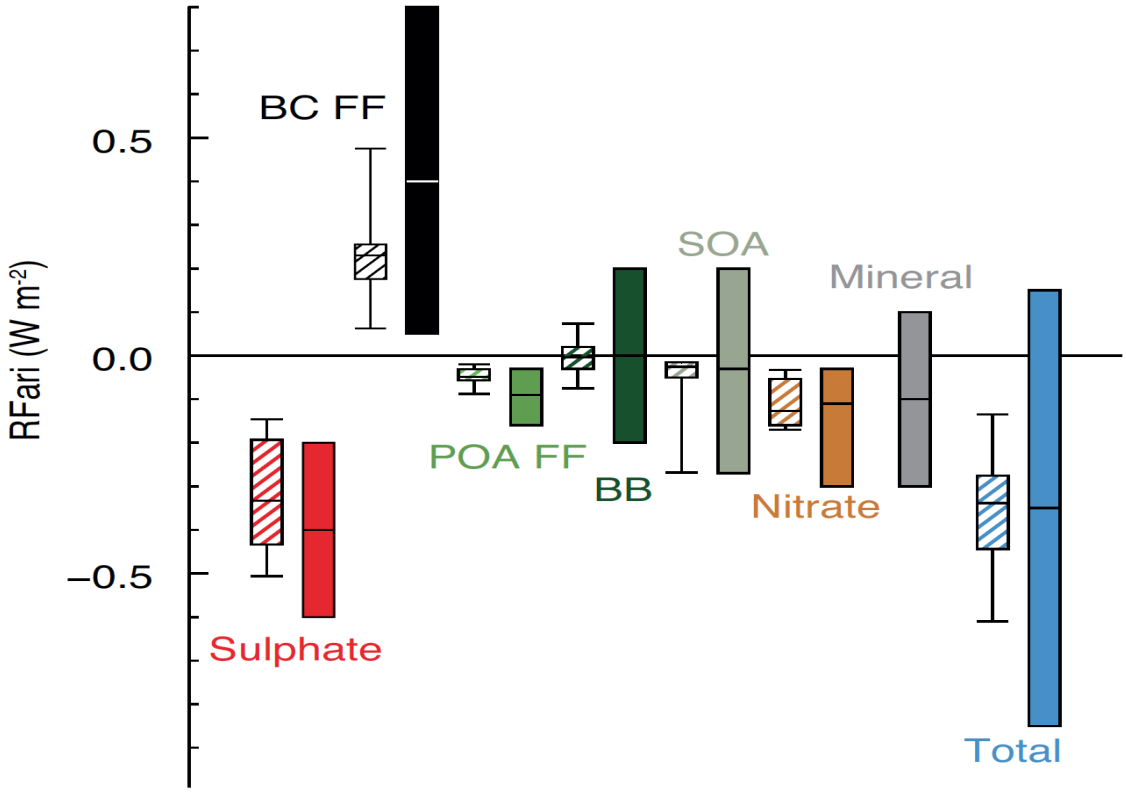
Note: The top panel shows RFari for all PM species, and the bottom panel shows RF for BC from fossil fuel and biofuel. Results are shown for only those ACCMIP models that provided results for 1980. Units are Wm^{-2}.

Source: Permission pending, Shindell et al. (2013).

Figure 13-25 Mean radiative forcings due to interactions of PM with radiation (RFARI) from a subset of the Atmospheric Chemistry and Climate Model Intercomparison Project (ACCMIP) models for the 1980 to 2000 time period.

13.3.5 Effects of PM on Climate by Species

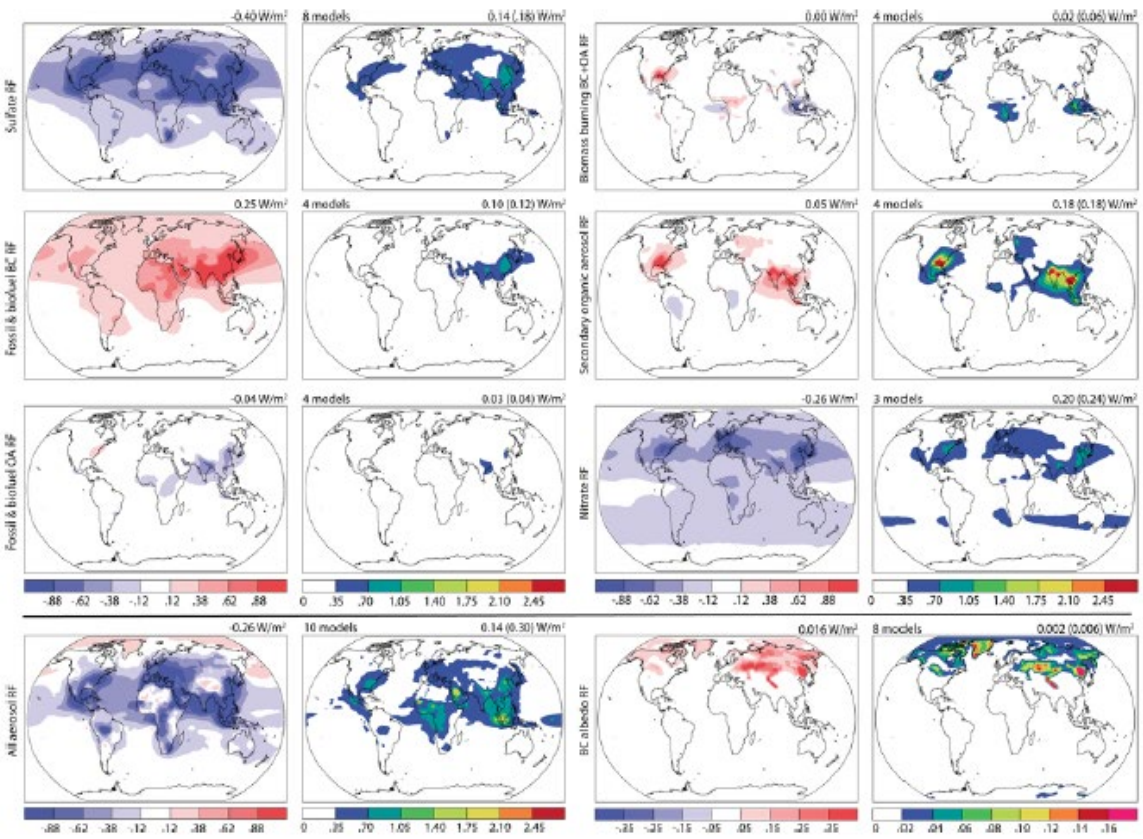
This section describes the individual climate effects associated with the following key PM species: sulfate, nitrate, OC, BC, and dust, to the extent that quantitative estimates of the radiative forcing associated with these individual species are available in the literature. Figure 13-26 shows the AeroCom and IPCC AR5 estimates of the annual mean TOA RFari for these different PM species discussed below. Figure 13-27 shows the global spatial distributions of the forcings by species type, as calculated in the ACCMIP ensemble.



Note: These interactions are also known as aerosol-radiation interactions (RFari), and values of RFari for different PM species are shown. Units are Wm^{-2}. Hatched boxes show results from an AeroCom model study, adjusted for the 1750–2010 period, with boxes denoting the 5% to 95% uncertainty ranges and whiskers denoting the minimum and maximum values across models (Myhre et al., 2013). Solid colored boxes show the IPCC AR5 best estimates and the 5% to 95% uncertainty ranges. BC FF indicates black carbon from fossil fuel and biofuel; POA FF, primary organic PM from fossil fuel and biofuel; BB, biomass burning PM; and SOA, secondary organic PM.

Source: Permission pending, Boucher (2013).

Figure 13-26 Estimated annual mean top-of-the-atmosphere radiative forcings due to interactions of PM with radiation for the 1750–2010 period.



Note: The top three rows show the forcings due to PM interactions with radiation (RFari) for different PM species, the bottom left corner shows the total RFari, and the bottom right corner shows the forcing due to the effect of BC on surface albedo. Units are Wm^{-2}. Values above the RF panels represent the global mean RF. Values above the standard deviation panels show the standard deviation across the model means, with the global mean of standard deviations across gridboxes in parentheses.

Source: Permission pending, Shindell et al. (2013).

Figure 13-27 Mean radiative forcings (RF, left columns) and their standard deviations (right columns) from the ACCMIP ensemble for the 1850–2000 time period.

13.3.5.1 Sulfate

Sulfate particles form through oxidation of SO_2 by OH in the gas phase and in the aqueous phase by a number of pathways, including in particular those involving ozone and H_2O_2. The main source of anthropogenic sulfate is from coal-fired power plants, and global trends in anthropogenic SO_2 emissions are estimated to have increased dramatically during the 20th and early 21st centuries (Lamarque et al., 2013). Many developed countries have recently implemented more stringent air pollution controls that have reversed such trends (Klimont et al., 2013; Smith et al., 2011), leading to cleaner air [e.g., (Keene et al., 2014; Ruckstuhl et al., 2008)].

Sulfate particles are highly reflective. On a global scale, the IPCC AR5 estimates that sulfate contributes more than other PM types to RF, with RFari of −0.4 (−0.6 to −0.2) Wm^{-2}, where the numbers in parentheses represent the 5% to 95% uncertainty range (Myhre, 2013). This range indicates the challenges of estimating both SO_2 sources in developing regions and the lifetime of sulfate against wet deposition. Other, more recent estimates are broadly consistent with the AR5 value. Heald et al. (2014) calculated a global RFari of −0.36 Wm^{-2}, while Zelinka et al. (2014) reported an average ERFari value of −0.52 Wm^{-2} across an ensemble of nine CMIP5 models. Sulfate is also a major contributor to the influence of PM on clouds (Takemura, 2012). In their multimodel study, Zelinka et al. (2014) estimated a total effective radiative forcing (ERFari+aci) from anthropogenic sulfate of nearly −1.0 Wm^{-2}.

13.3.5.2 Nitrate

Nitrate particles form through the oxidation of nitrogen oxides, and occur mainly in the form of ammonium nitrate. Ammonium, however, preferentially associates with sulfate rather than nitrate, leading to formation of ammonium sulfate at the expense of ammonium nitrate (Adams et al., 2001). As anthropogenic SO_2 emissions decline in response to air quality control programs, more ammonium will likely become available to react with nitrate, potentially leading to increases in this PM type (Hauglustaine et al., 2014; Shindell et al., 2013). On the other hand, a warming climate may decrease nitrate abundance, as this PM species is highly volatile at warmer temperatures (Tai et al., 2010). Like sulfate, nitrate particles are reflective. The IPCC AR5 estimates a present-day RFari of nitrate of −0.11 (−0.3 to −0.03) Wm^{-2}, approximately one-fourth of the effect of sulfate (Boucher, 2013). By the mid−21st century, however, as SO_2 emissions decline, ammonium nitrate may account for half the total PM global cooling effect (Bellouin et al., 2011).

13.3.5.3 Organic Carbon, Including Brown Carbon

Primary organic particles arise from wildfires, agricultural fires, and from biofuel or fossil fuel combustion. SOA, as mentioned above, forms when anthropogenic or biogenic nonmethane hydrocarbons are oxidized in the atmosphere, leading to less volatile products that may partition into PM [e.g., (Donahue et al., 2012; Jimenez et al., 2009)]. Organic particles are mostly reflective, but in the case of BrC, a portion is significantly absorbing at shorter wavelengths (<400 nm). BrC particles occur most frequently in smoke plumes and in urban areas in the developing world that depend on coal or biofuel for domestic heating (Liu et al., 2014; Feng et al., 2013; Arola et al., 2011).

