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Integrated Science Assessment for Sulfur Oxides – Health Criteria

(Second External Review Draft)

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Integrated Science Assessment for Sulfur Oxides – Health Criteria

National Center for Environmental Assessment-RTP Division
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Abbreviations and Acronyms

A	Alpha
ACS	American Cancer Society
ADS	annular denuder system
AHR	airways hyperreactiveness
AM	alveolar macrophages
APHEA	Air Pollution on Health: a European Approach (study)
APEX	Air Pollution Exposure (model)
APIMS	atmospheric pressure ionization mass spectrometer
ARIC	Atherosclerosis Risk in Communities (study)
ARP	Acid Rain Program
AQCD	Air Quality Criteria Document
asl	above sea level
atm	Atmosphere
β	beta; the calculated Health Effect Parameter
B[*a*]P	benzo[*a*]pyrene
BHR	bronchial hyperresponsiveness
BS	black smoke
CAMP	Childhood Asthma Management Program
CARB	California Air Resources Board
CASAC	Clean Air Scientific Advisory Committee
CASTNet	Clean Air Status and Trends Network
CDC	Centers for Disease Control and Prevention
CHAD	Consolidated Human Activities Database
CHF	congestive heart failure
CHS	Children's Health Study
CH_3-S-H	methyl mercaptan
CH_3-S-S-CH_3	dimethyl disulfide
CI	confidence interval
CMSA	consolidated metropolitan statistical area
CO	carbon monoxide
CoH	coefficient of haze
CONUS	continental United States
COPD	chronic obstructive pulmonary disease
CS_2	carbon disulfide
CVD	cardiovascular disease
DEN	diethylnitrosamine
DEP	diesel exhaust particle
DMS	dimethyl sulfide
ED	emergency department
ECG	electrocardiography; electrocardiogram
EIB	exercise-induced bronchial reactivity
ELF	epithelial lining fluid

EMECAM	Spanish Multicentre Study on Air Pollution and Mortality
EPA	U.S. Environmental Protection Agency
eNO	exhaled nitric oxide
ET	extrathoracic
Fe	iron
FEMs	Federal Equivalent Methods
$FEV_{0.75}$	forced expiratory volume in 0.75 second
FEV_1	forced expiratory volume in 1 second
FPD	flame photometric detection
FPD-TA	flame photometric detection-thermal analysis
FRM	Federal Reference Method
FVC	forced vital capacity
GAM	Generalized Additive Model(s)
GIS	Geographic Information System
GLM	Generalized Linear Model(s)
GSH	glutathione; reduced glutathione
GST	glutathione *S*-transferase (e.g., GSTM1, GSTP1, GSTT1)
H^+	hydrogen ion
HEADS	Harvard-EPA Annular Denuder System
HEI	Health Effects Institute
HF	high frequency
HNO_2	nitrous acid
HNO_3	nitric acid
HO_2	hydroperoxyl; hydroperoxy radical
H_2O	water
H_2O_2	hydrogen peroxide
HR	heart rate
HRV	heart rate variability
H_2S	hydrogen sulfide
HSO_3^-	hydrogen sulfite, bisulfite
HSO_4^-	bisulfate ion
H_2SO_4	sulfuric acid
h*v*	solar ultraviolet photon
IARC	International Agency for Research on Cancer
ICD9	International Classification of Diseases, Ninth Revision
ICDs	implanted cardioverter defibrillators
Ig	immunoglobulin (e.g., IgA, IgE, IgG)
IHD	ischemic heart disease
IIASA	International Institute for Applied Systems Analysis
IL	interleukin (e.g., IL-4, IL-6, IL-8)
IOM	Institute of Medicine
IQR	interquartile range
ISA	Integrated Science Assessment
ISAAC	International Study of Asthma and Allergies in Children

IUGR	intrauterine growth retardation
K	mass transfer coefficient
LF	low frequency
LOD	limit of detection
LRD	lower respiratory disease
MCh	methacholine
MENTOR	Modeling Environment for Total Risk for One-Atmosphere studies
MI	myocardial infarction
$MEF_{50\%}$	maximal midexpiratory flow at 50% of forced vital capacity
MMEF	maximal midexpiratory flow
Mn	manganese
MONICA	Monitoring Trend and Determinants in Cardiovascular Disease (registry)
MOZART-2	Model for Ozone and Related Chemical Tracers, version 2
MSA	metropolitan statistical area
N, n	number of observations
NAAQS	National Ambient Air Quality Standards
NaCl	sodium chloride
$NaCO_3$	sodium carbonate
NADP	National Atmospheric Deposition Program
NAMS	National Air Monitoring Stations
NAPAP	National Acid Precipitation Assessment Program
NAS	National Academy of Sciences
NCAR	National Center for Atmospheric Research
NCEP	National Center for Environmental Prediction
NCICAS	National Cooperative Inner-City Asthma Study
NCore	National Core Monitoring Network
NERL	National Exposure Research Laboratory
NH_4^+	ammonium ion
NHAPS	National Human Activity Pattern Survey
NHANES	National Health and Nutrition Examination Survey
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NO	nitric oxide
NO_2	nitrogen dioxide
NO_3	nitrate radical
NO_3^-	nitrate ion
NOAA	National Oceanic and Atmospheric Administration
NO_x	oxides of nitrogen
NR	not reported
NRC	National Research Council
NTN	National Trends Network
NTP	National Toxicology Program
O_2	molecular oxygen, diatomic oxygen
O_3	ozone
OCS	carbonyl sulfide

OH	hydroxyl radical
OR	odds ratio
P, p	probability value
PAARC	Air Pollution and Chronic Respiratory Diseases (study)
PAH	polycyclic aromatic hydrocarbon
PC(SO_2)	provocative concentration of SO_2 that produces a 100% increase in specific airway resistance
PD20FEV_1	20% decrease in forced expiratory volume in 1 second
PD20	provocative dose that produces a 20% decrease in FEV_1
PD100	provocative dose that produces a 100% increase in sRAW
PEACE	Pollution Effects on Asthmatic Children in Europe (study)
PEC	pulmonary endocrine cell
PEF	peak expiratory flow
PEMs	personal exposure monitors
PF	pulsed fluorescence
PM	particulate matter
$PM_{2.5}$	particulate matter with 50% upper cut point aerodynamic diameter of 2.5 µm for sample collection; surrogate for fine PM
PM_{10}	particulate matter with 50% upper cut point aerodynamic diameter of 10 µm for sample collection
$PM_{10-2.5}$	particulate matter with 10 µm as upper cut point aerodynamic diameter and 2.5 µm as lower cut point for sample collection; surrogate for thoracic coarse PM (does not include fine PM)
PM_{13}	particulate matter with 50% upper cut point aerodynamic diameter of 13 µm for sample collection
PMT	photomultiplier tube
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
pptv	parts per trillion by volume
PRB	policy relevant background
PS	passive sample
R, r	correlation coefficient
RAR	rapidly activating receptor
RAS	roll-around system
Raw	airway resistance
RH	relative humidity
r-MSSD	root mean square of successive differences in R-R intervals.
RR	rate ratio; relative risk
S^{2-}	sulfur radical
SAB	Science Advisory Board
SAPALDIA	Study of Air Pollution and Lung Diseases in Adults
SAVIAH	Small-Area Variation in Air Pollution and Health (study)
SD	standard deviation
SDNN	standard deviation of normal R-R intervals
SES	socioeconomic status

SHEDS	Simulation of Human Exposure and Dose System
SIDS	sudden infant death syndrome
SNP	single nucleotide polymorphism
^{35}S	sulfur-35 radionuclide
SLAMS	State and Local Air Monitoring Stations
SO	sulfur monoxide
SO_2	sulfur dioxide
SO_3	sulfur trioxide
SO_3^{2-}	sulfite ion
SO_4^{2-}	sulfate ion
SO_x	sulfur oxides
S_2O	disulfur monoxide
SPM	suspended particulate matter
sRaw	specific airway resistance
STN	Speciation Trends Network
τ	tau; atmospheric lifetime
TBARS	thiobarbituric acid reactive substances
TEA	triethanolamine
TNF	tumor necrosis factor (e.g., TNF-α)
TSP	total suspended particles
URI	upper respiratory infections
UV	ultraviolet
$\dot{V}_E$	minute ventilation

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Preface

Legislative Requirements

Section 109 (42 U.S. Code, 2003b) directs the Administrator to propose and promulgate "primary" and "secondary" National Ambient Air Quality Standards (NAAQS) for pollutants listed under section 108. 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."[1] 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 required to protect the public welfare from any known or anticipated adverse effects associated with the presence of [the] pollutant in the ambient air."[2] The requirement that primary standards include 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. See *Lead Industries Association v. EPA*, 647 F.2d 1130, 1154 (D.C. Cir 1980), cert. denied, 449 U.S. 1042 (1980); *American Petroleum Institute v. Costle*, 665 F.2d 1176, 1186 (D.C. Cir. 1981) cert. denied, 455 U.S. 1034 (1982). Both kinds of uncertainties 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 include 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.

In selecting a margin of safety, the EPA considers such factors as the nature and severity of the health effects involved, the size of sensitive population(s) at risk, and the kind and degree of the uncertainties that must be addressed. The selection of any particular approach to providing an adequate margin of safety is a policy choice left specifically to the Administrator's judgment. See *Lead Industries Association v. EPA*, supra, 647 F.2d at 1161-62.

[1] 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)]. (Senate., 1970)

[2] Welfare effects as defined in section 302(h) [42 U.S.C. 7602(h)] include, but are 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."

In setting standards that are "requisite" to protect public health and welfare, as provided in section 109(b), EPA's task is to establish standards that are neither more nor less stringent than necessary for these purposes. In so doing, EPA may not consider the costs of implementing the standards. See generally *Whitman v. American Trucking Associations*, 531 U.S. 457, 465472, 475-76 (D.C. Cir. 2001).

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) of EPA's Science Advisory Board.

History of Reviews of the Primary NAAQS for Sulfur Oxides

On April 30, 1971, the EPA promulgated primary NAAQS for sulfur oxides (SO_x). These primary standards, which were based on the findings outlined in the original 1969 Air Quality Criteria for Sulfur Oxides, were set at 0.14 parts per million (ppm) averaged over a 24-hour period, not to be exceeded more than once per year, and 0.030 ppm annual arithmetic mean with SO_2 as the indicator. In 1982, EPA published the *Air Quality Criteria for Particulate Matter and Sulfur Oxides* (EPA, 1982) along with an addendum of newly published controlled human exposure studies, which updated the scientific criteria upon which the initial standards were based. In 1986, a second addendum was published presenting newly available evidence from epidemiologic and controlled human exposure studies (EPA, 1986b). In 1988, EPA published a proposed decision not to revise the existing standards (53 FR 14926). However, EPA specifically requested public comment on the alternative of revising the current standards and adding a new 1-hour primary standard of 0.4 ppm.

As a result of public comments on the 1988 proposal and other post-proposal developments, EPA published a second proposal on November 15, 1994 (59 FR 58958). The

1994 re-proposal was based in part on a supplement to the second addendum of the criteria document, which evaluated new findings on short-term SO_2 exposures in asthmatics (EPA, 1994b). As in the 1988 proposal, EPA proposed to retain the existing 24-hour and annual standards. The EPA also solicited comment on three regulatory alternatives to further reduce the health risk posed by exposure to high 5-minute peaks of SO_2 if additional protection were judged to be necessary. The three alternatives were: 1) revising the existing primary SO_2 NAAQS by adding a new 5-minute standard of 0.60 ppm SO_2; 2) establishing a new regulatory program under section 303 of the Act to supplement protection provided by the existing NAAQS, with a trigger level of 0.60 ppm SO_2, one expected exceedance; and 3) augmenting implementation of existing standards by focusing on those sources or source types likely to produce high 5-minute peak concentrations of SO_2. On May 22, 1996, EPA's final decision, that revisions of the NAAQS for SO_x were not appropriate at that time, was announced in the Federal Register (61 FR 25566). In that decision, EPA announced an intention to propose guidance, under section 303 of the Act, to assist states in responding to short-term peak levels of SO_2. The basis for the decision, and subsequent litigation, is discussed in Annex A.

Chapter 1. Introduction

This second external review draft Integrated Science Assessment (ISA) presents a concise synthesis of the most policy-relevant science to form the scientific foundation for the review of the primary (health-based) NAAQS for SO_x. This document is intended to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health which may be expected from the presence of [a] pollutant in ambient air" (Clean Air Act, Section 108, 2003a)[1]. Contained herein are the key information and judgments formerly contained in the Air Quality Criteria Document (AQCD) for SO_x; additional details of the pertinent scientific literature published since the last review, as well as selected older studies of particular interest, are included in a series of annexes to the draft ISA. This second external review draft ISA thus serves to update and revise the information available at the time of the previous review of the NAAQS for SO_x in 1996.

SO_2 is the most important of the monomeric sulfur oxides (SO_x) for both atmospheric chemistry and health effects. SO_x is usually defined to include SO_3 and H_2SO_4 as well, but neither is present in the atmosphere in concentrations significant for human exposures. Descriptions of the atmospheric chemistry of SO_x include both gaseous and particulate species; a meaningful analysis would not be possible otherwise. Most studies on the health effects of gaseous SO_x focus on SO_2; effects of other gaseous species are considered as information is available. The health effects of particulate SO_x are included in the review of the NAAQS for particulate matter (PM). In evaluating the health evidence, this second external draft ISA considers possible influences of other atmospheric pollutants, including interactions of SO_2 with other co-occurring pollutants such as PM, nitrogen oxides (NO_x), carbon monoxide (CO), and ozone (O_3).