The IPCC AR5 estimates an RFari for primary organic PM from fossil fuel combustion and biofuel use of −0.09 (−0.16 to −0.03) Wm^{-2} (Myhre, 2013). The RFari estimate for SOA from these sources is −0.03 (−0.27 to +0.20) Wm^{-2}. The wide range of both these RFari estimates, with even the sign of the forcing not consistent across models, reflects uncertainties in both the optical properties of organic

PM and its atmospheric budgets, including the production pathways of anthropogenic SOA (Scott et al., 2014; Myhre et al., 2013; McNeill et al., 2012; Heald et al., 2010).

Trends in biogenic SOA may also have contributed to RFari. Recent work suggests that the expansion of global cropland since the preindustrial era has reduced emissions of biogenic species, resulting in a global mean warming of +0.09 Wm^{-2} due to a diminished concentration of SOA (Unger, 2014). For primary organic PM arising from biomass burning, the IPCC AR5 estimates an RFari of −0.2 Wm^{-2} (Boucher, 2013). Consideration of absorbing BrC may reduce that cooling by as much as 16−25% (Hammer et al., 2016; Lu et al., 2015). When deposited on snow or ice surfaces, BrC, like BC, may contribute to surface warming through the albedo effect, but this forcing has not been quantified.

Of the two types of organic particles—primary versus secondary—primary particles are more effective per unit mass in serving as cloud condensation nuclei (Trivitayanurak and Adams, 2014). Primary organic particles contribute both mass and number concentration in the size range needed to nucleate cloud droplets; they also contribute to the concentration of nanoparticles, which can subsequently grow to the appropriate size. Secondary organic particles (i.e., SOA) condense onto existing particles, which may fall outside the size range of cloud condensation nuclei; in addition, a large amount of SOA forms on particles that already act as cloud condensation nuclei, thereby not affecting the total number of nuclei available.

13.3.5.4 Black Carbon

BC particles occur as a result of inefficient combustion of carbon-containing fuels. Like primary organic PM, BC is emitted by biofuel and fossil fuel combustion and by biomass burning. BC is absorbing at all wavelengths and likely has a large impact on the Earth's energy budget (Bond et al., 2013). The IPCC AR5 estimates a BC RFari from anthropogenic fossil fuel and biofuel use of +0.4 (+0.05 to +0.8) Wm^{-2} (Myhre, 2013). Biomass burning contributes an additional +0.2 (+0.03 to +0.4) Wm^{-2} to BC RFari. The albedo effect of BC on snow and ice surfaces adds another +0.04 (+0.02 to +0.09) Wm^{-2} (Myhre, 2013) (see also Section 13.3.4.4 above).

BC forcing estimates are especially sensitive to the assumptions made about the mixing state of PM (Jacobson, 2012). In an external mixture, different PM types coexist, and each particle consists of a single species. In an internal mixture, each particle consists of a mixture of species. Such a mixture may be homogeneous, or it may occur as a core particle of one species coated with layers of one or more other species. Laboratory and field measurements suggest that BC particles acquire organic coatings as they age in the atmosphere, with subsequent increases in absorption of shortwave radiation (Cappa et al., 2012). These increases likely arise due to enhancement of absorption cross section as the particles grow in size. In addition, the coatings may act as a lens, focusing sunlight onto the BC core, thereby increasing absorption (Klingmueller et al., 2014). Knowledge of the photochemical aging of BC is poor.

As implied above, a large uncertainty in BC forcing involves the magnitude of emissions from biomass burning, which includes wildfire and other forms of open burning. BC is coemitted with OC by biomass burning, and the IPCC central estimate for the total 1750−2011 forcing from biomass burning is in fact zero (+0.2 Wm^{-2} BC forcing and −0.2 Wm^{-2} OC forcing). In the AeroCom ensemble, the total forcing from biomass burning varies in both magnitude and sign across models (Myhre et al., 2013). New field research suggests that biomass burning BC can form large superaggregates in plumes downwind, and that such particles would contribute nearly double the warming per unit optical depth typically assumed for smoke PM in models (Chakrabarty et al., 2014). In one recent study, however, Sena and Artaxo (2015) used satellite data to quantify TOA forcings due to biomass burning smoke during the dry season in Amazonia. They found an overall cooling effect of −5.2 ± 2.6 Wm^{-2}, averaged over 10 seasons.

13.3.5.5 Dust

Dust, also known as mineral dust, has traditionally been classified as scattering. A recent study, however, found that observed dust may be substantially coarser (and thus more light-absorbing) than currently represented in climate models (Kok et al., 2017). Dust mobilization occurs from dry or disturbed soils, and so is linked to both meteorological conditions and human activity, with anthropogenic sources making up about 25% of the total (Ginoux et al., 2012). Through analysis of lake sediment, Neff et al. (2008) determined that the expansion of livestock grazing likely increased dust deposition in the West by a factor of five since the 19th century. Once airborne, dust can strongly attenuate incoming solar radiation (Kavouras et al., 2009; Fairlie et al., 2007). If deposited on snow, dust may accelerate snow melt since dust is darker than snow and may decrease surface albedo (Painter et al., 2012; Skiles et al., 2012). Estimates of global RF related to the change in dust presence since the preindustrial era vary widely due to lack of knowledge both of dust trends (Mahowald et al., 2010) and of dust optical properties (Li et al., 2015). The IPCC AR5 estimates RFari due to dust change since 1750 as −0.1 ± 0.2 Wm^{-2} (Boucher, 2013). The Kok et al. (2017) result, however, suggests that the anthropogenic change in dust may have led to warming, not cooling. Dust may also influence cirrus cloud cover by serving as efficient ice nuclei, although quantifying the resulting forcing is challenging (Kuebbeler et al., 2014; Nenes et al., 2014).

13.3.6 Climate Response to Changing PM, Including Feedbacks

The radiative forcing due to PM elicits a number of responses in the climate system that can lead to significant effects on weather and climate over a wide range of space and time scales, mediated by a number of feedbacks that link PM and climate. For the purposes of this ISA, we focus primarily on climate impacts in the U.S., described in the following section (Section 13.3.7). Here we briefly summarize the mechanisms of climate responses and feedbacks to PM radiative forcing.

In contrast to long-lived greenhouse gases that are well-mixed in the atmosphere, PM has a very heterogeneous distribution across the Earth. The patterns of RFaci and RFari thus tend to correlate with PM loading, with the greatest forcings centered over continental regions (e.g., Figure 13-27). The climate response is more complicated, however, since the perturbation to one climate variable, such as temperature, cloud cover, or precipitation, typically leads to a cascade of effects on other variables. As a result, while the initial PM radiative forcing may be concentrated regionally, the eventual climate response can be spatially much broader (even, ultimately, global) or concentrated in remote regions. For example, increases in absorbing PM over Asia may induce shifts in atmospheric circulation patterns that may, in turn, affect U.S. regional climate (Teng et al., 2012). Because of the complexity of the potential climate system interactions, the spatial relationships between patterns of PM forcing and those of climate response vary greatly among models, with some studies showing relatively close correlation between forcing and surface temperature response [e.g., (Leibensperger et al., 2012a)] and other studies showing much less correlation [e.g., (Levy et al., 2013)].

These climate system responses themselves lead to feedbacks that in turn affect PM. Such PM-climate feedbacks involve a perturbation of regional climate by PM radiative forcing, which in turn leads to meteorologically driven changes in PM emissions, formation, or lifetime. A positive feedback increases PM concentration and amplifies the PM effect on climate, while a negative feedback decreases PM concentration and weakens the PM effect on climate. Examples of such feedbacks occurring on the regional scale include those involving wildfires, inversions, clouds, and convection, PM-albedo effects, and biogenic emissions.

For example, wildfires are expected to increase in a warming world [(Yue et al., 2013; Pechony and Shindell, 2010)], and agricultural fires may also increase as more land is cleared for crops and timber plantations, particularly in the tropics (Margono et al., 2012). Smoke from these fires contain a mix of absorbing (BC and BrC) and scattering particles and so may affect the climate in complex ways. In their model study, Tosca et al. (2010) found that smoke from fires reduced solar radiation at the surface by 1.3 Wm^{-2}, corresponding to a global mean temperature decrease of $-0.13 \pm 1°C$. Absorption of solar radiation by smoke particles warmed the troposphere, and that warming, together with the cooler surface temperatures, weakened the Hadley circulation and decreased precipitation over tropical forests. Such a positive feedback would further enhance fire activity in the tropics.

Another example of PM-climate feedback involves atmospheric inversions, especially over mountain basins. Such inversions limit ventilation and promote accumulation of surface PM; and the enhanced PM can further intensify the inversion. For example, over Salt Lake City in Utah, haze episodes during wintertime inversion events diminish the penetration of solar radiation and cool the surface further, strengthening the inversion and exacerbating the haze (Lareau et al., 2013). In their modeling study, Jacobson and Streets (2009) found a similar positive feedback of PM on pollution levels in Los Angeles: atmospheric stability over Los Angeles was enhanced by a combination of warming of the air by BC and

cooling of the ground by all particle types, including BC. The resulting decrease in precipitation lengthened the lifetime of PM in that study.

Invoking similar mechanisms, Cook et al. (2009) identified atmospheric dust as a probable amplifier of the Dust Bowl drought of the 1930s. The drought, together with the agricultural practices prevalent in that era, likely resulted in the mobilization of a massive amount of dust, which would, in turn, have warmed the local atmosphere, suppressing convection and exacerbating drought conditions [see also (Xing et al., 2016)]. In contrast, Zhang et al. (2010) calculated that heating by BC particles may invigorate convection under certain conditions, thereby increasing surface ventilation and precipitation. More recently, Mashayekhi and Sloan (2014) calculated a 15% decrease in convective precipitation due to PM radiative effects in the northeastern U.S., but a 30% increase in large-scale precipitation in this region due to the influence of PM on clouds.

As described in Section 13.3.3.3, deposition of BC and other absorbing species on Arctic snow and sea ice may decrease surface albedo and accelerate warming at high latitudes (Bond et al., 2013; Lee et al., 2013; Skeie et al., 2011; Flanner et al., 2007). Model studies have suggested that this rapid warming could shift the polar jet northward, decreasing cold front frequency over mid-latitudes and lengthening stagnation episodes (Turner et al., 2013; Leibensperger et al., 2008). An increase in stagnation would likely intensify pollutant events in source regions. Transport of pollution to the Arctic could also be affected, but this feedback onto Arctic BC deposition has not been studied.

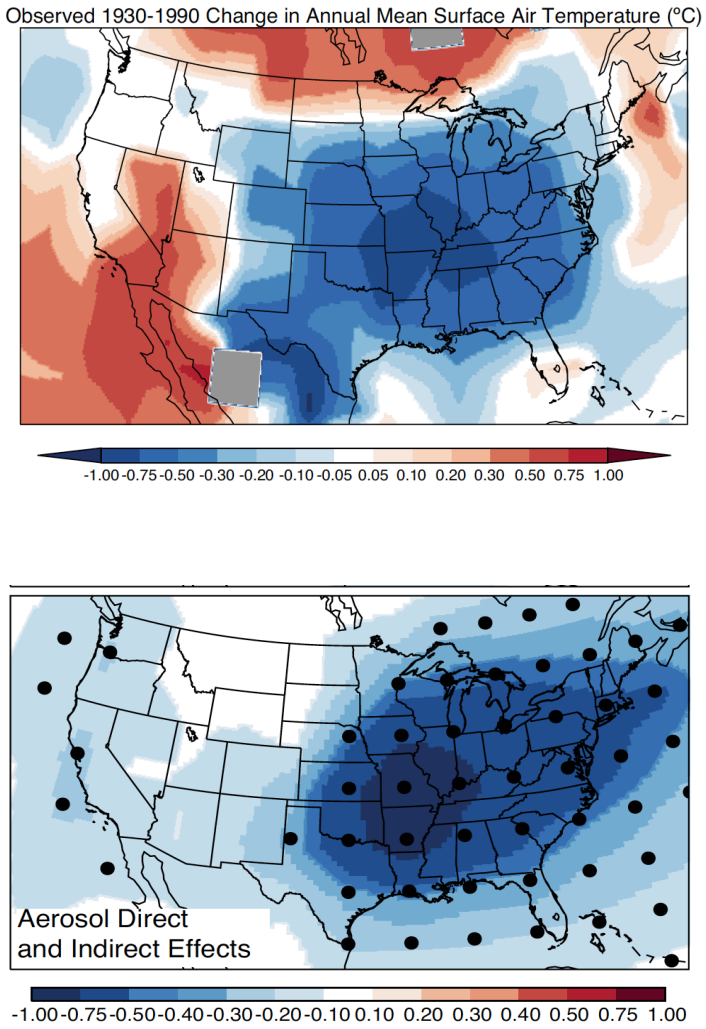
A final example involves biogenic SOA, which arises from the complex oxidation pathways of biogenic species such as isoprene and monoterpenes. As biogenic emissions are strongly temperature-dependent, SOA concentrations are expected to increase in a warming climate (Wu et al., 2012; Heald et al., 2008), even if the so-called "CO_2 inhibition effect" is taken into account (Tai et al., 2013). Such regional increases in reflective PM could significantly cool the underlying surface, thereby limiting the magnitude of SOA enhancement (Arneth et al., 2010).

13.3.7 Effect of PM on U.S. Regional Climate

The effects of PM on U.S. regional climate have been examined on several different spatial and temporal scales. Some studies have investigated the impact of PM on urban microclimates [e.g., (Jacobson et al., 2007)]. Other studies have diagnosed weekly cycles in temperature or precipitation, which taken together suggest that weekly variations in anthropogenic PM may influence regional weather patterns [e.g., (Bell et al., 2008; Forster and Solomon, 2003)]. A key question, however, is to what extent PM trends in the U.S. may have partially offset the warming effects of rising greenhouse gases over the course of the 20th century.

Over the contiguous U.S., surface temperatures warmed during the early decades of the 20th century, remained relatively flat from about 1960 to 1980, then rose rapidly by ~1°C from 1980 to 2010

(NAS, 2014). A closer look at spatial trends in these temperatures reveals a strong cooling trend of approximately −1°C from 1930 to 1990 in the Southeast, centered over Arkansas and Oklahoma (Leibensperger et al., 2012a) (Figure 13-28). Mascioli et al. (2017) pointed out that between 1950 and 2000 the cooling extended over much of the eastern U.S. This observed cooling, which took place even as much of the globe warmed in response to greenhouse gases, is sometimes referred to as the U.S. "warming hole" (Pan, 2004). Several studies have linked the U.S. warming hole to natural variability [e.g., (Banerjee et al., 2017)], in particular to decadal variation in North Atlantic or Pacific sea surface temperatures (SSTs) (Meehl et al., 2015; Kumar et al., 2012; Meehl et al., 2012; Kunkel et al., 2006). Such variability can influence large-scale meteorological processes, which in turn may affect temperatures in continental interiors such as the central or south-central U.S. In one multimodel study, those models that best represented the Atlantic Multidecadal Oscillation also best reproduced the warming hole, although even those models showed large discrepancies with observations (Kumar et al., 2012).



Top: Temperature change is based on a linear trend, and observations are from the NASA GISS Surface Temperature Analysis (GISTEMP, http://data.giss.nasa.gov/gistemp/).

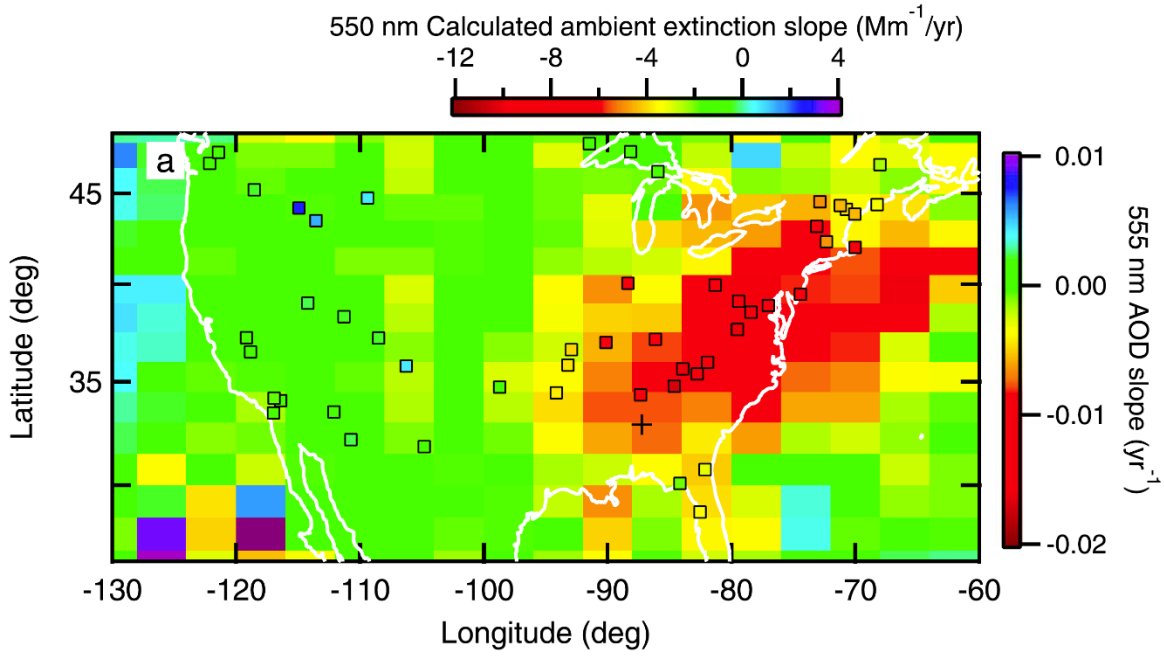
Bottom: Units are °C. Values represent the mean difference between two sets of 5-member ensemble simulations in a climate model; one set includes U.S. anthropogenic PM sources and one does not. Interactions of PM with both radiation and clouds are considered. Dots indicate differences significant at the 95th percentile.

Source: Permission pending, Leibensperger et al. (2012a).

Figure 13-28 Top: Observed change in surface air temperatures between 1930 and 1990. Bottom: Effect of U.S. anthropogenic PM sources on surface air temperatures for the 1970−1990 period when U.S. particulate loading was at its peak.

Other studies have suggested that trends in PM loading may be partly responsible for the unusual cooling trend in the southeastern U.S. during the mid-20th century (Section 13.3.2.1). PM in the Southeast is dominated by a mix of sulfate and organic species. In recent years, PM levels in this region have declined in response to emissions controls, possibly contributing to the observed increase in solar

radiation at the surface. For example, from 2001 to 2013, observed AOD across the Southeast decreased an average −4% per year (Figure 13-29), while surface solar radiation in the region increased by +8 Wm^{-2} (Attwood et al., 2014). Gan et al. (2014), however, reported increases in both direct and diffuse surface solar radiation, at least averaged over the whole of the eastern U.S. from 1995 to 2010. The results of Gan et al. (2014) are difficult to interpret due to the seeming discrepancy between a decrease in PM and an increase in diffuse radiation. Additionally, it is unclear why the greatest cooling occurred in the relatively rural Southeast, away from the historically large sources of anthropogenic PM such as power plants in the Ohio River Valley. As discussed above, climate responses to PM radiative forcing can be nonlocal, but it is not clear what may have caused this particular mismatch in forcing and climate response.



Note: The open squares denote trends in ambient extinction, a measure of how much solar radiation reaches the Earth's surface, from the IMPROVE network. The plus symbol indicates the site of the 2013 Southern Oxidant and Aerosol study, which analyzed aerosol extinction as a function of relative humidity.

Source: Permission pending, Attwood et al. (2014).

Figure 13-29 Trends in aerosol optical depth (AOD) measured by the Multi-angle Imaging SpectroRadiometer (MISR) satellite instrument over the 2001−2013 time period.

To address these issues, several model studies have tried to recreate the observed trends in AOD, surface radiation, and surface temperatures. Leibensperger et al. (2012a, 2012b) found that the regional RF from anthropogenic PM elicits a strong regional climate response, cooling the central and eastern U.S.

by 0.5−1.0°C on average during 1970−1990, with the strongest effects on maximum daytime temperatures in summer and autumn (Figure 13-28). In this study, the spatial mismatch between maximum PM loading and maximum cooling could be partly explained by the outflow of PM cooling the North Atlantic, which then strengthens the Bermuda High in the model and increases the flow of moist air into the south-central U.S. Local feedback effects involving soil moisture and cloud cover may also amplify the surface temperature response to changing PM loading in the Southeast (Mickley et al., 2012; Liang et al., 2005; Pan, 2004).

The Leibensperger et al. (2012a, 2012b) studies suggest that the influence of PM on radiation and clouds plays a significant role in driving regional cooling in the Southeast. In contrast, a more recent model study, Yu et al. (2014) determined that the U.S. warming hole can best be explained by the PM interactions with clouds alone. Meanwhile, Attwood et al. (2014) attributed 20% of the observed increase in surface solar radiation in the Southeast to a decrease in the sulfate/organic ratio of PM. As sulfate is more hygroscopic than organic material, a decline in sulfate would decrease particle water content and thus particle extinction, leading to local brightening—i.e., more sunlight reaching the surface. In contrast to Yu et al. (2014), the Attwood et al. (2014) result implies that at least some of the warming hole can be attributed to aerosol-radiation interactions. More recently, Mascioli et al. (2017) used an ensemble of observations and IPCC model simulations to conclude that both PM and natural variability contributed to the U.S. warming hole, at least in summer.

Overall, therefore, several lines of evidence suggest an important influence of PM on observed 20th century temperature trends over the southern and eastern U.S. A number of key uncertainties, however, mean that alternative explanations cannot be ruled out at this time, and further research is needed.

13.3.8 Uncertainties in Estimates of PM Effects on Radiative Forcing and Climate: Summary

In general, uncertainties associated with clouds and aerosols continue to be the largest contributors to overall uncertainty in evaluating climate change trends and projecting future climate changes (Boucher, 2013). With respect to PM-climate uncertainties specifically, there has been significant progress since the 2009 ISA. According to the IPCC AR5, "Climate-relevant aerosol processes are better understood, and climate-relevant aerosol properties better observed, than at the time of AR4" (Boucher, 2013). Nevertheless, significant uncertainties still remain which make it difficult to precisely quantify the climate effects of PM. This is because the properties of PM, and those of the clouds with which PM interacts, vary substantially on scales much smaller than those able to be represented in even the most recent generation of climate models. In addition, as described above, the initial radiative forcing effect of PM leads to a diverse range of regionally heterogeneous climate impacts associated with changes in the hydrologic cycle and atmospheric circulation patterns, mediated by a variety of feedbacks, and interacting

in complex ways with other forced and natural sources of climate variability and change occurring simultaneously. This makes it difficult to characterize the total net impact of PM on climate and to disentangle the unique contribution of PM to overall climate change.