As discussed in the Integrated Plan for Review of the Primary NAAQS for SO_x (EPA, 2007), a series of policy-relevant questions frames this review to provide a scientific basis for a decision about whether the current primary NAAQS for SO_x should be retained or revised. The primary NAAQS for SO_x, with SO_2 serving as the indicator, is set at 0.14 parts per million (ppm), averaged over a 24-h period, not to be exceeded more than once per year, and 0.030 ppm annual arithmetic mean. This second external review draft ISA focuses on evaluation of the newly

[1]A review of the secondary SO_x NAAQS, in conjunction with a review of the secondary NAAQS for NO_x, is underway independently, as is a review of the primary NAAQS for NO_x and a review of the primary and secondary effects of PM.

available scientific evidence to best inform consideration of these framing questions, including the following:

- How has new information altered/substantiated the scientific support for the occurrence of health effects following short- and/or long-term exposure to levels of SO_x found in the ambient air?
- How does new information influence conclusions from the previous review regarding the effects of SO_x on susceptible populations?
- At what levels of SO_x exposure do health effects of concern occur?
- How has new information altered conclusions from previous reviews regarding the plausibility of adverse health effects caused by SO_x exposure?
- To what extent have important uncertainties identified in the last review been reduced? Have new uncertainties emerged?
- What are the air quality relationships between short-term and long-term exposures to SO_x?

1.1. Document Development

EPA initiated the current formal review of the NAAQS for SO_x on May 15, 2006 with a call for information from the public (FR, 2006). In addition to the call for information, publications are identified through an ongoing literature search process that includes extensive computer database mining on specific topics. Additional publications were identified by EPA scientists in a variety of disciplines by combing through relevant, peer-reviewed scientific literature obtained through these ongoing literature searches, reviewing previous EPA reports, and a review of reference lists from important publications. All relevant epidemiological, human clinical, and animal toxicological studies, including those related to exposure-response relationships, mechanism(s) of action, or susceptible subpopulations published since the last review were considered. Added to the body of research were EPA's analyses of air quality and emissions data, studies on atmospheric chemistry, transport, and fate of these emissions, as well as issues related to exposure to SO_x. Further information was acquired from consultation with content and area experts and the public. Annex A has more discussion of search strategies and criteria for study selection.

1.2. Document Organization

This second external review draft ISA is composed of five chapters. This introductory chapter presents background information, discusses the purpose of the document, and characterizes the search, evaluation and retrieval process of policy-relevant scientific studies. Chapter 2 highlights key concepts or issues relevant to understanding the atmospheric chemistry, sources, exposure, and dosimetry of SO_x, following a "source-to-dose" paradigm. Chapter 3 evaluates and integrates epidemiological, human clinical, and animal toxicological information relevant to the review of the primary NAAQS for SO_x. Chapter 4 has information related to the public health impact of ambient SO_x exposure, with emphasis on potentially susceptible and vulnerable population groups. Finally, Chapter 5 summarizes key findings and conclusions from the atmospheric sciences, ambient air data analyses, exposure assessment, dosimetry, and health effects for consideration in the review of the NAAQS for SO_x.

A series of annexes supplement this second external review draft ISA. The annexes provide additional details of the pertinent literature published since the last review, as well as selected older studies of particular interest. These annexes contain information on:

- atmospheric chemistry of SO_x as well as the sampling and analytic methods for measurement of SO_x[1];
- environmental concentrations and human exposure to SO_x;
- toxicological studies of health effects in laboratory animals;
- human clinical studies of health effects related to peak (5-10 min) and short-term (1-h or longer) exposure to SO_x; and
- epidemiological studies of health effects from short- and long-term exposure to SO_x.

Detailed information about methods and results of health studies is summarized in tabular format, and generally includes information about: concentrations of SO_x and averaging times; study methods employed; results and comments; and quantitative results for relationships between effects and exposure to SO_x.

[1] This section also includes information on NO_2, in order to support the reviews of the primary and secondary NAAQS for both SO_2 and NO_2. The atmospheric chemistry of NO_x and SO_x are intricately linked; discussion of their combined chemistry is more effective and more efficient than a separate discussion of each pollutant.

1.3. EPA Framework for Causal Determinations

It is important to have a consistent and transparent basis to evaluate the causal nature of air pollution-induced health effects. The framework described below establishes uniform language concerning causality and brings more specificity to the findings. It draws standardized language from across the Federal government and wider scientific community, especially from the recent National Academy of Sciences (NAS) Institute of Medicine (IOM) document, *Improving the Presumptive Disability Decision-Making Process for Veterans* (IOM, 2007), the most recent comprehensive work on evaluating the causality of health effects. This section:

- describes the kinds of scientific evidence used in establishing a general causal relationship between exposure and health effects;
- defines cause, in contrast to statistical association;
- discusses the sources of evidence necessary to reach a conclusion about the existence of a causal relationship;
- highlights the issue of multifactorial causation;
- identifies issues and approaches related to uncertainty; and
- provides a framework for classifying and characterizing the weight of evidence in support of a general causal relationship.

Approaches to assessing the separate and combined lines of evidence (e.g., epidemiological, human clinical, animal toxicological, and in vitro studies) have been formulated by a number of regulatory and science agencies, including the IOM of the National Academies of Science (IOM, 2008), International Agency for Research on Cancer (IARC, 2006), EPA Guidelines for Carcinogen Risk Assessment (EPA, 2005), Centers for Disease Control and Prevention (CDC, 2004), and National Acid Precipitation Assessment Program (NAPAP, 1991). Highlights or excerpts from the various decision framework documents are included in Annex A.

These formalized approaches offer guidance for assessing causality. The frameworks are similar in nature, although adapted to different purposes, and have proved effective in providing a uniform structure and language for causal determinations. Moreover, these frameworks must support decision-making under conditions of uncertainty.

1.3.1. Scientific Evidence Used in Establishing Causality

The most compelling evidence of a causal relationship between pollutant exposures and human health effects comes from human clinical studies. This type of study experimentally evaluates the health effects of administered exposures in humans under highly-controlled laboratory conditions.

In epidemiological or observational studies of humans, the investigator does not control exposures or intervene with the study population. Broadly, observational studies can describe associations between exposures and effects. These studies fall into several categories: cross-sectional, prospective cohort, time-series, and panel studies. "Natural experiments" occur occasionally in epidemiology; these include comparisons of health effects before and after a change in population exposures, such as closure of a pollution source.

Experimental animal data complements the clinical and observational data; these studies can help characterize effects of concern, exposure-response relationships, sensitive subpopulations and modes of action. In the absence of clinical or epidemiological data, animal data alone may be sufficient to support a likely causal determination, assuming that humans respond similarly to the experimental species.

1.3.2. Association and Causation

Association and causation are not the same. "Cause" conveys the notion of a significant, effectual relationship between an agent and an associated disorder or disease in the population. "Association" is the statistical dependence among multiple (two or more) events, characteristics, or other variables. An association is merely prima facie evidence for causation; alone, it is not sufficient for proof of a causal relationship between exposure and disease. Unlike an association, a causal claim supports the creation of counterfactual claims; that is, a claim about what the world would have been like under different or changed circumstances (IOM, 2008). Currently, much of the newly available health information evaluated in the draft ISA comes from epidemiological studies that report a statistical association between exposure and health outcome.

It is recognized that many of the health outcomes evaluated in ISAs have complex etiologies. Most diseases, such as cancer or coronary heart disease, result from a complex web of causation, whereby one or more agents can initiate a disease process. The outcome could depend

on many factors, including age, genetic susceptibility, nutritional status, immune competence, social factors, and others (Gee and Payne-Sturges, 2004; IOM, 2008). Figure 1-1 shows a diagram of a variety of etiologic factors that contribute to disease. Exposure to multiple agents together could result in synergistic or antagonistic effects that are different from what might result from exposure to each agent separately.[1] The results are the net effect of many actions and counteractions.

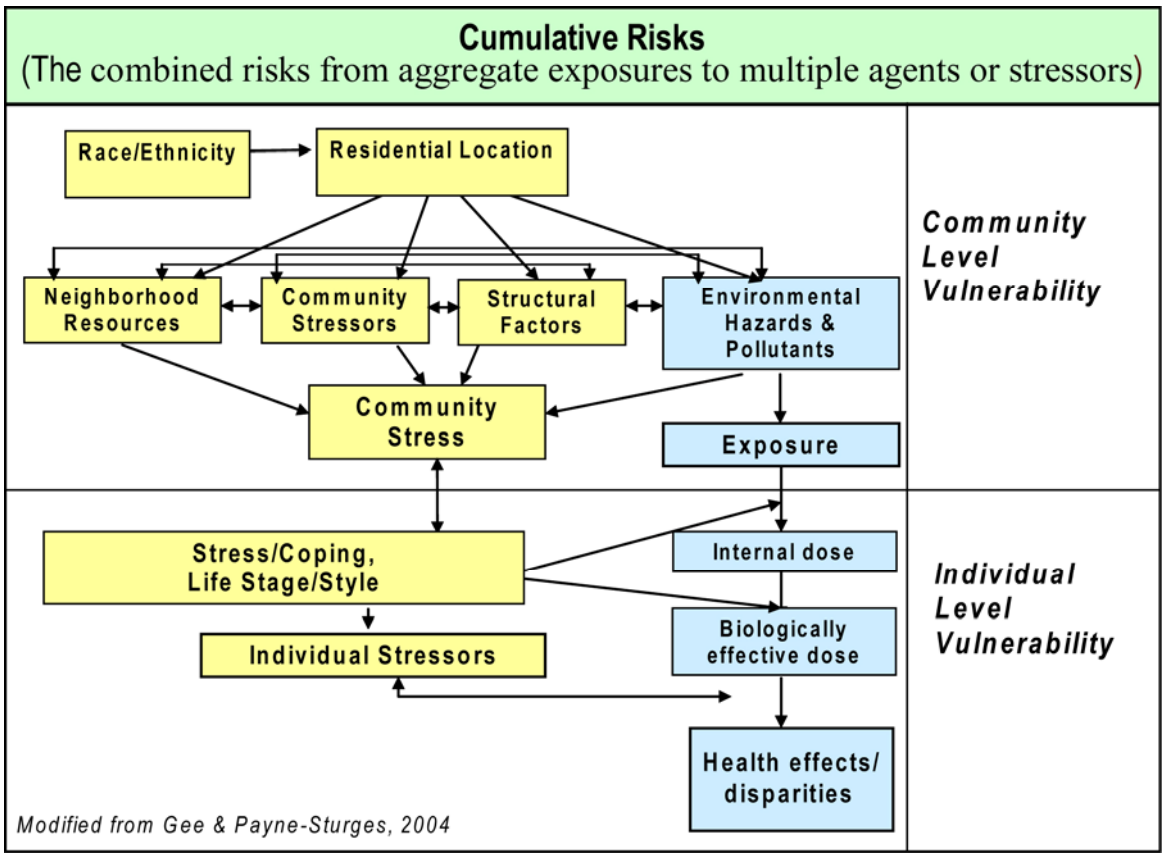

Figure 1-1. Exposure–disease–stress model for environmental health disparities.

1.3.3. Evidence for Going beyond Association to Causation

Moving from association to causation involves elimination of alternative explanations for the association. Human clinical studies are experiments in which subjects in a population are

[1] For example, a multiplicative interaction relative risk (RR) could be defined as $RR_{Int(mult)} = RR_{joint}/RR_E \times RR_S$. An additive interaction RR could bedefined as $RR_{Int(add)} = RR_{joint} - RR_E - RR_S + 1$

randomly allocated into groups, usually called study and control groups, and exposed to a pollutant or a sham. The results are assessed by rigorous comparison of rates of appropriate outcomes between the study and control groups. Randomized human clinical studies are generally regarded as the most scientifically rigorous method of hypothesis testing available. By assigning exposure randomly, the study design attempts to remove the effect of any factor that might influence exposure. Done properly, and setting aside randomness, only a causal relationship between exposure and health outcome should produce observed associations in randomized clinical trials. In another type of human clinical study, the same subject is exposed to a pollutant and a sham at different time points, and the responses to the two types of exposures are compared. This study design is also effective at controlling for any potential confounders, since the subject is serving as his/her own control. A lack of observation of effects from human clinical studies does not necessarily mean that a causal relationship does not occur. Human clinical studies are often limited because the study population is generally small, which restricts the ability to discern statistically significant findings. In addition, the most susceptible individuals may be explicitly excluded (for ethical reasons), and other susceptible individuals or groups, such as those with nutritional deficits, may not be included.

Inferring causation from epidemiological studies requires consideration of potential confounders. When associations are found in epidemiological studies, one approach to remove spurious association from possible confounders is statistical control on characteristics that may differ between exposed and unexposed persons; this is frequently termed "adjustment." Multivariable regression models constitute one tool for estimating the association between exposure and outcome after adjusting for characteristics of participants that might confound the results. Another way to adjust for potential confounding is through stratified analysis, i.e., examining the association within homogeneous groups with the confounding variable. The use of stratified analyses has an additional benefit: it allows examination of effect modification through comparison of the effect estimates across different groups. If investigators successfully measured characteristics that distort the results, adjustment of these factors help separate a spurious from a true causal association. Appropriate statistical adjustment for confounders requires identifying and measuring all reasonably expected confounders. Deciding which variables to control for in a statistical analysis of the association between exposure and disease depends on knowledge about

possible mechanisms. Identifying these mechanisms makes it possible to control for potential sources that may result in a spurious association.

Measurement error is another problem encountered when adjusting for spurious associations. In multivariate analyses, the effects of a well-measured covariate may be overestimated, in contrast to a more poorly measured covariate. There are several components that contribute to exposure measurement error in these studies, including the difference between true and measured ambient concentrations, the difference between average personal exposure to ambient pollutants and ambient concentrations at central monitoring sites, and the use of average population exposure rather than individual exposure estimates.

It is difficult to identify and measure all potential confounders in epidemiological studies. Confidence that unmeasured confounders are not producing the findings is increased when multiple studies are conducted in various settings using different subjects or exposures; each of which might eliminate another source of confounding from consideration. Thus, multi-city studies which use a consistent method to analyze data from across locations with different levels of covariates can provide insight on potential confounding in associations. The number and degree of diversity of covariates, as well as their relevance to the potential confounders, remain matters of scientific judgment. Intervention studies, because of their experimental nature, can be particularly useful in characterizing causation.

In addition to clinical and epidemiological studies, the tools of experimental biology have been valuable for developing insights into human physiology and pathology. Laboratory tools have been extended to explore the effects of putative toxicants on human health, especially through the study of model systems in other species. Background knowledge of the biological mechanisms by which an exposure might or might not cause disease can prove crucial in establishing, or negating, a causal claim. At the same time, species can differ from each other in fundamental aspects of physiology and anatomy (e.g., metabolism, airway branching, hormonal regulation) that may limit extrapolation. Testable hypotheses about the causal nature of proposed mechanisms or modes of action are central to utilizing experimental data in causal determinations.

1.3.4. Multifactorial Causation

Scientific judgment is needed regarding likely sources and magnitude of confounding, together with judgment about how well the existing constellation of study designs, results, and analyses address this potential threat to inferential validity. One key consideration in this review is evaluation of the potential contribution of SO_x to health effects, when it is a component of a complex air pollutant mixture. There are multiple ways by which SO_x might cause or be associated with adverse health effects. First, the reported SO_x effect estimates in epidemiological studies may reflect independent SO_x effects on respiratory health. Second, ambient SO_x may be serving as an indicator of complex ambient air pollution mixtures that share the same source as SO_x (i.e., combustion of sulfur-containing fuels or metal smelting). Finally, copollutants may mediate the effects of SO_x or SO_x may influence the toxicity of copollutants. Epidemiologists use the term "interaction" or "effect modification" to denote the departure of the observed joint risk from what might be expected based on the separate effects of the factors. These possibilities are not necessarily exclusive. In addition, confounding can result in the production of an association between adverse health effects and SO_2 that is actually attributable to another factor that is associated with SO_2 in a particular study. Multivariate models are the most widely used strategy to address confounding in epidemiological studies, but such models are not readily interpreted when assessing effects of covarying pollutants such as PM, SO_2, and nitrogen dioxide (NO_2).

1.3.5. Uncertainty

The science of estimating the causal influence of an exposure on disease is an uncertain one. There are two distinct levels of uncertainty to be considered here:

- Model uncertainty—uncertainty regarding gaps in scientific theory required to make predictions on the basis of causal inferences.
- Parameter uncertainty—uncertainty as to the statistical estimates within each model.

Assessment of model uncertainty involves:

- whether exposure causes the health outcome;
- the set of confounders associated with exposure and health outcome;

- which parametric forms best describe the relations of exposure and confounders with outcome; and
- whether other forms of bias could be affecting the association.

Model uncertainty is not limited to the qualitative causal structure: it also involves factors such as uncertainty about the parametric form of the model specified, the variables included and whether or not measurement error is modeled. When mechanistic knowledge exists, this important source of uncertainty can be reduced. In contrast, uncertainty about the parameter estimates (regression coefficients) for a given model is a well-studied problem. The important point is that these reports of uncertainty are conditional on the model providing a sufficiently adequate approximation of reality so that inferences are valid. The overall scientific inference involves evaluation of model uncertainty and uncertainty about parameter estimates given to each model.

There are systematic, quantitative approaches for including uncertainty about the model in an assessment of overall uncertainty about a causal inference, such as sensitivity analysis and model averaging. Sensitivity analysis attempts to quantify the sensitivity of the parameter estimate in relation to assumptions about the model. Uncertainty ranges can be estimated using classical analysis (Robinson, 1989) or the Monte Carlo technique (Eggleston, 1993). By averaging over many different competing models, Bayesian Model Averaging incorporates model uncertainty into conclusions about parameters and prediction.

1.3.6. Application of Framework

EPA uses a two-step approach to evaluate the scientific evidence on health effects of exposure to criteria pollutants. These two steps address two policy relevant questions noted in the beginning of this chapter – what are (if any) the effects of SO_x on susceptible populations, given the total body of evidence, and at what levels of SO_x exposure do health effects of concern occur. The first step determines the weight of evidence in support of causation and characterizes the strength of any resulting causal classification. The second step includes further evaluation of the quantitative evidence regarding the concentration-response relationships and the levels, duration and pattern of exposures at which effects are observed.

To aid judgment, various "aspects"[1] of causality have been discussed by many philosophers and scientists. The most widely cited aspects of causality in epidemiology, and public health in general, were articulated by Sir Austin Bradford Hill in 1965 and have been widely used (EPA, 2005; IARC, 2006; Surgeon General, 2004; IOM, 2008). These nine aspects (Hill, 1965) have been modified (below) for use in causal determinations specific to health and environmental effects and pollutant exposures.[2]

Table 1-1 Aspects to aid in judging causality.

1. ***Consistency of the observed association.*** An inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies. The reproducibility of findings constitutes one of the strongest arguments for causality. If there are discordant results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered.

2. ***Strength of the observed association.*** The finding of large, precise risks increases confidence that the association is not likely due to chance, bias, or other factors. A modest risk, however, does not preclude a causal association and may reflect a lower level of exposure, an agent of lower potency, or a common disease with a high background level.

3. ***Specificity of the observed association.*** As originally intended, this refers to increased inference of causality if one cause is associated with a single effect or disease (Hill, 1965). Based on our current understanding this is now considered one of the weaker guidelines for causality; for example, many agents cause respiratory disease and respiratory disease has multiple causes. The ability to demonstrate specificity under certain conditions remains, however, a powerful attribute of experimental studies. Thus, although the presence of specificity may support causality, its absence does not exclude it.

4. ***Temporal relationship of the observed association.*** A causal interpretation is strengthened when exposure is known to precede development of the disease.

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[1]The "aspects" describe by Hill (1965) have become, in the subsequent literature, more commonly described as "criteria." The original term "aspects" is used here to avoid confusion with 'criteria' as it is used, with different meaning, in the Clean Air Act.

[2] The Hill apects were developed for use with epidemiology data. They have been modified here for use with a broader array of data, i.e., epidemiological, controlled human exposure, and animal toxicological studies, as well as *in vitro* data, and to be more consistent with EPA's Guidelines for Carcinogen Risk Assessment.

5. ***Biological gradient (exposure-response relationship).*** A clear exposure-response relationship (e.g., increasing effects associated with greater exposure) strongly suggests cause and effect, especially when such relationships are also observed for duration of exposure (e.g., increasing effects observed following longer exposure times). There are, however, many possible reasons that a study may fail to detect an exposure-response relationship. Thus, although the presence of a biologic gradient may support causality, the absence of an exposure-response relationship does not exclude a causal relationship.

6. ***Biological plausibility***. An inference of causality tends to be strengthened by consistency with data from experimental studies or other sources demonstrating plausible biological mechanisms. A lack of biologic understanding, however, is not a reason to reject causality.

7. ***Coherence.*** An inference of causality may be strengthened by other lines of evidence (e.g., clinical and animal studies) that support a cause-and-effect interpretation of the association. The absence of other lines of evidence, however, is not a reason to reject causality.

8. ***Experimental evidence (from human populations).*** Experimental evidence is generally available from human populations for the criteria pollutants. The strongest evidence for causality can be provided when a change in exposure brings about a change in adverse health effect or disease frequency in either clinical or observational studies.

9. ***Analogy.*** Structure activity relationships and information on the agent's structural analogs can provide insight into whether an association is causal. Similarly, information on mode of action for a chemical, as one of many structural analogs, can inform decisions regarding likely causality.

While these aspects provide a framework for assessing the evidence, they do not lend themselves to being considered in terms of simple formulas or fixed rules of evidence leading to conclusions about causality (Hill, 1965). For example, one cannot simply count the number of studies reporting statistically significant results or statistically nonsignificant results for health effects and reach credible conclusions about the relative weight of the evidence and the likelihood of causality. Rather, these important considerations are taken into account with the goal of producing an objective appraisal of the evidence, informed by peer and public comment and advice, which includes weighing alternative views on controversial issues. Additionally, it is important to note that the principles in Table 1-1 cannot be used as a strict checklist, but rather to determine the weight of the evidence for inferring causality. In particular, the absence of one or more of the principles does not automatically exclude a study from consideration (e.g., see discussion in U.S. Surgeon General's Report, 2004).

1.3.7. First Step—Determination of Causality

In the ISA, EPA assesses results of recent publications, in light of evidence available during the previous NAAQS review, to draw conclusions on the causal relationships between relevant pollutant exposures and health outcomes. This second external review draft ISA uses a five-level hierarchy that classifies the weight of evidence for causation, not just association.[1]; that is, whether the weight of scientific evidence makes causation at least as likely as not, in the judgment of the reviewing group. In developing this hierarchy, EPA has drawn on the work of previous evaluations, most prominently the IOM's Improving the Presumptive Disability Decision-Making Process for Veterans (IOM, 2008), EPA's Guidelines for Carcinogen Risk Assessment (EPA, 1986a), and the U.S. Surgeon General's smoking reports (U.S. Surgeon General's Report, 2004). These efforts are presented in more detail in Annex A. In the draft ISA, EPA uses a series of five descriptors to characterize the weight of evidence on whether associations are in fact causal. This weight of evidence evaluation is based on various lines of evidence from epidemiological studies, animal studies, or other mechanistic, toxicological, or biological sources. These separate judgments are integrated into a qualitative statement about the overall weight of the evidence and causality. The five descriptors for causal determination are described in Table 1-2.

Table 1-2. Weight of evidence for causal determination.

Sufficient to infer a causal relationship	Evidence is sufficient to conclude that there is a causal relationship between relevant pollutant exposure and the outcome. That is, a positive association has been observed between the pollutant and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example, controlled human exposures, epidemiologic "natural experiments," or observational studies supported by other lines of evidence. Generally, determination is based on multiple studies by multiple investigators.
Sufficient to infer a likely causal relationship (i.e., more likely than than not).	Evidence is sufficient to conclude a likely causal association between relevant pollutant exposures and the outcome. That is, a positive association has been observed between the pollutant and the outcome in studies in which chance and bias can be ruled out with reasonable confidence but potential confounding issues remain. For example, a) observational studies show positive associations but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mechanism of action information) are limited or inconsistent; or b) animal evidence from multiple studies, sex, or species is positive but limited or no human data are available. Generally, determination is based on multiple studies by multiple investigators.

[1] It should be noted that the CDC and IOM frameworks use a four-category hierarchy for the strength of the evidence. A five-level hierarchy is used here to be consistent with the EPA Guidelines for Carcinogen Risk Assessment and to provide a more nuanced set of categories.

Suggestive, but not sufficient to infer a causal relationship	Evidence is suggestive of an association between relevant pollutant exposures and the outcome, but is limited because chance, bias and confounding cannot be ruled out. For example, at least one high-quality study shows a positive association but the results of other studies are inconsistent.
Inadequate to infer the presence or absence of a causal relationship	The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an association between relevant pollutant exposure and the outcome. For example, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency.
Suggestive of no causal relationship	Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering sensitive subpopulations, are mutually consistent in not showing a positive association between exposure and the outcome at any level of exposures. In addition, the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded.

1.3.8. Second Step—Evaluation of Population Response

Beyond judgments regarding causality are questions relevant to characterizing exposure and risk to populations (i.e., at what levels do health effects occur). Such questions include:

- Under what exposure conditions (dose or exposure, duration and pattern) are effects seen?
- What is the shape of the concentration-response or dose-response relationship?
- What population groups appear to be affected or more susceptible to effects?

On the population level, causal and likely causal claims typically characterize how risk—the probability of health effects—changes in response to exposure. Initially, the response is evaluated within the range of observation. Approaches to analysis of the range of observation of epidemiological and human clinical studies are determined by the type of study and methods of exposure/dose and response measurement. Extensive human data for concentration-response analyses exists for all criteria pollutants, unlike most other environmental pollutants. Animal data also can inform concentration-response, particularly relative to dosimetry, mechanisms of action, and characteristics of sensitive subpopulations.

An important consideration in characterizing the public health impacts associated with exposure to a pollutant is whether the concentration-response relationship is linear across the full concentration range encountered, or if nonlinear relationships exist along any part of this range. Of particular interest is the shape of the concentration-response curve at and below the level of the current standards. The complex molecular and cellular events that underlie cancer and noncancer toxicity are likely to be both linear and nonlinear, and vary depending on dose.

Additionally, many chemicals and agents may act by perturbing naturally occurring background processes that lead to disease. At the human population level, however, various sources of variability and uncertainty tend to smooth and "linearize" the concentration-response function (such as the low data density in the lower concentration range, possible influence of measurement error, and individual differences in susceptibility to air pollution health effects). These attributes of population dose-response may explain why the available human data at ambient concentrations for some environmental pollutants (e.g.,ozone, lead [Pb], PM, secondhand tobacco smoke, radiation) do not exhibit evident thresholds for cancer or noncancer health effects, even though likely mechanisms of action include nonlinear processes for some key events. These attributes of human population dose-response relationships have been extensively discussed in the broader epidemiological literature (e.g., Rothman and Greenland, 1998).