As discussed throughout this section, uncertainties in estimates of PM effects on climate arise from many sources. First, there is a lack of knowledge of PM abundance. Unlike the well-mixed greenhouse gases, PM is not uniformly distributed through the atmosphere and the current spatial distribution of PM concentrations is not well quantified (Myhre, 2013). Long-term measurements of PM are rare and mainly surface-based, making it challenging to estimate trends in AOD, which are key to estimating climate impacts (Koch et al., 2011). In particular, calculation of the RF of anthropogenic PM requires precise knowledge of preindustrial particle load; this is especially true for determining RFaci (Carslaw et al., 2013). Measurements from ice cores and lake-core sediments offer the only constraints on PM of the preindustrial era; such sparse measurements cannot capture the spatial distribution of this era. Another difficulty in estimating the climate impacts of anthropogenic PM lies in quantifying the contribution of natural PM to observed trends (Heald et al., 2014). The production and loss rates of natural PM depend on meteorological variables such as temperature, and so change with changing climate. The sensitivity of these rates to meteorology is not well characterized.

Anthropogenic emissions of PM or their precursors are also not well constrained in models (Boucher, 2013), but even application of the same emission inventories to an ensemble of climate models yields a large range of PM concentrations (Shindell et al., 2013). Some of the discrepancies among models likely arise from uncertainties in the oxidation pathways leading to PM production or in PM lifetime against wet deposition (Achakulwisut et al., 2015; Wang et al., 2011b). Discrepancies in RF estimates of PM arise in part from uncertainties in the optical properties of particles. Particle size, complex refractive index, shape, and lifetime are functions of particle water content, and these properties all influence the magnitude of PM RF. Finally, the microphysics of the effects of PM on clouds are not well represented in coarse-grid climate models (Trivitayanurak and Adams, 2014; Boucher, 2013). Some processes driving the interactions between PM and clouds are relatively well understood (e.g., cloud droplet activation), while scientific knowledge of other processes is lacking (e.g., ice nucleation) (Rosenfeld et al., 2014). Both kinds of processes are challenging to translate into macroscale processes such as large-scale precipitation or radiative fluxes (Rosenfeld et al., 2014). Better knowledge of the number and size distributions of emitted particles, including nanoparticles from vehicle exhaust, is also needed to constrain PM-cloud interactions (Adams et al., 2013).

As discussed in the previous subsection, several model studies point to the possibly large influence of changing sulfate on regional surface temperatures in the southeastern U.S. However, reconciling the observed increase in diffuse radiation at some sites with decreasing PM load is challenging (Gan et al., 2014). Another uncertainty in studies of the PM effects on U.S. regional climate involves biogenic SOA. The gas/particle partitioning of organic material depends in part on ambient PM concentrations, with more SOA formed in the presence of sulfate PM (Weber et al., 2007; Donahue et al.,

2006). Recent model studies have attempted to determine to what extent trends in anthropogenic PM in recent decades may have also influenced biogenic SOA formation (Marais et al., 2017; Carlton et al., 2010) and thus surface cooling. The uncertainties in such studies, however, are large.

More indirectly, there is a growing body of evidence that aerosol forcing may drive shifts in internal modes of long-term (e.g., multidecadal) climate variability in the North Atlantic (Zhang et al., 2013a; Booth et al., 2012; Evan et al., 2009), in turn can potentially affecting regional temperature and rainfall patterns in North America, as well as Atlantic tropical storms (Dunstone et al., 2013).

Finally, while trends in PM may affect climate at the regional scale, global climate change may, in turn, influence PM abundance. For example, climate-driven changes in monsoon strength will almost certainly affect PM abundance over Asia (Turner and Annamalai, 2012), while increasing warming surface temperatures over the western U.S. may enhance wildfire PM (Yue et al., 2014; Yue et al., 2013). Absent future changes in land use, the concentration of biogenic SOA will likely increase in response to warming temperatures and greater isoprene emissions over the 21st century (Shen et al., 2017; Tai et al., 2013), though declines in anthropogenic emissions have the potential to at least partially counteract this effect (Carlton et al., 2010). Observations also reveal a strong positive dependence of sulfate PM to temperature in the eastern U.S., which could likewise have implications in the future warmer climate (Shen et al., 2017). Disentangling these different effects on PM abundance—the influence of global climate change versus feedbacks from the regional climate response to changing PM—remains challenging and continues to be the subject of active research.

13.3.9 Summary and Causality Determination

The 2009 ISA concluded that there was sufficient evidence that a causal relationship exists between PM and climate effects—specifically on the radiative forcing of the climate system, including both direct effects of PM on radiative forcing and indirect effects involving cloud processes. Recent research reinforces and strengthens the evidence evaluated in the 2009 PM ISA. New evidence provides greater specificity about the details of these radiative forcing effects and increased understanding of additional climate impacts driven by PM radiative effects. This section describes the evaluation of evidence for climate effects, with respect to the causality determination, using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015).

The scientific consensus is that anthropogenic PM has generally cooled the atmosphere over the 20th and early 21st century, masking some of the effects of greenhouse gas warming (Myhre, 2013). In response to health concerns, PM concentrations have begun declining in many developed nations [e.g., (De Meij et al., 2012)], a trend that can be observed from space (Jongeward et al., 2016). Such declines likely contributed to the current trend in global "brightening," which follows a decades-long period of global "dimming" (Wild, 2009). The brightening, in turn, may have led to rapid warming in North America and Europe, as greenhouse-gas warming was unmasked (Turnock et al., 2015;

Leibensperger et al., 2012a, b; Philipona et al., 2009; Ruckstuhl et al., 2008). In contrast, PM concentrations have increased in recent decades over developing countries in much of Asia (Jongeward et al., 2016; Shindell et al., 2013). The sign of recent RF over developing countries, however, is very uncertain due to lack of accurate information on emissions and the relative abundances of reflecting species versus absorbing species. Research since the 2009 PM ISA has also improved characterization of the key sources of uncertainty in estimating PM climate effects, particularly with respect to PM-cloud interactions. The IPCC AR5 states that "Climate-relevant aerosol processes are better understood, and climate-relevant aerosol properties better observed, than at the time of AR4" (Boucher, 2013). Substantial uncertainties, however, still remain with respect to key processes linking PM and climate, both because of the small scale of PM-relevant cloud microphysical processes compared to the resolution of state-of-the-art models, and because of the complex cascade of indirect impacts and feedbacks in the climate system that result from a given initial radiative perturbation caused by PM. These uncertainties continue to limit the precision with which these effects can be quantified. **Despite these remaining uncertainties, though, overall the evidence is sufficient to conclude that a causal relationship exists between PM and climate effects.**

13.4 Effects on Materials

13.4.1 Introduction

The 2009 PM ISA (U.S. EPA, 2009) concluded a causal relationship between PM and effects on materials, noting that building materials including metals, stone, cement, and paint undergo natural weathering processes that are enhanced by exposure to anthropogenic pollutants. Effects of PM deposition to materials include both physical damage and impaired aesthetic qualities. It was concluded that particulate deposition can result in increased cleaning frequency and reduced usefulness of soiled material, and that although attempts had been made to quantify pollutant exposure corresponding to perceived soiling and damage, insufficient data were available to improve understanding of perception thresholds with respect to pollutant concentration, particle size, and chemical composition.

The two major processes by which air pollution in general and PM in particular can bring about materials damage are soiling and corrosion. Soiling has been defined generally as "a visual nuisance resulting from the darkening of exposed surfaces by deposition of atmospheric particles" (Lombardo et al., 2005) and more precisely as "a surface degradation that can be undone by cleaning," and the physical measure of soiling has been defined as "the contrast in reflectance of particles on a substrate to the reflectance of the bare substrate," definitions that remain widely used (Watt et al., 2008; Saiz-Jimenez, 2004; Haynie, 1986a). Corrosion is a chemical attack of a material surface that degrades a material surface and decreases aesthetic value and mechanical strength (Watt et al., 2016) (Watt et al., 2008), and in ambient air it typically involves reactions of acidic PM (i.e., acidic sulfate or nitrate) with material

surfaces, but gases like SO_2 and HNO_3 also contribute to atmospheric corrosion, and recent research on materials damage by both gaseous and particulate oxides of nitrogen and sulfur will also be considered in this section.

The increased cleaning, washing, and repainting of solid surfaces create a major economic cost and reduces the useful life of soiled material. Long-term effects of soiling are primarily from fine rather than coarse particles, as coarse particles are relatively easily removed by wind and rain (Creighton et al., 1990; Haynie and Lemmons, 1990). As reviewed in the 2009 PM ISA (U.S. EPA, 2009), soiling is dependent on atmospheric particle concentration, particle size distribution, deposition rate, and the horizontal or vertical orientation and texture of the exposed surface (Haynie, 1986b). The chemical composition and morphology of the particles and the optical properties of the surface being soiled will determine the time at which soiling is perceived by human observers (Nazaroff and Cass, 1991). Since the 2009 PM ISA (U.S. EPA, 2009), additional research has enabled further characterization of PM effects on materials, although uncertainties remain such as quantitative relationships between particle concentration and frequency of repair, deposition rates of airborne PM to surfaces, and the interaction of copollutants in regard to materials damage effects. There is new information on the soiling process, types of materials, such as glass, and dose-response and damage functions described below. Most of the recent work on this topic has been conducted outside of the U.S. on buildings and other items of cultural heritage.

13.4.2 Soiling and Corrosion

Soiling and corrosion are complex, interdependent processes, typically beginning with deposition of atmospheric PM to exposed surfaces. Constituents of deposited PM can interact directly with materials or undergo further chemical and/or physical transformation to cause soiling, corrosion, and physical damage. Weathering, including exposure to moisture, ultraviolet (UV) radiation and temperature fluctuations affects rate and degree of damage.

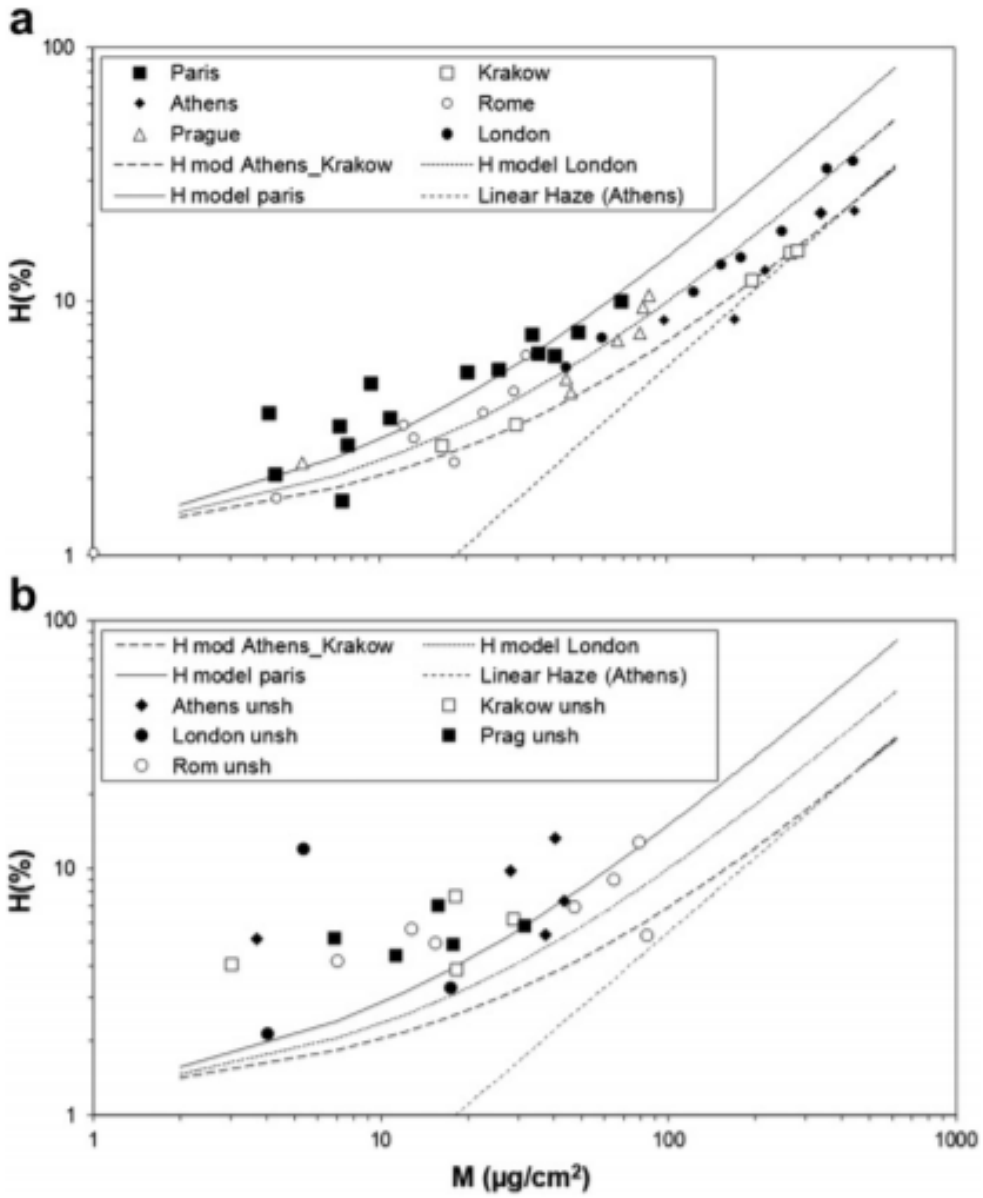
Deposition of SO_2 to materials such as limestone ($CaCO_3$), granite, and metal intensifies soiling. Deposited SO_2 is oxidized to sulfate, in the case of limestone ($CaCO_3$), transforming it into gypsum ($CaSO_4$). As gypsum forms, the surface becomes rougher, further increasing PM deposition (Camuffo and Bernardi, 1993). Organic and elemental carbon from deposited PM both contribute substantially to black crusts (Bonazza et al., 2005; Sabbioni et al., 2003). This not only enhances soiling because of carbonaceous PM, but the deposited PM also forms coatings, creating ideal conditions for more rapid SO_2 oxidation catalyzed by carbon and metals present in the deposited PM (McAlister et al., 2008; Grossi et al., 2007).