1.4. Conclusions

This second external review draft ISA strives to present a concise review, synthesis, and evaluation of the most policy-relevant science, and communicates critical science judgments relevant to the NAAQS review. It reviews the most policy relevant evidence from epidemiological, human clinical, and animal toxicological studies, including mechanistic evidence from basic biological science. Annexes to the ISA provide additional details of the literature published since the last review. A framework for making critical judgments concerning causality is presented in this chapter. It relies on a widely accepted set of principles and standardized language to express evaluation of the evidence. This approach can bring rigor and clarity to the current and future assessments. This ISA should assist EPA and others, now and in the future, to represent accurately what is presently known—and what remains unknown—concerning the effects of sulfur oxides on human health.

Chapter 2. Source to Tissue Dose

This chapter contains basic information about concepts and findings in atmospheric sciences, human exposure assessment, and human dosimetry. It is meant to serve as a prologue for the detailed discussions of health effects data in Chapters 3 and 4. Section 2.1 gives an overview of the sources of SO_2. Atmospheric chemistry processes involved in the oxidation of SO_2 and those involved in the production of SO_2 from reduced sulfur gases in the atmosphere are discussed in Section 2.2. A description of SO_2 measurement methods and related issues are presented in Section 2.3. Data for ambient SO_2 concentrations are characterized in Section 2.4. Policy relevant background concentrations of SO_2, i.e., those concentrations defined to result from uncontrollable emissions, are also presented in Section 2.4. Factors related to personal exposure to SO_2 are discussed in Section 2.5. Finally, Section 2.6 covers the dosimetry of SO_2 in the respiratory tract. This organization generally follows that given in the National Research Council (NRC) paradigm for integrating air pollutant research (NRC, 1998).

2.1. Sources of Sulfur Oxides

Industrial emissions of SO_2 in the United States are mainly due to combustion of fossil fuels by electrical utilities (~66 %) and industry (~29%); transportation-related sources contribute minimally (~5%) (2002 statistics) (EPA, 2006d). Thus, most SO_2 emissions originate from point sources. Annex B has a detailed breakdown of emissions by source category. Almost all of the sulfur in fuel is released as volatile components (SO_2 or SO_3) during combustion. Hence, based on sulfur content in fuel stocks, sulfur emissions can be calculated to a higher degree of accuracy than other pollutants such as nitrogen oxides or primary PM. However, these estimates given above are national averages and may not accurately reflect the contribution of specific local sources for determining individual exposure to SO_2 at a particular location and time. For example, shipping and in-port activities may be a significant source of SO_2 in some coastal cities (Wang et al., 2007).[1]

[1] Ships and commercial boats contribute approximately 25% of the SO_2 emissions in the South Coast Air Basin, and 50% of statewide SO_2 emissions (Dabdub and Vutukuru, 2008). Because of the importance of SO_2 emissions, the ports of Long Beach and Los Angeles are part of a Sulfur Emissions Control Area in which sulfur contents of fuels are not to exceed 1.5%. Modeling studies by Vutukuru (2008) also indicate that ships contribute just over 1 part per billion (ppb) SO_2 (for a 24-h avg) to Long Beach, and a few tenths of a ppb to locations further inland .

The largest natural sources of SO_2 are volcanoes and wildfires. Although SO_2 constitutes a relatively minor fraction (0.005% by volume) of total volcanic emissions (Holland, 1978), concentrations in volcanic plumes can be in the range of several to tens of ppm. Volcanic sources of SO_2 in the U.S. are limited to the Pacific Northwest, Alaska, and Hawaii. Emissions of SO_2 from burning vegetation are generally in the range of 1 to 2% of the biomass burned (Levine and Pinto, 1998). Sulfur is a component of amino acids in vegetation and is released during combustion. Gaseous sulfur emissions from this source are mainly in the form of SO_2.

In addition to its role as an emitted primary pollutant, SO_2 is also produced by the photochemical oxidation of reduced sulfur compounds such as dimethyl sulfide (CH_3-S-CH_3, or DMS), hydrogen sulfide (H_2S), carbon disulfide (CS_2), carbonyl sulfide (OCS), methyl mercaptan (CH_3-S-H), and dimethyl disulfide (CH_3-S-S-CH_3). The sources for these compounds are mainly biogenic (see Annex Table B-6). Emissions of reduced sulfur species are associated typically with marine organisms living either in pelagic or coastal zones, and with anaerobic bacteria in marshes and estuaries. Emissions of DMS from marine plankton represent the largest single atmospheric source of reduced sulfur species (Berresheim et al., 1995). Other than OCS, which is lost mainly by photolysis (e-folding lifetime, [τ] ~6 months), species are lost mainly by reaction with hydroxyl radical (OH) and NO_3 radicals, and are relatively short-lived; lifetimes range from a few hours to a few days (see Annex Table B-2). Reaction with NO_3 radicals at night most likely represents the major loss process for DMS and methyl mercaptan. Although the mechanisms for the oxidation of DMS are not completely understood, excess sulfate in marine aerosol appears related mainly to the production of SO_2 from the oxidation of DMS. Emissions of sulfur from natural sources are small compared to industrial emissions within the U.S. However, important exceptions occur locally as the result of volcanic activity, wildfires and in certain coastal zones as described above.

Because OCS is relatively long-lived, it can survive oxidation in the troposphere and be transported upward into the stratosphere. Crutzen (1976) proposed that its oxidation to sulfate in the stratosphere serves as the major source of the stratospheric aerosol layer. However, Myhre et al. (2004) proposed that SO_2 transported upward from the troposphere by deep convection is the most likely source, since the flux of OCS is too small. In addition, in situ measurements of the isotopic composition of sulfur in stratospheric sulfate do not match those of OCS (Leung,

2002). Thus, anthropogenic SO_2 emissions could be important precursors to the formation of the stratospheric aerosol layer.

2.2. Atmospheric Chemistry

The only forms of monomeric sulfur oxides of interest in tropospheric chemistry are SO_2 and SO_3. SO_3 can be emitted from the stacks of power plants and factories; however, it reacts extremely rapidly with H_2O in the stacks or immediately after release into the atmosphere to form H_2SO_4, which mainly condenses onto existing particles when particle loadings are high; it can nucleate to form new particles under lower concentration conditions. Thus, only SO_2 is present in the tropospheric boundary layer at concentrations of concern for human exposures. The gas phase oxidation of SO_2 is initiated by the reaction

$$SO_2 + OH + M \rightarrow HSO_3 + M \qquad \text{(Reaction 2-1)}$$

where M is an atmospheric constituent such as N_2 and O_2 that helps stabilize the reaction product. Reaction 2-1 is followed by

$$HSO_3 + O_2 \rightarrow SO_3 + HO_2 \qquad \text{(Reaction 2-2)}$$

$$SO_3 + H_2O \rightarrow H_2SO_4 \qquad \text{(Reaction 2-3)}$$

Because the saturation vapor pressure of H_2SO_4 is extremely low, it will be removed rapidly by transfer to the aqueous phase of aerosol particles and cloud drops. Depending on atmospheric conditions and concentrations of ambient particles and gaseous species that can participate in new particle formation, it can also nucleate to form new particles. Rate coefficients for the reactions of SO_2 with either the hydroperoxyl radical (HO_2) or NO_3 are too low to be significant (Jet Propulsion Laboratory, 2003).

The major sulfur species in clouds are hydrogen sulfite (HSO_3^-) and the sulfite ion (SO_3^{2-}). Both are derived from the dissolution of SO_2 in water, and are referred to as S(IV); bisulfate ion (HSO_4^-) and sulfate (sulfate) are referred to as S(VI). The chief species capable of oxidizing S(IV) to S(VI) in cloud water are O_3, peroxides (either hydrogen peroxide [H_2O_2] or organic peroxides), hydroxyl (OH) radicals, and ions of transition metals such as iron (Fe), manganese (Mn) and copper (Cu) that can catalyze the oxidation of S(IV) to S(VI) by O_2. The basic

mechanism of the aqueous phase oxidation of SO_2 has long been studied and can be found in numerous texts on atmospheric chemistry, e.g., Seinfeld and Pandis (1998), Finlayson-Pitts and Pitts (1999), Jacob (1999), and Jacobson (2002). Following Jacobson (2002), the steps involved in the aqueous phase oxidation of SO_2 can be summarized as

Dissolution of SO_2

$$SO_2(g) \Leftrightarrow SO_2(aq) \qquad \text{(Reaction 2-4)}$$

The formation and dissociation of H_2SO_3

$$SO_2(aq) + H_2O(aq) \Leftrightarrow H_2SO_3 \Leftrightarrow H^+ + HSO_3^- \Leftrightarrow 2H^+ + SO_3^{2-} \qquad \text{(Reaction 2-5)}$$

In the pH range commonly found in rainwater (pH 2 to 6), the most important reaction converting S(IV) to S(VI) is

$$HSO_3^- + H_2O_2 + H^+ \Leftrightarrow SO_4^{2-} + H_2O + 2H^+ \qquad \text{(Reaction 2-6)}$$

as SO_3^{2-} is much less abundant than HSO_3^-.

For pH up to about 5.3, H_2O_2 is the dominant oxidant, while at pH > 5.3, O_3 becomes dominant, followed by Fe(III), using characteristic values found in Seinfeld and Pandis (1998). However, differences in concentrations of oxidants result in differences in the pH at which this transition occurs. It should also be noted that the oxidation of SO_2 by O_3 and O_2 tends to be self-limiting: as sulfate is formed, the pH decreases and the rates of these reactions decrease. Higher pH levels are expected to be found mainly in marine aerosols. However, in marine aerosols, the chloride-catalyzed oxidation of S(IV) may be more important (Hoppel and Caffrey, 2005; Zhang and Millero, 1991). Because the ammonium ion (NH_4^+) is so effective in neutralizing acidity, it affects the rate of oxidation of S(IV) to S(VI) and the rate of dissolution of SO_2 in particles and cloud drops.

A comparison of the relative rates of oxidation by gas and aqueous phase reactions by Warneck (1999) indicates that on average only about 20% of SO_2 is oxidized by gas phase reactions; the remainder is oxidized by aqueous phase reactions. In areas away from strong pollution sources, the SO_2 τ is ~7 days, based on measurements of the rate constant for Reaction 2-1 (Jet Propulsion Laboratory, 2003) and a nominal concentration for the OH radical of 10^6/cm^3.

However, the mechanism of SO_2 oxidation at a particular location depends on local environmental conditions. For example, near stacks, oxidants such as OH radicals are depleted and almost no SO_2 is oxidized in the gas phase. Further downwind, as the plume is diluted with background air, the gas phase oxidation of SO_2 increases in importance. Finally, even further downwind when conditions in the plume can become more oxidizing than in background air, the SO_2 oxidation rate could exceed that in background air. SO_2 in the planetary boundary layer is also removed from the atmosphere by dry deposition to moist surfaces, resulting in an atmospheric τ with respect to dry deposition of approximately 1 day to 1 week. Wet deposition of sulfur naturally depends on the variable nature of rainfall, but in general results in a τ of SO_2 ~7 days, too. These two processes, oxidation and deposition, lead to an overall lifetime of SO_2 in the atmosphere of 3 to 4 days.

2.3. Measurement Methods and Associated Issues

Currently, ambient SO_2 is measured using instruments based on pulsed ultraviolet (UV) fluorescence. The UV fluorescence monitoring method for atmospheric SO_2 was developed to improve on the flame photometric detection (FPD) method, which in turn had replaced the pararosaniline wet chemical method. This latter method is still the EPA's Federal Reference Method (FRM) for atmospheric SO_2, but is rarely used due to its complexity and slow response, even in its automated forms. Both the UV fluorescence and FPD methods are designated as Federal Equivalent Methods (FEMs) by EPA, but UV fluorescence has largely supplanted the FPD approach because of the UV method's inherent linearity and because the FPD method needs consumable hydrogen gas.

In the UV fluorescence method, SO_2 molecules absorb UV light at one wavelength and emit UV light at longer wavelengths in the process known as fluorescence, through excitation of the SO_2 molecule to a higher energy (singlet) electronic state. Once excited, the molecule decays nonradiatively to a lower-energy electronic state from which it then decays to the original or electronic state by emitting a photon of light at a longer wavelength (i.e., a lower-energy photon) than the original, incident photon. The intensity of the emitted light is thus proportional to the number of SO_2 molecules in the sample gas.

In commercial analyzers, light from a high-intensity UV lamp passes through a bandwidth filter, allowing only photons with wavelengths around the SO_2 absorption peak (near 214

nanometers [nm]) to enter the optical chamber. The light passing through the source bandwidth filter is collimated using a UV lens and passes through the optical chamber, where it is detected on the opposite side of the chamber by the reference detector. A photomultiplier tube (PMT) is offset from and placed perpendicular to the light path to detect the SO_2 fluorescence. Since the SO_2 fluorescence at 330 nm is different from its excitation wavelength, an optical bandwidth filter is placed in front of the PMT to filter out any stray light from the UV lamp. A lens is located between the filter and the PMT to focus the fluorescence onto the active area of the detector and optimize the fluorescence signal. The limit of detection (LOD) for a non-trace level SO_2 analyzer is required to be 10 ppb (FR, 2006). However, most commercial analyzers have detection limits of about 3 ppb; many monitors might have lower effective detection limits. The EPA, through its National Core (NCore) initiative (EPA, 2005) is in the process of supporting state, local, tribal, and federal networks in the implementation of newer trace-level SO_2 instrumentation. These new trace-level instruments have detection limits of 0.1 ppb or lower. More information related to SO_2 sampling and measurement is in Annex B.5.