Research has progressed on theoretical understanding of soiling of cultural heritage since the 2009 PM ISA (U.S. EPA, 2009). Trace element concentrations were measured and heavy metals were detected in black crusts on stone monuments (Barca et al., 2010), and the nature, causes, and mitigation strategies for decay of stone-built heritage have been reviewed (Smith et al., 2008). Isotope tracers have

also been applied to understand the origin of contaminant sources in black crusts (Kloppmann et al., 2011). Biological marker compounds indicating the presence of biogenically derived material confirmed that biological activity played a major role in producing black films on granite (de Oliveira et al., 2011). Indoor penetration and accumulation of PM and gaseous pollutants into historical buildings was also studied (Worobiec et al., 2010).

There has also been considerable progress understanding soiling of materials besides stone. Gypsum was found to be the main damage product in concrete, and organic and elemental carbon were also found in concrete damage layers (Ozga et al., 2011). Gypsum formation was also observed after exposure of rendering mortars to sulfuric acid (Lanzon and Garcia-Ruiz, 2010). A new physically based model was recently developed to predict haze[85] forming on modern glass that takes into account differences in particle size distributions observed in different locations (Alfaro et al., 2012). Results are plotted in Figure 13-30, showing good model fits under sheltered conditions from the rain and haze on the glass reaching a 50% ratio of diffuse transmitted light to direct transmitted light.

[85]In this section (13.4) haze is used as it has been defined in the scientific literature on soiling of glass, i.e., the ratio of diffuse transmitted light to direct transmitted light (Lombardo et al., 2010). This differs from the use of the word haze in Sections 13.2 and Section 13.3, where it is used as a qualitative description of the blockage of sunlight by dust, smoke, and pollution. This usage is widespread in the scientific literature on visibility and in discussion of the Regional Haze Rule. Both definitions are used in this chapter because use of the word haze in discussion of either regional haze and glass soiling is unavoidable.



Source: Permission pending, Alfaro et al. (2012).

Figure 13-30 Increase of haze (H in %) with mass of deposit on glass (M µg/cm^2) under a) sheltered conditions and b) conditions where glass panes were exposed directly to the weather.

Corrosion of stone has been discussed in the 2009 PM ISA, and decay of stone building materials by acid deposition and sulfate salts were described (U.S. EPA, 2009). Advances since the 2009 PM ISA include quantification of degradation rates and further characterization of factors that influence damage of stone materials. Measurable losses of surface material were used to determine decay rates of marble grave stones up to 2.5 to 3.0 mm/century in heavily polluted areas compared to natural background decay rates from a relatively pristine area of 0.25 mm/century (Mooers et al., 2016). Both time of wetness and the number of dissolution/crystallization cycles were identified as hazard indicators for stone materials, with the greatest hazard in spring and fall when both time of wetness and the number of dissolution and crystallization cycles were relatively high (Casati et al., 2015). Improvements of facilities for further research to simulate interactions between cultural heritage materials and realistic atmospheric environments that facilitate controlled experimental conditions in order to investigate various factors influencing decay are also underway (Chabas et al., 2015).

Corrosion of steel as a function of PM composition and size was also recently studied, and changes in composition of resulting rust varied with particle size (Lau et al., 2008). A multipollutant study of damage to metal materials under ambient conditions in severely polluted Hong Kong concluded that iron and steel were corroded more by air pollution than copper and copper alloys, which were in turn more corroded by air pollution than aluminum and aluminum alloys (Liu et al., 2015). SO_2, NO_2, and PM contributed to corrosion of iron and steel, while SO_2 and O_3 were mainly responsible for corrosion of copper and copper alloys, and NO_2 and PM for damage to aluminum and aluminum alloys (Liu et al., 2015).

Other atmospheric gases besides SO_2, and other components of particulate matter besides sulfate and black carbon can damage materials. Nitrates are more soluble than sulfates, and do not form stable compounds with stone building materials (Sabbioni et al., 1998). However, calcium nitrate can be formed by NO_X attack (Haneef et al., 1993). Also, NO_X can enhance sulfate attack on calcium rich building materials, and synergistic effects between NO_2 and SO_2 at high relative humidity have been reported (Johansson et al., 1988). Airborne organic compounds have also been observed on building material surfaces and can participate in damage, (Sanjurjo Sanchez et al., 2009; Sabbioni et al., 1998; Saiz-Jimenez, 1993), serving as nucleation sites for growth of gypsum crystals (Cultrone et al., 2000; Saiz-Jimenez, 1993). In some cases, soiling of limestone and building material surfaces has been attributed to biological processes (Viles and Gorbushina, 2003), and carbonaceous particles and organic compounds also enhance biological colonization (Sanjurjo-Sanchez and Alves, 2012). Black carbon has recently been observed to induce structural, composition, and functional changes in biofilms, to produce thicker and more complex biofilms, and potentially to act as a novel signal to induce biofilm formation (Hussey et al., 2017).

In addition to structural and aesthetic impacts, energy efficiency is also becoming an important consideration for impacts of air pollutants on materials. A growing area of research is the impact of air pollution on the energy yield from photovoltaic panels, especially in desert environments. Results indicate

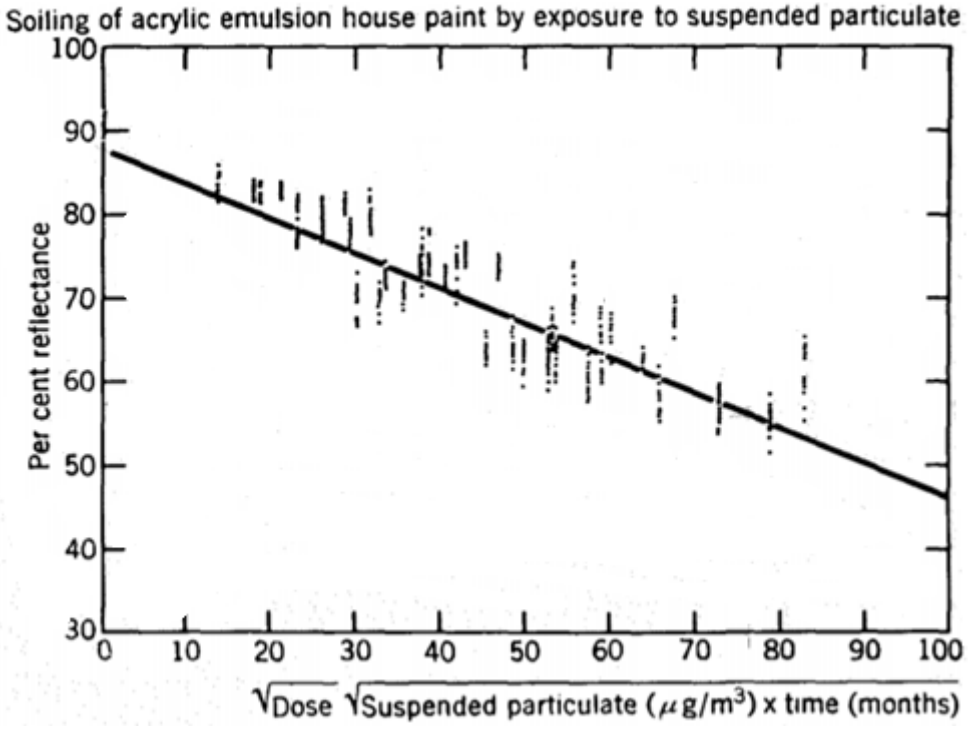
the type of dust deposited and glazing temperature influence light transmission (Abderrezek and Fathi, 2017). For example, on average, carbon soiling decreased solar modular efficiency by 37.6% while soil particles reduced efficiency by 68% and $CaCO_3$ by 37.6% (Radonjic et al., 2017). The relationship between the rate of degradation of photovoltaic power output due to soiling has been investigated and related to dust accumulation rate, and impacts of season and dust storms were observed (Besson et al., 2017; Boyle et al., 2017; Javed et al., 2017). In five sites in the continental U.S. (Cocoa, FL, Albuquerque, NM, and a rural, suburban, and urban location in the Front Range of Colorado) photovoltaic module power transmission was reduced by 2.8% for every g/m^2 of PM deposited on the cover plate independent of geographical location (Boyle et al., 2017). Mean deposition velocities were 1.5 cm/s. In arid environments dust fouling was observed to reduce photovoltaic module power output by 40% after 10 months without cleaning (Walwil et al., 2017). There is on-going research to reduce soiling of photovoltaic cells with transparent coatings (Quan and Zhang, 2017).

The use of materials able to reflect a large portion of solar radiation for passive cooling, such as light-colored marble panels on building exteriors, are another example of an approach to improving energy efficiency, and also to countering the urban heat island effect. Exposure to acidic pollutants in urban environments reduces solar reflectance of marble, decreasing the cooling effect of the marble envelope (Rosso et al., 2016).

13.4.3 Dose-Response Relationships

Typically, empirical models are used to estimate dose-response relationships from field measurements of data relevant to deposition and meteorological processes (Hamilton and Mansfield, 1993). There has been considerable progress since the 2009 PM ISA (U.S. EPA, 2009) in the development of dose-response relationships for soiling of building materials, although some key relationships remain poorly characterized. Dose-response estimates can be traced back to early research on surface repainting, showing a direct correlation between ambient PM concentration and the number of years between repainting (U.S. EPA, 1972). Consistent and reliable dose-response relationships for soiling of stone building materials have proved difficult to estimate, but there is a growing literature of dose-response relationships for newer building materials, such as glass, metals, and polymers.

The first general dose-response relationships for soiling of materials by particles were generated by measuring the contrast in reflectance of a soiled surface to the reflectance of the unsoiled substrate for different materials, including acrylic house paint, cedar siding, concrete, brick, limestone, asphalt shingles, and window glass in different areas with total suspended particulate (TSP) concentrations from 59 to 289 $\mu g/m^3$(Beloin and Haynie, 1975). The dose-response curve for acrylic house paint in Figure 13-31 plots change in reflectance against the square root of the dose, defined as the product of TSP and number of months exposed (Beloin and Haynie, 1975).



Source: Permission pending, Beloin and Haynie (1975).

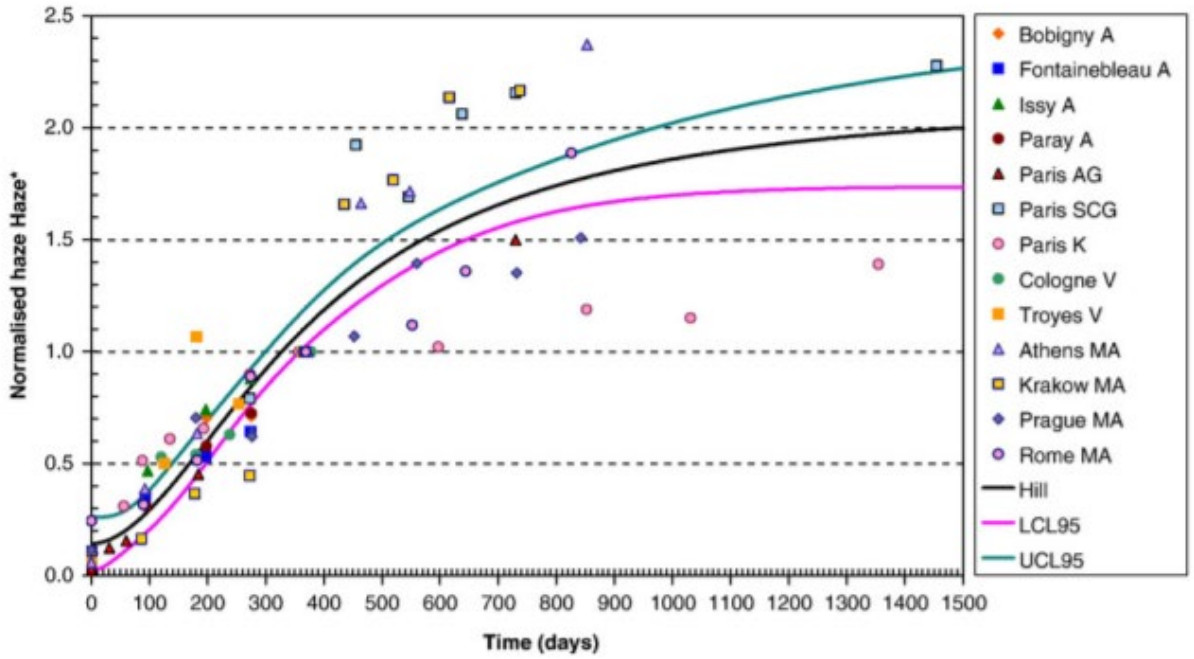
Figure 13-31 Example of a dose-response curve for effects on materials, showing change in reflectance vs. square root of dose for acrylic emulsion house paint.

Efforts to develop accurate dose-response curves similar to those in Figure 13-31 have proved difficult because of multiple influences and considerable scatter in the data for most materials. Continued efforts to develop dose-response curves for soiling have led to some advancements for modern materials, but remain poorly characterized for limestone. PM_{10} measurements and collocated reflectance measurements of material surfaces for limestone, painted steel, white plastic, and polycarbonate filter material were recently used to quantify dose-response relationships between PM_{10} and soiling. In this recent case also, there was too much scatter in the data for limestone to produce a dose-response relationship (Watt et al., 2008). A dose-response relationship for silica-soda-lime window glass soiling by PM_{10}, NO_2, and SO_2 based on 31 different locations was quantified (Lombardo et al., 2010), and described by Equation 13-8:

$$Haze = (0.2529[SO_2] + 0.1080[NO_2] + 0.1473[PM_{10}]) \times \frac{1}{1 + \left(\frac{382}{t}\right)^{1.86}}$$

Equation 13-8

Figure 13-32 shows the raw data on which this dose-response curve was based, illustrating that long observation times of several years required as well as the challenges posed by response differences among locations.



Source: Permission pending, Lombardo et al. (2010).

Figure 13-32 Temporal trend in haze values of glass at different locations. The x-axis is normalized haze values where 1-year data series were combined with longer data series and scaled by the 1-year value. Black line represents a fitted model of the data and pink and green lines represent 95% confidence.

Glass soiling was intensively studied to evaluate deposited PM composition and optical properties including reflectance, transmittance, and absorption in several European cities. After more than two years, there was no saturation phenomenon, i.e., material continued to accumulate through deposition, although disappearance of ammonium and possible particulate organic matter were reported. Absorption and transmittance changed "quasi-linearly" with species concentrations for elemental carbon and major ions

for thin deposits, but for thicker deposits saturation was reached for absorption of 16% when elemental carbon concentrations reached 15 µg/cm^2 and for diffuse transmittance of about 30% for 65 µg/cm^2 of ions, and the overall saturation level for transmittance was dependent of composition and particle size (Favez et al., 2006).

As these studies indicate, for some materials it can sometimes take years to develop dose-response relationships that relate reflectance of materials surfaces to ambient PM concentrations. There has also been progress in developing methods to more rapidly evaluate soiling of different materials by PM mixtures. Modern buildings typically have simpler lines, more limited surface detail, and greater use of glass, tile, and metal that are easier to clean than stone. There have also been major changes in types of materials used for buildings, including a wide variety of polymers available for coatings and sealants. In addition, new economic and environmental considerations beyond aesthetic appeal and structural damage are emerging. For example, cool roofs have been designed and constructed to increase reflectance from buildings in urban areas, to decrease both air conditioning needs and urban heat island effects, and these efforts can be impeded by soiling of materials. Sleiman et al. (2014) developed a reliable and repeatable accelerated aging method for roofing products that simultaneously simulates soiling by urban PM and weathering and can be adjusted to local PM composition.

13.4.4 Damage Functions

Dose-response functions and damage functions have been used to quantify material decay as a function of pollutant type and load. The damage function approach follows a number of steps (ApSimon and Cowell, 1996). First, a dose-response function is determined with dose based on either concentration or deposition. Alternatively, damage can be determined from sample surveys or inspection of actual damage (ApSimon and Cowell, 1996). Second, a physical damage function is developed. This can then be linked to the rate of material damage to time of replacement or maintenance. Finally, a cost function links time for replacement and maintenance to a monetary cost, and an economic function links cost to dose of pollution. Figure 13-33 shows an example of how damage functions are used to assess economic damage and replacement costs (ApSimon and Cowell, 1996; Kucera et al., 1993).

Source: Permission pending, Kucera et al. (1993) as cited by ApSimon and Cowell (1996).

Figure 13-33 Damage functions and their use to determine maintenance and replacement costs for materials damaged by SO_2.

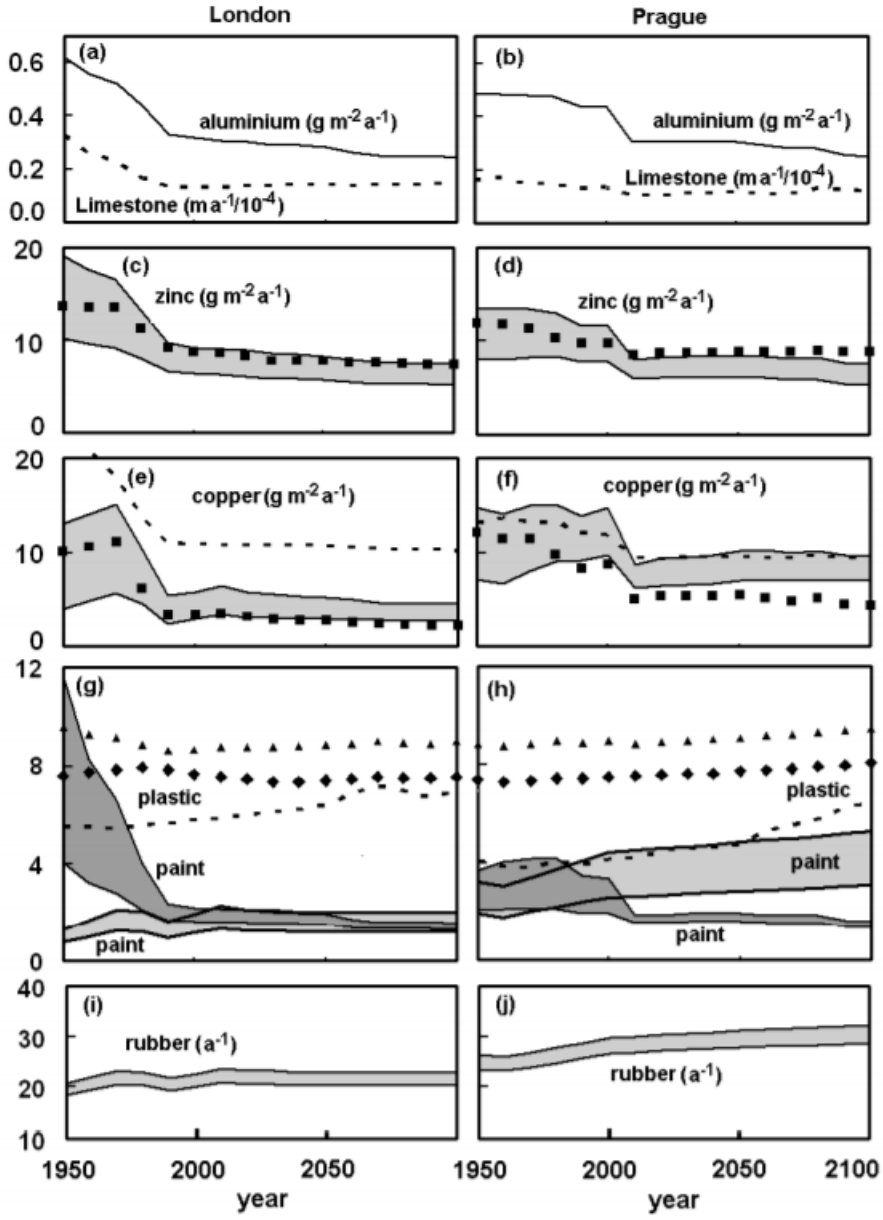
The physical damage function is also difficult to assess because it depends on human perception of the level of soiling to be tolerated. Damage functions based on steady state loss mechanism for erosion have been calculated but did not account for effects of black crusts (Lipfert, 1989). An example of a damage function from Lipfert (1989) is given by Equation 13-9, expressing the loss of calcerous stone in mm thickness as a result of wet deposition of SO_2 in rain with pH of 3−5:

$$Loss/_{m\ rain} = 18.8 + (0.016)H^+ + (0.18)V_d \times \frac{SO_2}{R}$$

Equation 13-9

H^+ is H^+ concentration in rain, V_d is deposition velocity of SO_2, SO_2 is SO_2 concentration in $\mu g/m^3$, and R is rain in m.

Damage functions for aluminum, zinc, copper, plastic, paint, and rubber have also been estimated and applied along with the "Lipfert function" for stone to evaluate potential damage to modern building materials expected in the 21st century. In the process, an extensive list of damage functions for a wide range of building materials from various sources was reviewed and published and used to predict potential damage to various materials under local air pollution and climate conditions, as shown in Figure 13-34 (Brimblecombe and Grossi, 2010).