2.3.1. Sources of Positive Interference

The most common source of interference to the UV fluorescence method for SO_2 is from other gases that fluoresce in a similar fashion when exposed to UV radiation. The most significant of these are polycyclic aromatic hydrocarbons (PAHs), of which naphthalene is a prominent example. Xylene is another common hydrocarbon that can cause fluorescent interference. Consequently, any such aromatic hydrocarbons in the optical chamber can act as positive interference. To remove this source of interference, high-sensitivity SO_2 analyzers, such as those to be used in the NCore network (EPA, 2005), have hydrocarbon scrubbers to remove these compounds from the sample stream before the sample air enters the optical chamber.

Luke (1997) reported positive artifacts of a modified pulsed fluorescence detector generated by the coexistence of nitric oxide (NO), carbon disulfide (CS_2), and a number of highly fluorescent aromatic hydrocarbons such as benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, *m*-ethyltoluene, ethylbenzene, and 1,2,4-trimethylbenzene. The positive artifacts could be reduced by using a hydrocarbon "kicker" membrane. At a flow rate of 300 standard cc min^{-1} and a pressure drop of 645 torr across the membrane, the interference from ppm levels of many aromatic hydrocarbons was eliminated. NO fluoresces in a spectral region close to that of SO_2.

However, in high-sensitivity SO_2 analyzers, the bandpass filter in front of the PMT is designed to prevent NO fluorescence from being detected at the PMT. Care must be exercised when using multicomponent calibration gases containing both NO and SO_2, so that the NO rejection ratio of the SO_2 analyzer is sufficient to prevent NO interference.

The most common source of positive bias (as contrasted with positive spectral interference) in high-sensitivity SO_2 monitoring is stray light in the optical chamber. Since SO_2 can be electronically excited by a broad range of UV wavelengths, any stray light with an appropriate wavelength that enters the optical chamber can excite SO_2 in the sample and increase the fluorescence signal. Furthermore, stray light at the wavelength of the SO_2 fluorescence that enters the optical chamber may impinge on the PMT and increase the fluorescence signal. Several design features minimize stray light, including the use of light filters, dark surfaces, and opaque tubing.

Nicks and Benner (2001) reported a sensitive SO_2 chemiluminescence detector based on a differential measurement: response from ambient SO_2 is determined by the difference between air containing SO_2 and air scrubbed of SO_2 when both air samples contain other detectable sulfur species. Assuming monotonic efficiency of the sulfur scrubber, all positive artifacts should also be reduced with this technique.

2.3.2. Sources of Negative Interference

Nonradiative deactivation (quenching) of excited SO_2 molecules can occur from collisions with common molecules in air, including nitrogen, oxygen, and water. During collisional quenching, the excited SO_2 molecule transfers energy, kinetically allowing the SO_2 molecule to return to the original lower energy state without emitting a photon. Collisional quenching results in a decrease in the SO_2 fluorescence and, hence, an underestimation of SO_2 concentration in the air sample. Of particular concern is the variable water vapor content of air. Luke (1997) reported that the response of the detector could be reduced by an amount of ~7 to 15% at water vapor mixing ratios of 1 to 1.5 mole percent (relative humidity [RH] = 35 to 50% at 20 to 25°C and 1 atmosphere [atm] for a modified pulsed fluorescence detector [Thermo Environmental Instruments, Model 43s]). Condensation of water vapor in sampling lines must be avoided, as water on the inlet surfaces can absorb SO_2 from the sample air. The simplest approach to avoid condensation is to heat sampling lines to a temperature above the expected dew point and to

within a few degrees of the controlled optical bench temperature. At very high SO_2 concentrations, reactions between electronically excited SO_2 and ground state SO_2 might occur, forming SO_3 and SO (Calvert et al., 1978). However, the possibility that this artifact might be affecting measurements at very high SO_2 levels has not been examined.

2.3.3. Other Techniques for Measuring SO_2

More sensitive techniques for measuring SO_2 are available, but most of these systems are too complex and expensive for routine monitoring applications. However, techniques such as those described by Luke (1997) can be used to improve the sensitivity of ambient SO_2 monitors by eliminating sources of common interference. See descriptions in Annex section B.5.

2.4. Environmental Concentrations of SO_x

2.4.1. Design Criteria for the NAAQS SO_2 Monitoring Networks[1]

Trace level SO_2 monitoring is currently required at the approximately 75 proposed NCore sites, as noted in CFR 40 Part 58 Appendices C and D. Continued operation of existing State and Local Air Monitoring Sites (SLAMS) for SO_2 using Federal Reference Methods (FRM) or Federal Equivalent Methods (FEM) is required until discontinuation is approved by the EPA Regional Administrator. Where SLAMS SO_2 monitoring is required, at least one of the sites must be a maximum concentration site for that specific area. In 2007, there were ~500 SO_2 monitors reporting values to the EPA Air Quality System database (AQS).

The appropriate spatial scales for SO_2 SLAMS monitoring are the microscale, middle, and possibly neighborhood scales.

- ***Micro and middle scale***—Some data uses associated with microscale and middle scale measurements for SO_2 include assessing the effects of control strategies to reduce concentrations (especially for the 3-hour and 24-hour averaging times), and monitoring air pollution episodes.

- ***Neighborhood scale***—This scale applies where there is a need to collect air quality data as part of an ongoing SO_2 stationary source impact investigation. Typical locations might include suburban areas adjacent to SO_2 stationary sources, for example, or for

[1] This section is adapted from Code of the Federal Register 40 CFR Parts 53 and 58 and Appendix E to Part 58, as revised: Vol. 71, No. 200 / 17 October 2006

determining background concentrations as part of studies of population responses to SO_2 exposure.

Horizontal and Vertical Placement

The probe, or at least 80 percent of the monitoring path, must be located between 2 and 15 meters above ground level for all SO_2 monitoring sites. The probe, or at least 90 percent of the monitoring path, must be positioned at least 1 meter vertically or horizontally from any supporting structure, walls, parapets, penthouses, etc., and away from dusty or dirty areas. If the probe, or a significant portion of the monitoring path, is located near the side of a building, it should be located on the windward side relative to the prevailing wind direction during the season of highest concentration potential for the pollutant being measured.

Spacing from Minor Sources

Local minor sources of a primary pollutant such as SO_2 can affect concentrations of that particular pollutant at a monitoring site. If the objective for that site is to investigate these local primary pollutant emissions, then the site should be located where the spatial and temporal variability in these emissions can be captured. This type of monitoring site would likely be the microscale type. If a monitoring site is to be used to determine air quality over a much larger area, such as a neighborhood or city, a monitoring agency should avoid placing a monitor probe, path, or inlet near local, minor sources. The plume from the local minor sources should not be allowed to inappropriately influence the air quality data collected.

To minimize these potential interferences, the probe, or at least 90 percent of the monitoring path, must be placed away from furnace or incineration flues, or other minor sources of SO_2. The separation distance should take into account the heights of the flues, type of waste or fuel burned, and the sulfur content of the fuel.

Spacing from Obstructions

Buildings and other obstacles may possibly scavenge SO_2, and can act to restrict airflow for any pollutant. To avoid this interference, the probe, inlet, or at least 90 percent of the monitoring path must have unrestricted airflow and be located away from obstacles. The distance from the obstacle to the probe, inlet, or monitoring path must be at least twice the height of the obstruction's protrusion. An exception can be made for measurements taken in street canyons or

at source-oriented sites where buildings and other structures are unavoidable. Generally, a probe or monitoring path located near or along a vertical wall is undesirable, because air moving along the wall may be subject to possible removal mechanisms. A probe, inlet, or monitoring path must have unrestricted airflow in an arc of at least 180 degrees. This arc must include the predominant wind direction for the season of greatest pollutant concentration potential.

Special consideration must be devoted to the use of open path analyzers, due to their inherent potential sensitivity to certain types of interferences, or optical obstructions. A monitoring path must be clear of all trees, brush, buildings, plumes, dust, or other optical obstructions, including potential obstructions that may move due to wind, human activity, growth of vegetation, etc. Temporary optical obstructions, such as rain, particles, fog, or snow, should be considered when locating an open path analyzer. Any temporary obstructions that are of sufficient density to obscure the light beam will affect the ability of the open path analyzer to measure pollutant concentrations continuously. Transient, but significant obscuration of especially longer measurement paths could occur because certain meteorological conditions (e.g., heavy fog, rain, snow) and/or aerosol levels are of sufficient density to prevent the analyzer's light transmission. If certain compensating measures are not otherwise implemented at the onset of monitoring (e.g., shorter path lengths, higher light source intensity), data recovery during periods of greatest primary pollutant potential could be compromised. For instance, if heavy fog or high particulate levels are coincident with periods of projected NAAQS-threatening pollutant potential, the resulting data may not be representative for reflecting maximum pollutant concentrations, despite the fact that the site may otherwise exhibit an acceptable, even exceedingly high overall valid data capture rate.

Spacing from Trees

Trees can provide surfaces for SO_2 adsorption or reactions, and surfaces for particle deposition. Trees can also act as obstructions in cases where they are located between the air pollutant sources or source areas and the monitoring site, and where the trees are of sufficient height and leaf canopy density to interfere with normal airflow around the probe, inlet, or monitoring path. To reduce possible interference, the probe, inlet, or at least 90 percent of the monitoring path must be at least 10 meters or further from the drip line of trees.

For microscale sites, no trees or shrubs should be located between the probe and the source under investigation, such as a roadway or a stationary source.

2.4.2. Monitor Locations in Selected Areas of the U.S.

Figures 2-1 through 2-6 illustrate the 2005 geospatial locations of monitors for SO_2, NO_2, CO, particulate matter ≤ 10 μm (PM_{10}), particulate matter ≤ 2.5 μm ($PM_{2.5}$), and O_3. These locations, sited in several cities in six states, were selected as relevant for SO_2 health effects studies; see the summaries and assessments of health effects in Chapter 4, and the discussion of intracity SO_2 correlations that follows. For each state, Figure A shows locations of each monitor for all six pollutants; Figure B shows only the SO_2 monitor locations. Totals for each monitor type are included. These figures demonstrate the important point that not all SO_2 monitors in any Consolidated Metropolitan Statistical Area (CMSA) are co-located with monitors for other pollutants. Two examples are given below.

Table 2-1. Monitor counts for California and San Diego County, 2005.

	SO_2	NO_2	O_3	CO	PM_{10}	$PM_{2.5}$
California (all)	35	105	176	86	177	97
San Diego County	4	9	10	6	7	7

Table 2-2. Monitor counts for Ohio and Cuyahoga County, 2005.

	SO_2	NO_2	O_3	CO	PM_{10}	$PM_{2.5}$
Ohio (all)	31	4	49	15	49	49
Cuyahoga County	4	2	3	4	6	7

Table 2-1 lists the totals for all criteria air pollutant monitors (except Pb) in California, as well as the subset of these monitors in San Diego County. At each of the four sites where SO_2 was measured, NO_2, CO, PM_{10}, $PM_{2.5}$, and O_3 were also measured, with the exception of $PM_{2.5}$ at one site (AQS ID 060732007) in Otay Mesa, CA. Table 2-2 lists the totals for all criteria air pollutant monitors (except Pb) in Ohio, as well as the subset of in Cuyahoga County.

In Cuyahoga County, PM_{10} and $PM_{2.5}$ were measured at all four sites where SO_2 was also measured in 2005, but O_3 and CO were not measured at any of those four sites; NO_2 was only measured at one site (AQS ID 39050060) near Cleveland's city center and ~0.5 km from the intersection of Interstate Highways 77 and 90.

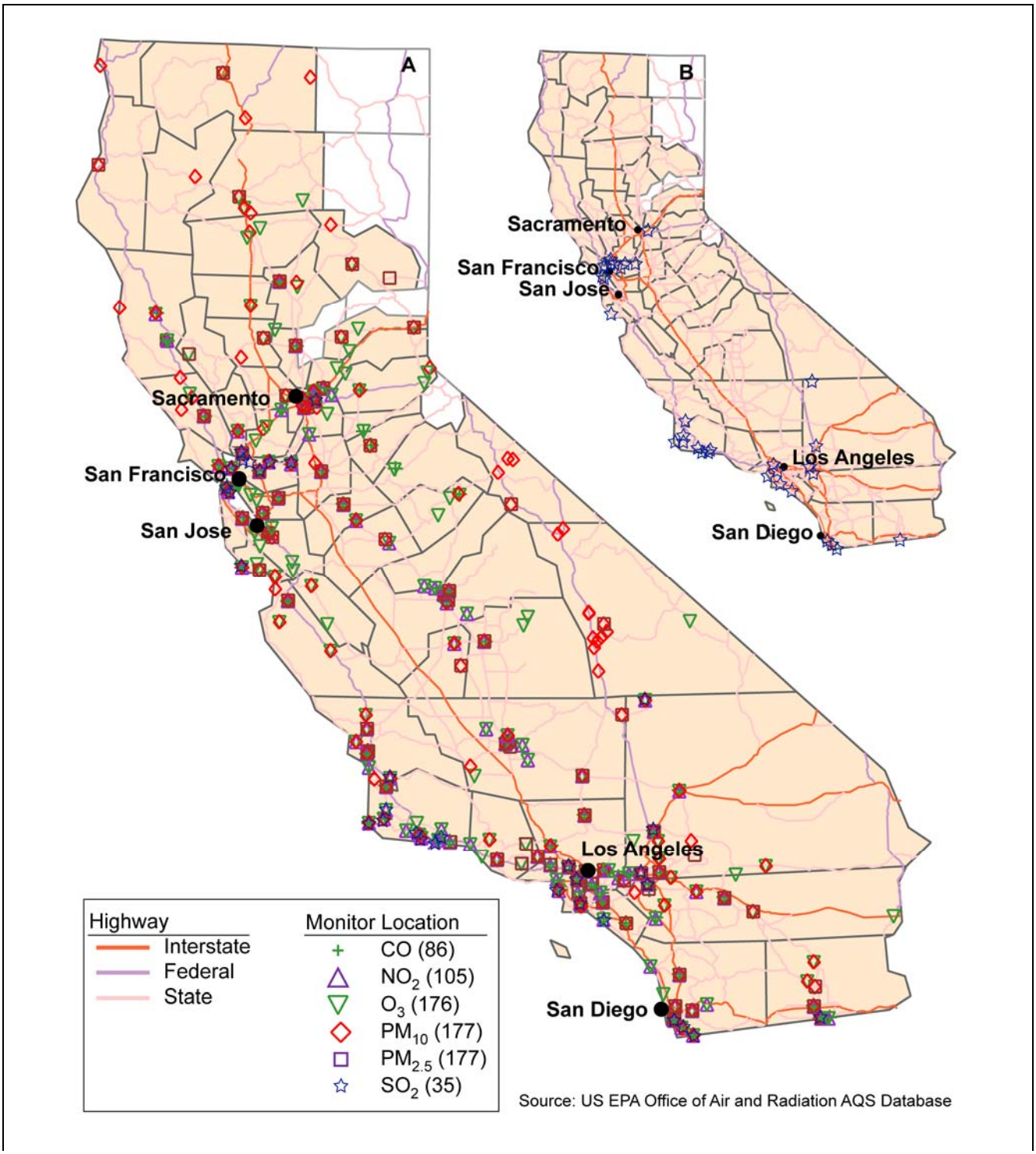

Figure 2-1. Criteria pollutant monitor locations (A) and SO_2 monitor locations (B), California, 2005. Shaded counties have at least one monitor.

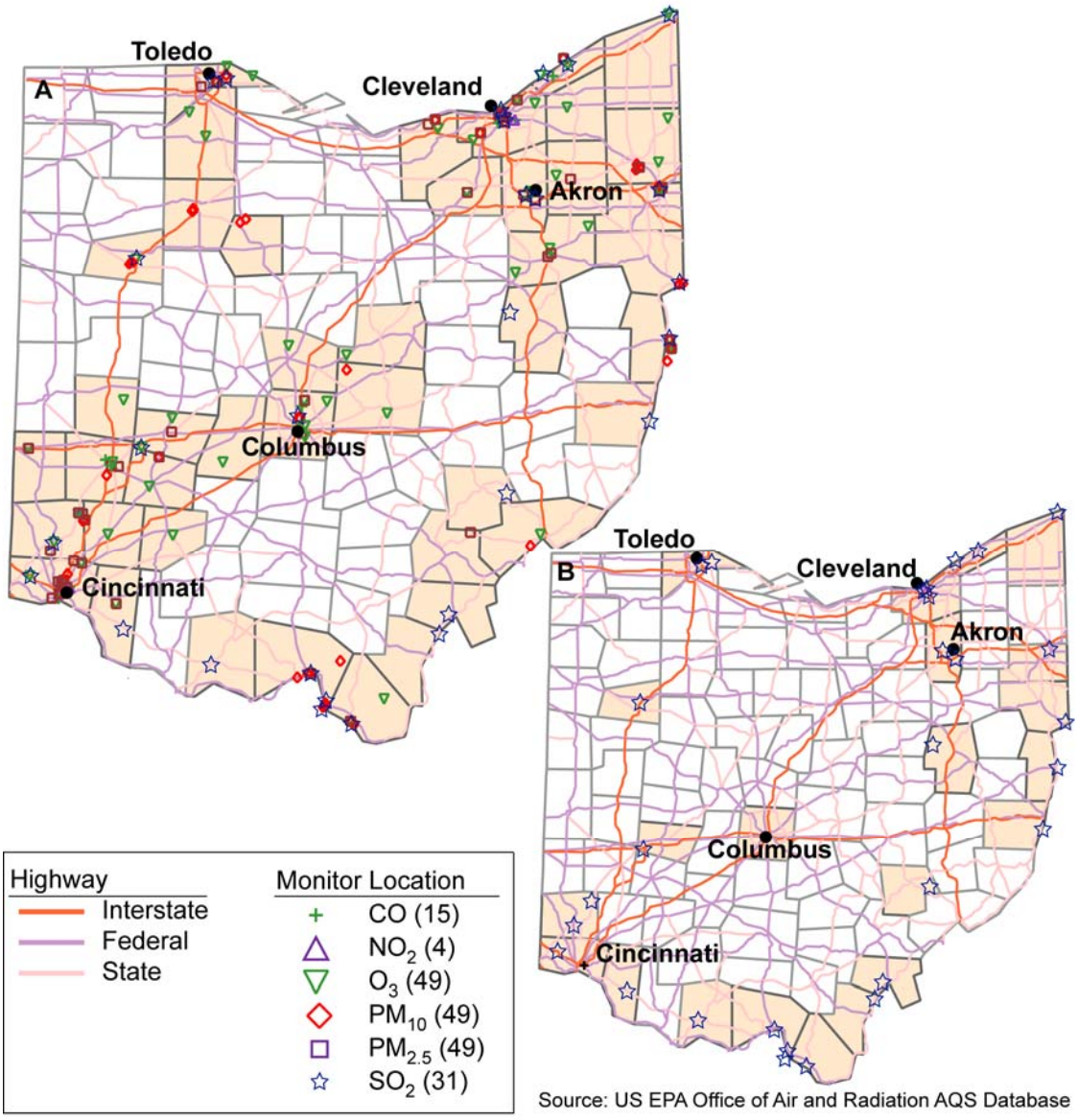

Figure 2-2. Criteria pollutant monitor locations (A) and SO_2 monitor locations (B), Ohio, 2005. Shaded counties have at least one monitor.

2.4.3. Ambient SO_2 Concentrations in Relation to SO_2 Sources

SO_2 data collected from the SLAMS and NAMS networks, like those illustrated in Figures 2-1 through 2-6, show that the decline in SO_2 emissions from electric generating utilities has substantially improved air quality. Not one monitored exceedance of the SO_2 annual ambient

air quality standard in the lower 48 States of the United States has been recorded since 2000, according to the EPA Acid Rain Program (ARP) 2005 Progress Report (EPA, 2006a). EPA's trends data (www.epa.gov/airtrends) reveal that the national composite average SO_2 annual mean ambient concentration decreased by 48% from 1990 to 2005; the largest single-year reduction was 1994-95, the ARP's first operating year (EPA, 2006a). Figure 2-7 depicts data for SO_2 emissions in the contiguous United States (CONUS) during those years, with state-level totals.

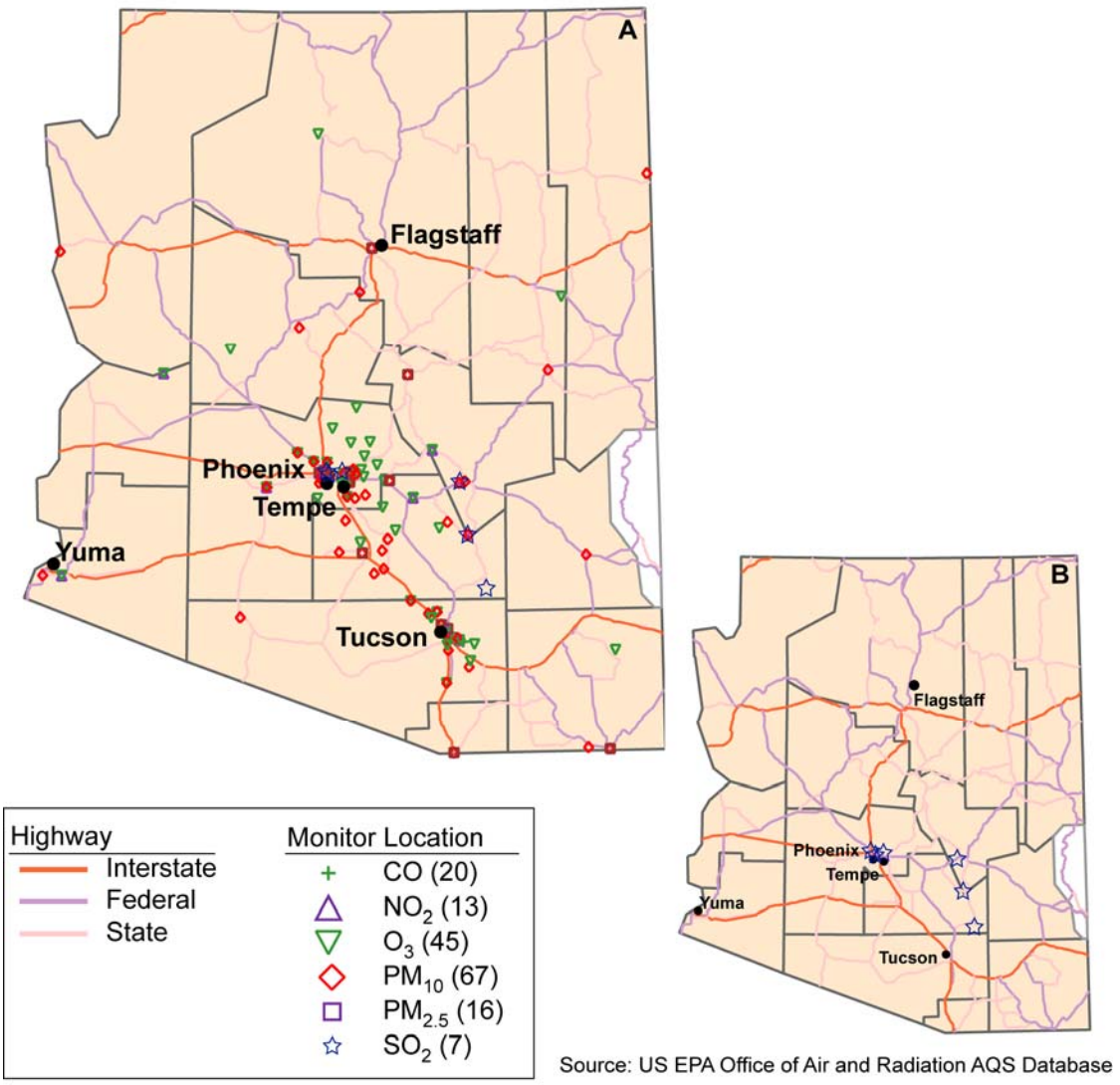

Figure 2-3. Criteria pollutant monitor locations (A) and SO_2 monitor locations (B), Arizona, 2005. Shaded counties have at least one monitor.

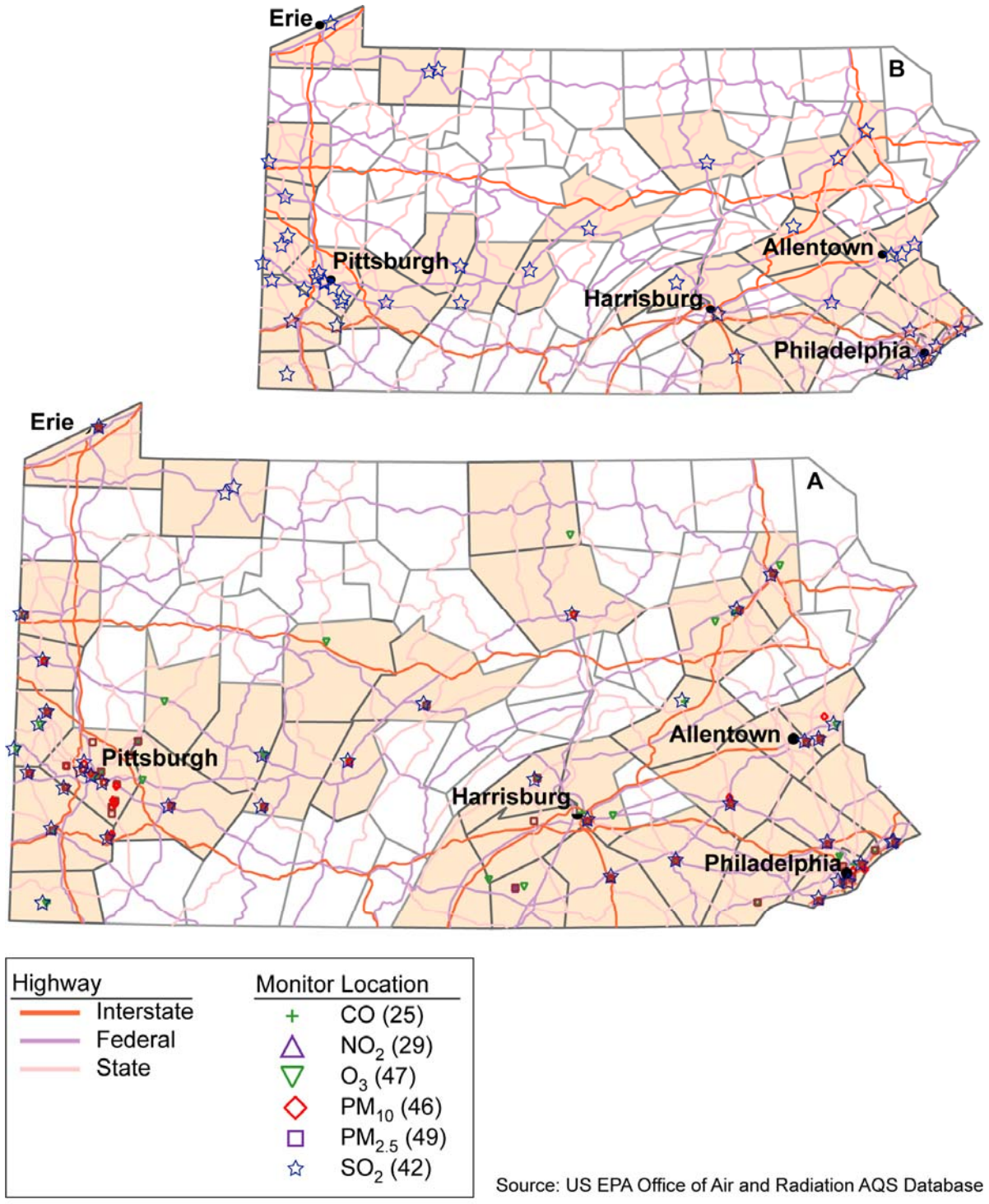

Figure 2-4. Criteria pollutant monitor locations (A) and SO_2 monitor locations (B), Pennsylvania, 2005. Shaded counties have at least one monitor.