Source: Permission pending, Brimblecombe and Grossi (2010).

Figure 13-34 Predictions of materials damage to various materials based on damage functions. Rate of damage (rate of mass loss per area in the case of aluminum, limestone, zinc, copper; rate of deterioration for plastic paint and rubber) is shown on the y axis. Years are shown on the x axis.

Damage functions were also used to estimate long-term deterioration of limestone, iron, and copper, and the blackening of stone surfaces in London between 1100−2100 using meteorological and pollution input (Brimblecombe and Grossi, 2009). Deterioration of limestone and possibly copper intensified in the 18th century, and soiling was especially rapid in the 19th century. Based on these observations it was concluded that damage to durable building material is no longer controlled by pollution as in earlier centuries, with natural weathering becoming a more important influence in modern times. However, even as damage to stone and metals from PM have decreased in modern times, potentially higher degradation rates for polymeric materials, plastic, paint, and rubber are predicted due to increased oxidant concentrations and solar radiation (Brimblecombe and Grossi, 2009).

13.4.5 Summary and Causality Determination

The conclusion in the 2009 PM ISA (U.S. EPA, 2009) that PM deposition can result in increased cleaning and maintenance costs and reduced usefulness of soiled material is supported by additional studies detailing new evidence , and there has been steady progress in understanding soiling and corrosion processes and developing approaches to quantify pollutant exposure corresponding to perceived soiling and damage, with respect to pollutant concentration, particle size, and chemical composition. The combination of this evidence further reinforces and supports the conclusion of the 2009 PM ISA of a causal relationship between PM and effects on materials. This section describes the evaluation of evidence for materials effects, with respect to the causality determination, using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015).

Materials damage from particulate matter and other pollutants generally involves one or both of two processes, soiling and corrosion (Section 13.4.2). Soiling is a visible darkening or decrease in reflectance of a material, and corrosion is damage to a material over time caused by chemical reactions with the material surface. Quantitative assessments of materials damage have been carried out by developing dose-response relationships (Section 13.4.3) and applying damage functions (Section 13.4.4), but much of the scientific literature on soiling, corrosion, dose-response relationships and damage functions have focused on stone used for historic monuments and buildings, and there has been a substantial gap in our understanding of processes and quantitative relationships involving other materials. It is still the case that the majority of the literature available on materials damage concerns cultural heritage and stone materials, including differences in elemental composition between crusts on building surfaces and unaffected stone surfaces, as well as documentation of an important role of microbial processes in stone decay.

Although most research on materials damage has concerned stone materials, there has been steady progress in understanding soiling and corrosion processes for glass and metals. These advances include modeling of glass soiling, identifying which pollutants are most influential in metal corrosion in a multipollutant environment, and how that varies between metals. Since the 2009 ISA characterization of

quantitative dose-response relationships and damage functions for materials besides stone has also progressed, with a new dose-response curves published for glass, and a new summary of available materials damage functions. In addition to structural damage, aesthetic qualities, and cleaning costs that are longstanding concerns for PM and air pollution effects, a growing body of research on PM and air pollution impacts concerns energy costs. Applications from climate control and energy consumption of large buildings to efficient operation of photovoltaic systems are influenced by atmospheric soiling. **Overall, the evidence is sufficient to conclude that a causal relationship exists between PM and effects on materials.**

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APPENDIX 1 EVALUATION OF STUDIES ON HEALTH EFFECTS OF PARTICULATE MATTER

This appendix describes the approach used in the Integrated Science Assessment (ISA) for Particulate Matter (PM) to evaluate study quality in the available health effects literature. As described in the Preamble to the ISA (U.S. EPA, 2015), causality determinations were informed by the integration of evidence across scientific disciplines (e.g., exposure, animal toxicology, epidemiology) and related outcomes and by judgments of the strength of inference in individual studies. Table A-1 describes aspects considered in evaluating study quality of controlled human exposure, animal toxicological, and epidemiologic studies. The aspects found in Table A-1 are consistent with current best practices for reporting or evaluating health science data.[86] Additionally, the aspects are compatible with published U.S. EPA guidelines related to cancer, neurotoxicity, reproductive toxicity, and developmental toxicity (U.S. EPA, 2005, 1998, 1996, 1991).

These aspects were not used as a checklist, and judgments were made without considering the results of a study. The presence or absence of particular features in a study did not necessarily lead to the conclusion that a study was less informative or to exclude it from consideration in the ISA. Further, these aspects were not used as criteria for determining causality in the five-level hierarchy. As described in the Preamble, causality determinations were based on judgments of the overall strengths and limitations of the collective body of available studies and the coherence of evidence across scientific disciplines and related outcomes. Table A-1 is not intended to be a complete list of aspects that define a study's ability to inform the relationship between PM and health effects, but it describes the major aspects considered in this ISA to evaluate studies. Where possible, study elements, such as exposure assessment and confounding (i.e., bias due to a relationship with the outcome and correlation with exposures to PM), are considered specifically for PM. Thus, judgments on the ability of a study to inform the relationship between an air pollutant and health can vary depending on the specific pollutant being assessed.

[86]For example, NTP OHAT approach (Rooney et al., 2014), IRIS Preamble (U.S. EPA, 2013), ToxRTool (Klimisch et al., 1997), STROBE guidelines (von Elm et al., 2007), and ARRIVE guidelines (Kilkenny et al., 2010).

Table A-1 Scientific considerations for evaluating the strength of inference from studies on the health effects of particulate matter.

Study Design
Controlled Human Exposure
Studies should clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested. Study subjects should be randomly exposed without knowledge of the exposure condition. Preference is given to balanced crossover (repeated measures) or parallel design studies which include control exposures (e.g., to clean filtered air). In crossover studies, a sufficient and specified time between exposure days should be provided to avoid carry over effects from prior exposure days. In parallel design studies, all arms should be matched for individual characteristics such as age, sex, race, anthropometric properties, and health status. In studies evaluating effects of disease, appropriately matched healthy controls are desired for interpretative purposes.
Animal Toxicology
Studies should clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested. Studies should include appropriately matched control exposures (e.g., to clean filtered air, time matched). Studies should use methods to limit differences in baseline characteristics of control and exposure groups. Studies should randomize assignment to exposure groups and where possible conceal allocation to research personnel. Groups should be subjected to identical experimental procedures and conditions; animal care including housing, husbandry, etc. should be identical between groups. Blinding of research personnel to study group may not be possible due to animal welfare and experimental considerations; however, differences in the monitoring or handling of animals in all groups by research personnel should be minimized.
Epidemiology
Inference is stronger for studies that clearly describe the primary and any secondary aims of the study, or specific hypotheses being tested. For short-term exposure, time-series, case crossover, and panel studies are emphasized over cross-sectional studies because they examine temporal correlations and are less prone to confounding by factors that differ between individuals (e.g., SES, age). Panel studies with scripted exposures, in particular, can contribute to inference because they have consistent, well-defined exposure durations across subjects, measure personal ambient pollutant exposures, and measure outcomes at consistent, well-defined lags after exposures. Studies with large sample sizes and conducted over multiple years are considered to produce more reliable results. Additionally, multi-city studies are preferred over single-city studies because they examine associations large diverse geographic areas using a consistent statistical methodology, avoiding the publication bias often associated with single-city studies[a]. If other quality parameters are equal, multicity studies carry more weight than single-city studies because they tend to have larger sample sizes and lower potential for publication bias. For long-term exposure, inference is considered to be stronger for prospective cohort studies and case-control studies nested within a cohort (e.g., for rare diseases) than cross-sectional, other case-control, or ecologic studies. Cohort studies can better inform the temporality of exposure and effect. Other designs can have uncertainty related to the appropriateness of the control group or validity of inference about individuals from group-level data. Study design limitations can bias health effect associations in either direction.

Table A-1 (Continued): Scientific considerations for evaluating the strength of inference from studies on the health effects of particulate matter.

Study Population/Test Model
Controlled Human Exposure
In general, the subjects recruited into study groups should be similarly matched for age, sex, race, anthropometric properties, and health status. In studies evaluating effects of specific subject characteristics (e.g., disease, genetic polymorphism, etc.), appropriately matched healthy controls are preferred. Relevant characteristics and health status should be reported for each experimental group. Criteria for including and excluding subjects should be clearly indicated. For the examination of populations with an underlying health condition (e.g., asthma), independent, clinical assessment of the health condition is ideal, but self-report of physician diagnosis generally is considered to be reliable for respiratory and cardiovascular disease outcomes[b]. The loss or withdrawal of recruited subjects during the course of a study should be reported. Specific rationale for excluding subject(s) from any portion of a protocol should be explained.
Animal Toxicology
Ideally, studies should report species, strain, substrain, genetic background, age, sex, and weight. Unless data indicate otherwise, all animal species and strains are considered appropriate for evaluating effects of PM exposure. It is preferred that the authors test for effects in both sexes and multiple lifestages, and report the result for each group separately. All animals used in a study should be accounted for, and rationale for exclusion of animals or data should be specified.
Epidemiology
There is greater confidence in results for study populations that are recruited from and representative of the target population. Studies with high participation and low drop-out over time that is not dependent on exposure or health status are considered to have low potential for selection bias. Clearly specified criteria for including and excluding subjects can aid assessment of selection bias. For populations with an underlying health condition, independent, clinical assessment of the health condition is valuable, but self-report of physician diagnosis generally is considered to be reliable for respiratory and cardiovascular diseases[b]. Comparisons of groups with and without an underlying health condition are more informative if groups are from the same source population. Selection bias can influence results in either direction or may not affect the validity of results but rather reduce the generalizability of findings to the target population.
Pollutant
Controlled Human Exposure
Studies should: (1) include a composite measure of PM (i.e., $PM_{2.5}$, $PM_{10-2.5}$, or ultrafine particles [UFP][c]) or (2) apply some approach (e.g., particle trap or filter) to assess the effects of PM in a complex air pollution mixture (i.e., diesel exhaust, gasoline exhaust, wood smoke).
Animal Toxicology
Studies should: (1) include a composite measure of PM (i.e., $PM_{2.5}$, $PM_{10-2.5}$, or ultrafine particles [UFP][c]) or (2) apply some approach (e.g., particle trap or filter) to assess the effects of PM in a complex air pollution mixture (i.e., diesel exhaust, gasoline exhaust, wood smoke).
Epidemiology
Health effects are evaluated primarily using a composite measure of PM (i.e., $PM_{2.5}$, $PM_{10-2.5}$, or ultrafine particles [UFP][c]) from studies using ambient measurements, model predictions, or a combination of measured and modeled data. Studies of PM components must also include a composite measure of PM. Studies of source-related indicators are also evaluated where the indicator is derived using ambient PM concentrations.

Table A-1 (Continued): Scientific considerations for evaluating the strength of inference from studies on the health effects of particulate matter.

Exposure Assessment or Assignment
Controlled Human Exposure
For this assessment, the focus is on studies that utilize PM concentrations <2 mg/m^3. Studies that use higher exposure concentrations may provide information relevant to biological plausibility, dosimetry, or inter-species variation. Studies should have well-characterized pollutant concentration, temperature, and relative humidity and/or have measures in place to adequately control the exposure conditions. Preference is given to balanced crossover or parallel design studies which include control exposures (e.g., to clean filtered air). Study subjects should be randomly exposed without knowledge of the exposure condition. Method of exposure (e.g., chamber, facemask, etc.) should be specified and activity level of subjects during exposures should be well characterized.
Animal Toxicology
For this assessment, the focus is on studies that utilize PM concentrations <2 mg/m^3. Studies that use higher exposure concentrations may provide information relevant to biological plausibility, dosimetry, or inter-species variation. Studies should characterize pollutant concentration, temperature, and relative humidity and/or have measures in place to adequately control the exposure conditions. The focus is on inhalation exposure. Non-inhalation exposure experiments (i.e., intratracheal instillation [IT]) are informative for size fractions (e.g., $PM_{10-2.5}$) that cannot penetrate the airway of a study animal and may provide information relevant to biological plausibility and dosimetry. In vitro studies may be included if they provide mechanistic insight or examine similar effects as in vivo studies, but are generally not included. All studies should include exposure control groups (e.g., clean filtered air).