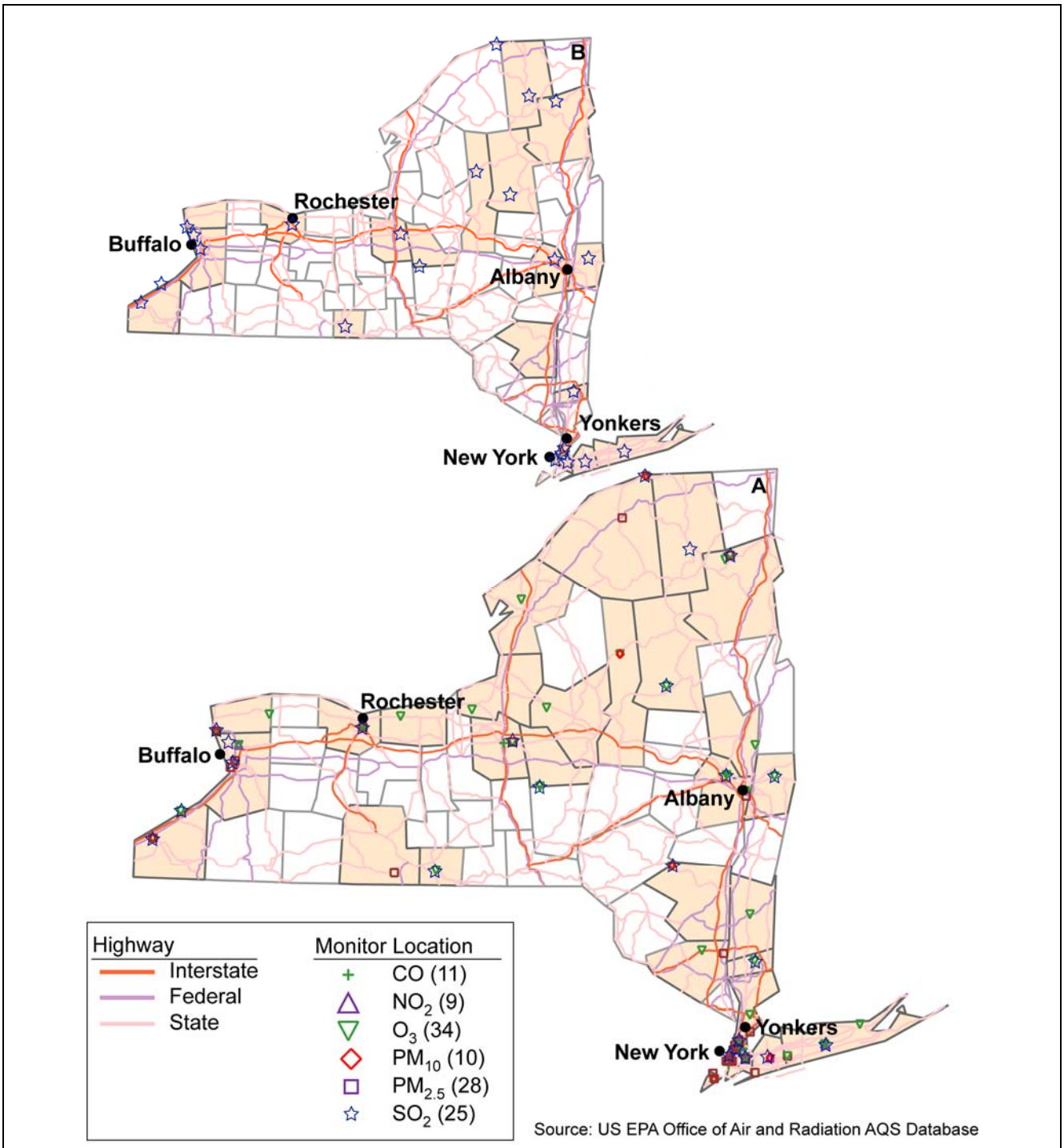

Figure 2-5. Criteria pollutant monitor locations (A) and SO_2 monitor locations (B), New York, 2005. Shaded counties have at least one monitor.

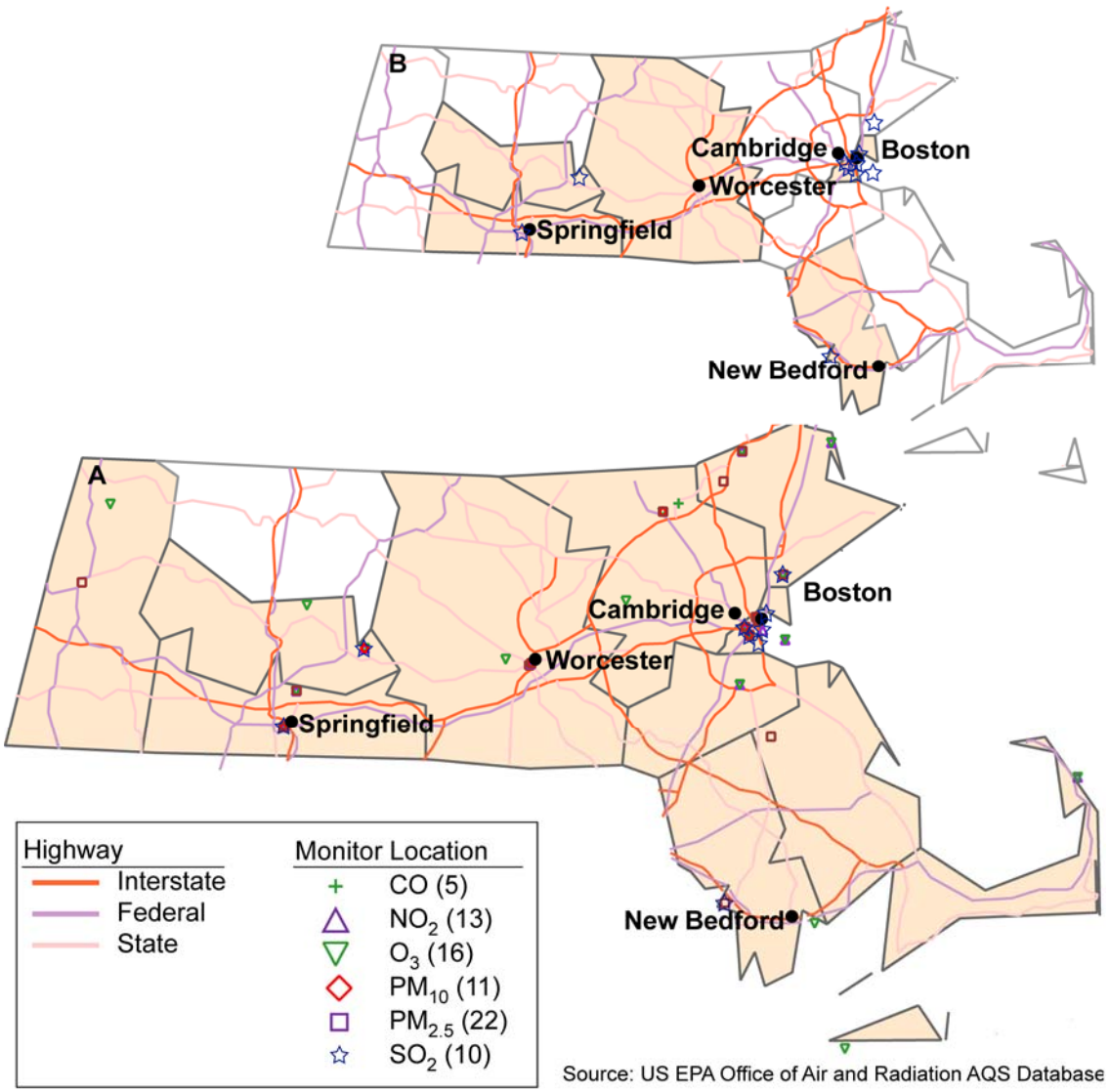

Figure 2-6. Criteria pollutant monitor locations (A) and SO_2 monitor locations (B), Massachusetts, 2005. Shaded counties have at least one monitor.

These emissions data trends are consistent with the trends in the observed ambient concentrations from the Clean Air Status and Trends Network (CASTNet). Following implementation of the Phase I controls on ARP sources between 1995 and 2000, significant reductions in SO_2 and ambient SO_4^{2-} concentrations were observed at CASTNet sites throughout the eastern United States. The mean annual concentrations of SO_2 and SO_4^{2-} from CASTNet's long-term monitoring sites can be compared using two 3-year periods, 1989–1991 and 2003-2005, shown in Figure 2-8 for SO_2 and Figure 2-9 for SO_4^{2-}.

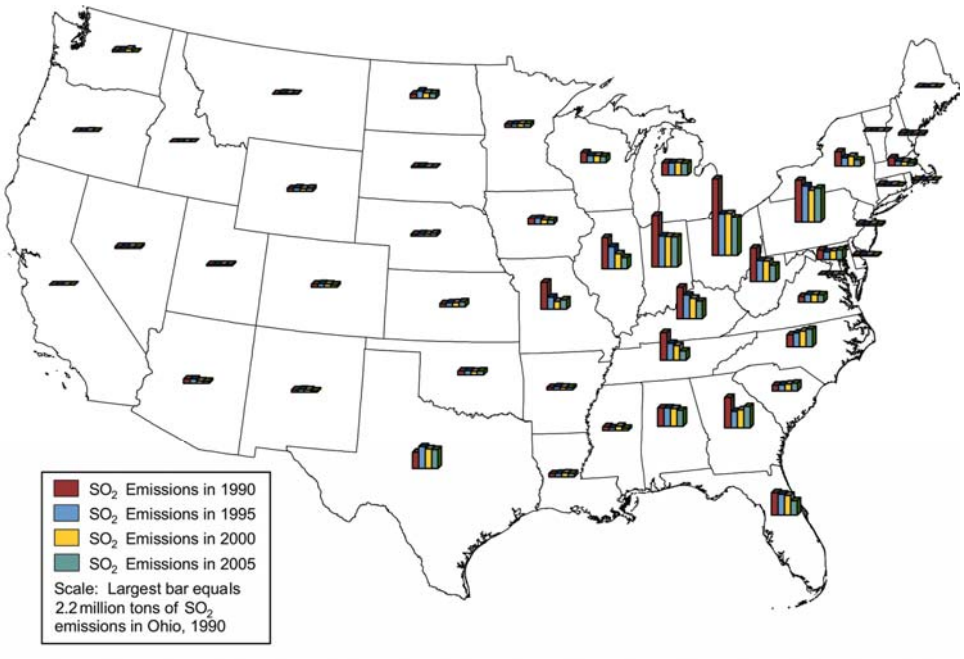

Figure 2-7. State-level SO_2 emissions, 1990-2005.

Source: Environmental Protection Agency Clean Air Markets Division (www.epa.gov/airmarkets/index.html).

From 1989 through 1991—that is, in the years prior to implementation of the ARP Phase I— the highest ambient mean concentrations of SO_2 and SO_4^{2-} were observed in western Pennsylvania and along the Ohio River Valley: > 20 µg/m^3 (~8 ppb) SO_2 and > 15 µg/m^3 SO_4^{2-}. As with SO_2, in the years since the ARP controls were enacted, both the magnitude of SO_4^{2-} concentrations and their areal extent have been significantly reduced, with the largest decreases again along the Ohio River Valley.

Figure 2-10 depicts the magnitude and spatial distribution of SO_2 emissions in 2006 from sources in the ARP for the CONUS. This depiction clearly shows the continuing overrepresentation of SO_2 sources in the United States east of the Mississippi River, a trend even stronger in the central Ohio River Valley, as evident in the smoothed concentration plots in Figure 2-8. As shown in Table 2-3, regional distributions of SO_2 and SO_4^{2-} concentrations averaged for 2003–2005 reflect this geospatial emissions source difference as well.