Table A-1 (Continued): Scientific considerations for evaluating the strength of inference from studies on the health effects of particulate matter.

Epidemiology
Of primary relevance are relationships of health effects with the ambient component of PM exposure. However, information about ambient exposure rarely is available for individual subjects; most often, inference is based on ambient concentrations. Studies that compare exposure assessment methods are considered to be particularly informative. Inference is stronger when the duration or lag of the exposure metric corresponds with the time course for physiological changes in the outcome (e.g., up to a few days for symptoms) or latency of disease (e.g., several years for cancer).
Given that the spatial variability of PM composite measures varies among size fractions, with more homogeneity for $PM_{2.5}$ than either $PM_{10-2.5}$ or UFP, the need for capturing spatial contrasts is stronger for $PM_{10-2.5}$ or UFP compared with $PM_{2.5}$. Validated measurements, whether averaged across multiple monitors or assigned from the nearest or single available monitor, adequately capture temporal or spatial variation in exposure to $PM_{2.5}$ due to the high correlation between personal exposure and ambient concentration. However, for more spatially heterogeneous $PM_{10-2.5}$ and UFP, the spatial correlation between personal exposure and ambient concentrations is lower. Similarly, PM components show increased spatial variability relative to $PM_{2.5}$. In this case, validated methods that capture the extent of variability for the particular study design (temporal vs. spatial contrasts) and location carry greater weight. Inference based on central site measurements can be adequate if correlated with personal exposures, closely located to study subjects, highly correlated across monitors within a location, used in locations with well-distributed sources, or combined with time-activity information.
In studies of short-term exposure, temporal variability of the exposure metric is of primary interest. For all PM size fractions, studies that incorporate time-activity data with personal or microenvironmental monitoring or modeling data may carry greater weight because residential, in-vehicle, and workplace PM exposures may differ in their temporal variability. Results for total personal and indoor PM exposure are other lines of evidence that may inform judgments about causality of PM because inference is based on an individual's microenvironmental exposures and the potential for copollutant confounding may be reduced compared to ambient exposures. Results for total personal exposure can inform understanding of the effects of ambient exposure when well correlated with ambient concentrations.
For long-term exposures, methods that well represent within-community spatial variation in individual exposure may be given more weight for spatially-variable ambient $PM_{10-2.5}$ or ultrafine particles. For $PM_{2.5}$, within-community variation in exposure is less important given that $PM_{2.5}$ tends to be more homogeneous.
Exposure measurement error often attenuates health effect estimates or increases the imprecision of the association (i.e., width of 95% CIs), particularly associations based on temporal variation in short-term exposure. However, exposure measurement error can bias estimates away from the null in some epidemiologic studies of long-term exposures where the PM size fraction is more spatially heterogeneous (i.e., $PM_{10-2.5}$ or UFP), depending on the locations of the monitor and sources with respect to the study population.
To streamline the health effects discussion on studies that are most policy-relevant, for those health categories where the 2009 PM ISA concluded a "causal relationship" the focus is on studies with mean $PM_{2.5}$ concentrations <20 $\mu g/m^3$. However, studies that examine a previously identified uncertainty or limitation in the evidence are evaluated even if mean $PM_{2.5}$ concentrations are >20 $\mu g/m^3$.
Outcome Assessment/Evaluation
Controlled Human Exposure
Endpoints should be assessed in the same manner for control and exposure groups (e.g., time after exposure, methods, endpoint evaluator) using valid, reliable methods. Blinding of endpoint evaluators is ideal, especially for qualitative endpoints (e.g., histopathology). For each experiment and each experimental group, including controls, precise details of all procedures carried out should be provided including how, when, and where. Time of the endpoint evaluations is a key consideration that will vary depending on endpoint evaluated. Endpoints should be assessed at time points that are appropriate for the research questions.

Table A-1 (Continued): Scientific considerations for evaluating the strength of inference from studies on the health effects of particulate matter.

Animal Toxicology
Endpoints should be assessed in the same manner for control and exposure groups (e.g., time after exposure, methods, endpoint evaluator) using valid, reliable methods. Blinding of endpoint evaluators is ideal, especially for qualitative endpoints (e.g., histopathology). For each experiment and each experimental group, including controls, precise details of all procedures carried out should be provided including how, when, and where. Time of the endpoint evaluations is a key consideration that will vary depending on endpoint evaluated. Endpoints should be assessed at time points that are appropriate for the research questions.
Epidemiology
Inference is stronger when outcomes are assessed or reported without knowledge of exposure status. Knowledge of exposure status could produce artefactual associations. Confidence is greater when outcomes assessed by interview, self-report, clinical examination, or analysis of biological indicators are defined by consistent criteria and collected by validated, reliable methods. Independent, clinical assessment is valuable for outcomes such as lung function or incidence of disease, but report of physician diagnosis has shown good reliability[b]. When examining short-term exposures, evaluation of the evidence focuses on specific lags based on the evidence presented in individual studies. Specifically, the following hierarchy is used in the process of selecting results from individual studies to assess in the context of results across all studies for a specific health effect or outcome: • Distributed lag models; • Average of multiple days (e.g., 0−2); • If a priori lag days were used by the study authors these are the effect estimates presented; or • If a study focuses on only a series of individual lag days, expert judgment is applied to select the appropriate result to focus on considering the time course for physiologic changes for the health effect or outcome being evaluated. When health effects of long-term exposure are assessed by acute events such as symptoms or hospital admissions, inference is strengthened when results are adjusted for short-term exposure. Validated questionnaires for subjective outcomes such as symptoms are regarded to be reliable[c], particularly when collected frequently and not subject to long recall. For biological samples, the stability of the compound of interest and the sensitivity and precision of the analytical method is considered. If not based on knowledge of exposure status, errors in outcome assessment tend to bias results toward the null.
Potential Copollutant Confounding
Controlled Human Exposure
Exposure should be well characterized to evaluate independent effects of PM of various size fractions. Studies should apply some approach (e.g., particle trap or filter) to assess the effects of PM when examining exposures to complex air pollution mixtures (i.e., diesel exhaust, gasoline exhaust, wood smoke).
Animal Toxicology
Exposure should be well characterized to evaluate independent effects of PM of various size fractions. Studies should apply some approach (e.g., particle trap or filter) to assess the effects of PM when examining exposures to complex air pollution mixtures (i.e., diesel exhaust, gasoline exhaust, wood smoke).

Table A-1 (Continued): Scientific considerations for evaluating the strength of inference from studies on the health effects of particulate matter.

Epidemiology
Not accounting for potential copollutant confounding can produce artefactual associations; thus, studies that examine copollutant confounding carry greater weight. The predominant method is copollutant modeling (i.e., two-pollutant models), which is especially informative when correlations are not high. However, when correlations are high (r > 0.7), such as those often encountered for UFP and other traffic-related copollutants, copollutant modeling is less informative. Although the use of single-pollutant models to examine the association between PM and a health effect or outcome are informative, ideally studies should also include copollutant analyses. Copollutant confounding is evaluated on an individual study basis considering the extent of correlations observed between the copollutant and PM, and relationships observed with PM and health effects in copollutant models.
Other Potential Confounding Factors[d]
Controlled Human Exposure
Preference is given to studies utilizing experimental and control groups that are matched for individual level characteristics (e.g., race/ethnicity, sex, body weight, smoking history, age) and time varying factors (e.g., seasonal and diurnal patterns).
Animal Toxicology
Preference is given to studies utilizing experimental and control groups that are matched for individual level characteristics (e.g., strain, sex, body weight, litter size, food and water consumption) and time varying factors (e.g., seasonal and diurnal patterns).
Epidemiology
Factors are considered to be potential confounders if demonstrated in the scientific literature to be related to health effects and correlated with PM. Not accounting for confounders can produce artefactual associations; thus, studies that statistically adjust for multiple factors or control for them in the study design are emphasized. Less weight is placed on studies that adjust for factors that mediate the relationship between PM and health effects, which can bias results toward the null. Confounders vary according to study design, exposure duration, and health effect and may include, but are not limited to the following: Short-term exposure studies: Meteorology, day of week, season, medication use, allergen exposure, and long-term temporal trends. Long-term exposure studies: Socioeconomic status, race, age, medication use, smoking status, stress, noise, and occupational exposures.
Statistical Methodology
Controlled Human Exposure
Statistical methods should be clearly described and appropriate for the study design and research question (e.g., correction for multiple comparisons). Generally, statistical significance is used to evaluate the findings of controlled human exposure studies. However, consistent trends are also informative. Detection of statistical significance is influenced by a variety of factors including, but not limited to, the size of the study, exposure and outcome measurement error, and statistical model specifications. Sample size is not a criterion for exclusion; ideally, the sample size should provide adequate power to detect hypothesized effects (e.g., sample sizes less than 3 are considered less informative). Because statistical tests have limitations, consideration is given to both trends in data and reproducibility of results.

Table A-1 (Continued): Scientific considerations for evaluating the strength of inference from studies on the health effects of particulate matter.

Animal Toxicology
Statistical methods should be clearly described and appropriate for the study design and research question (e.g., correction for multiple comparisons). Generally, statistical significance is used to evaluate the findings of animal toxicology studies. However, consistent trends are also informative. Detection of statistical significance is influenced by a variety of factors including, but not limited to, the size of the study, exposure and outcome measurement error, and statistical model specifications. Sample size is not a criterion for exclusion; ideally, the sample size should provide adequate power to detect hypothesized effects (e.g., sample sizes less than 3 are considered less informative). Because statistical tests have limitations, consideration is given to both trends in data and reproducibility of results.
Epidemiology
Multivariable regression models that include potential confounding factors are emphasized. However, multipollutant models (more than two pollutants) are considered to produce too much uncertainty due to copollutant collinearity to be informative. Models with interaction terms aid in the evaluation of potential confounding as well as effect modification. Sensitivity analyses with alternate specifications for potential confounding inform the stability of findings and aid in judgments of the strength of inference from results. In the case of multiple comparisons, consistency in the pattern of association can increase confidence that associations were not found by chance alone. Statistical methods that are appropriate for the power of the study carry greater weight. For example, categorical analyses with small sample sizes can be prone to bias results toward or away from the null. Statistical tests such as *t*-tests and Chi-squared tests are not considered sensitive enough for adequate inferences regarding PM-health effect associations. For all methods, the effect estimate and precision of the estimate (i.e., width of 95% CI) are important considerations rather than statistical significance.

[a](U.S. EPA, 2008).

[b]Murgia et al. (2014); Weakley et al. (2013); Yang et al. (2011); Heckbert et al. (2004); Barr et al. (2002); Muhajarine et al. (1997); Toren et al. (1993); Burney et al. (1989).

[c]UFPs are defined as particles <100 nm in size, but studies often include size fractions larger than 100 nm in the assessment of the relationship between UFP exposure and health effects.

[d]Many factors evaluated as potential confounders can be effect measure modifiers (e.g., season, comorbid health condition) or mediators of health effects related to PM (comorbid health condition).

the relationship between an air pollutant and health can vary depending on the specific pollutant being assessed.

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