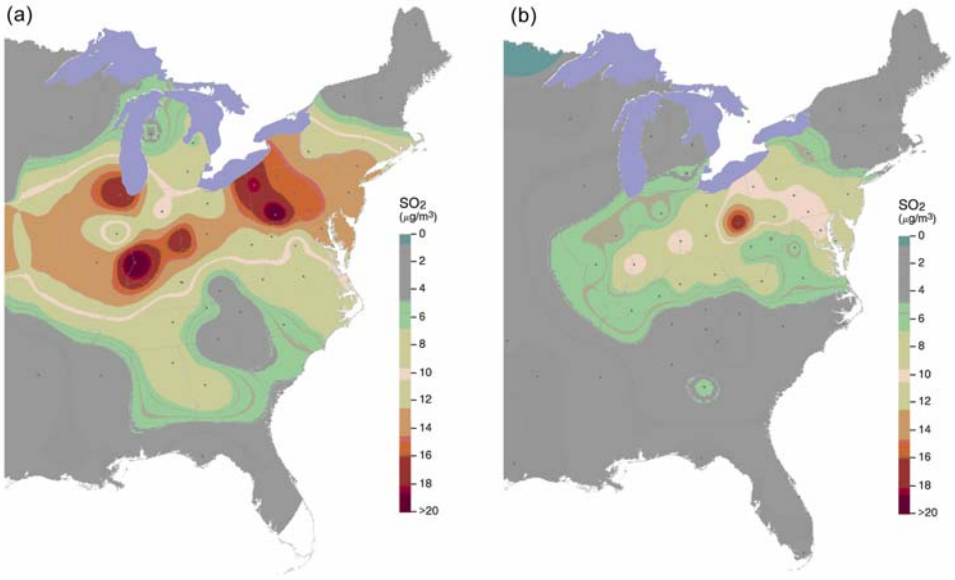

Figure 2-8. Annual mean ambient SO_2 concentration, 1989 through 1991 (a), and 2003 through 2005 (b).

Source: U.S. EPA CASTNet

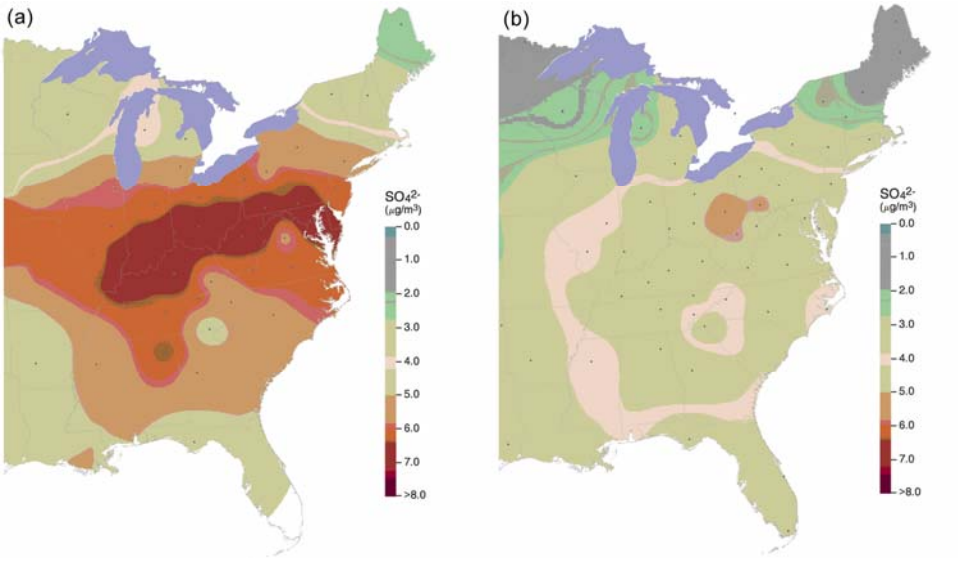

Figure 2-9. Annual mean ambient SO_4^{2-} concentration, 1989 through 1991 (a), and 2003 through 2005 (b).

Source: U.S. EPA CASTNet

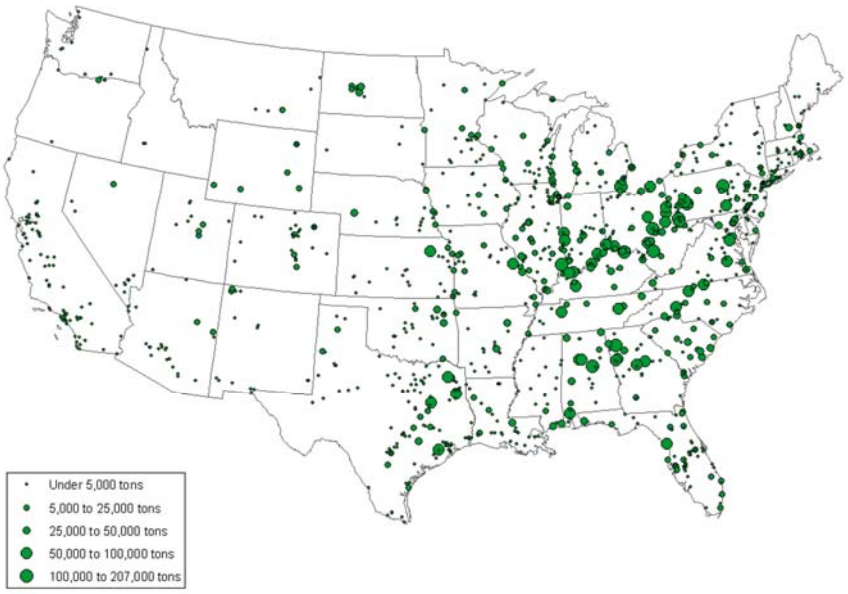

Figure 2-10. Annual SO_2 emissions for Acid Rain Program cooperating facilities, 2006.

Dots represent monitoring sites. Lack of shading for Southern Florida indicates lack of monitoring coverage.
Source: Environmental Protection Agency, Clean Air Markets Division (www.epa.gov/airmarkets/index.html).

2.4.4. Spatial and Temporal Variability of Ambient SO_2 Concentrations

SO_2 concentrations have been falling throughout all regions of the CONUS, as demonstrated by the CASTNet data reviewed above. In and around most individual CMSAs, the trends are also toward lower SO_2 levels. Table 2-4 shows that many annual and even 1-h mean concentrations for the years 2003 through 2005 were consistently at or below the operating LOD of ~3 ppb for the standard sensitivity UV fluorescence SO_2 monitors deployed in the regulatory networks, while the aggregate mean value over all 3 years and all sites in and around the CMSAs was just above the LOD at ~4 ppb, and identical to the 1-h and 24-h means. Hence, it appears reasonable to aggregate up in time from available 1-h samples to daily and even annual exposure estimates.

Figure 2-11 shows the composite diel variation in hourly SO_2 concentrations in boxplot form from all monitors reporting SO_2 data into AQS. The AQS contains measurements of air pollutant concentrations in the 50 states, plus the District of Columbia, Puerto Rico, and the Virgin Islands, for the six criteria air pollutants (SO_2, NO_2, PM, CO, Pb, O_3), as well as for hazardous air pollutants.

Table 2-3. Regional distribution of SO_2 and SO_4^{2-} ambient concentrations, averaged for 2003-05.

REGION	CONCENTRATION	
	SO_2 (ppb)	SO_4^{2-} (µg/m^3)
Mid-Atlantic	3.3	4.5
Midwest	2.3	3.8
Northeast	1.2	2.5
Southeast	1.3	4.1

Table 2-4. Distributions of temporal averaging inside and outside CMSAs.

AVERAGING TIME MONITOR LOCATIONS	N	MEAN	PERCENTILES											MAX
			1	5	10	25	30	50	70	75	90	95	99	
1-h Max Concentration														
Inside CMSAs	332405	13	1	1	1	3	4	7	13	16	30	45	92	714
Outside CMSAs	53417	13	1	1	1	1	2	5	10	13	31	51	116	636
1-h Avg Concentration														
Inside CMSAs	7408145	4	1	1	1	1	1	2	4	5	10	15	34	714
Outside CMSAs	1197179	4	1	1	1	1	1	2	3	3	7	13	36	636
24-h Avg Concentration														
Inside CMSAs	327918	4	1	1	1	1	2	3	5	6	10	13	23	148
Outside CMSAs	52871	4	1	1	1	1	1	2	3	4	8	12	25	123
Annual Avg Concentration														
Inside CMSAs	898	4	1	1	1	1	2	4	5	6	8	10	12	15
Outside CMSAs	143	4	1	1	1	1	2	3	4	5	8	9	13	14
Aggregate 3-yr Avg Concentration, 2003-2005														
Inside CMSAs	283	4	1	1	1	2	3	3	5	5	8	10	12	14
Outside CMSAs	42	4	1	1	1	2	2	3	4	5	8	9	13	13

* Values are ppb
** CMSA = Consolidated Metropolitan Statistical Area

To be sure, the max 1-h concentration observed at some sites in and around some CMSAs still exceeded the mean by a large margin, with max 1-h values of > 600 ppb. However, the 50th percentile maximum value outside CMSAs, 5 ppb, was only slightly greater than the 1-h, 24-h, and annual mean value, 4 ppb. The 50th percentile maximum value inside CMSAs, 7 ppb, was 75% greater than these longer-term averages, reflecting heterogeneity in source strength and

location. In addition, even with 1-h max values of > 600 ppb, the maximum annualized mean value for all CMSAs was still < 16 ppb, which is below the current annual primary SO_2 NAAQS.

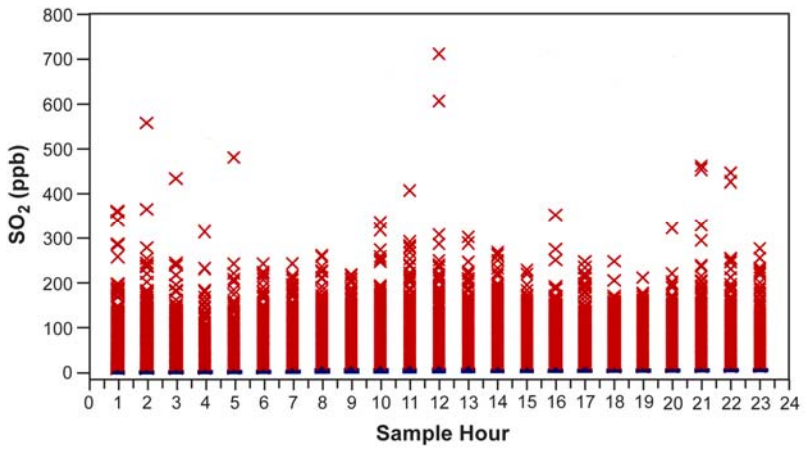

Figure 2-11. Boxplot of hourly SO_2 concentrations across all cities in focus.

The strong west-to-east increasing gradient in SO_2 emissions described above is well-replicated in the observed concentrations in individual CMSAs. For example, Table 2-5 shows the mean annual concentrations from 2003–2005 for the 12 CMSAs with four or more SO_2 regulatory monitors. Values ranged from a reported low of ~1 ppb in Riverside, CA and San Francisco, CA to a high of ~12 ppb in Pittsburgh, PA and Steubenville, OH, in the highest SO_2 source region.

The Pearson correlation coefficients (r) for multiple monitors in these CMSAs were generally very low for all cities, especially at the lower end of the observed concentration ranges, and even negative at the very lowest levels on the West Coast (see Table 2-5). This reflects strong heterogeneity in SO_2 ambient concentrations even within any one CMSA and, therefore, indicates possibly different exposures of spatially distinct subgroups of humans in these CMSAs to these very low concentrations of SO_2. At higher concentrations, the r values were also higher. In some CMSAs, this heterogeneity may result from meteorological effects, whereby a generally well-mixed subsiding air mass containing one or more SO_2 plumes with relatively high concentration would be more uniformly spread than faster-moving plumes with lower concentrations. However, instrument error may also play a role, because the highest r values, i.e., those > 0.7, correspond to the highest SO_2 concentrations, i.e., > 6 and > 10 ppb. Since the lowest SO_2 concentrations are at or below the operating LOD, and demonstrate the lowest correlation

across monitors that share at least some air mass characteristics most of the year, the unbiased instrument error in this range may be confounding interpretation of any possible correlation. This could be because the same actual ambient value would be reported by different monitors (with different error profiles) in the CMSA as different values in this lowest concentration range.

To better characterize the extent and spatiotemporal variance of SO_2 concentrations within each of the CMSAs having four or more SO_2 monitors, the means, minima, and maxima were computed from daily mean data across all available monitors for each month for the years 2003 through 2005. Because many of these CMSAs with SO_2 monitors also reported SO_4^{2-}, it is possible to compute the degree of correlation between SO_2, the emitted species, and SO_4^{2-}, the most prominent oxidized product from SO_2. SO_4^{2-} values, however, while averaged over all available data at each site are generally available at their monitoring sites on a schedule of only 1 in 3 days or 1 in 6 days. Furthermore, SO_2 and SO_4^{2-} monitors are not all co-located throughout the CMSAs. For each of the five example CMSAs in Figures 2-12 through 2-16, monthly aggregated values are depicted from daily means of: (a) the monthly mean, minimum, and maximum SO_2 concentrations; (b) the monthly mean, minimum and maximum SO_4^{2-} concentrations; and (c) a scatterplot of SO_2 versus SO_4^{2-} concentrations.

Table 2-5. Range of mean annual SO_2 concentrations and Pearson correlation coefficients in urban areas having at least four regulatory monitors, 2003–2005.

CMSA (# MONITORS)	MEAN SO_2 CONCENTRATION (ppb)	PEARSON CORRELATION COEFFICIENT
Philadelphia, PA (10)	3.6 – 5.9	0.37 – 0.84
Washington, DC (5)	3.2 – 6.5	0.30 – 0.68
Jacksonville, FL (5)	1.7 – 3.4	−0.03 – 0.51
Tampa, FL (8)	2.0 – 4.6	−0.02 – 0.18
Pittsburgh, PA (10)	6.8 – 12	0.07 – 0.77
Steubenville, OH (13)	8.6 – 14	0.11 – 0.88
Chicago, IL (9)	2.4 – 6.7	0.04 – 0.45
Salt Lake City, UT (5)	2.2 – 4.1	0.01 – 0.25
Phoenix, AZ (4)	1.6 – 2.8	−0.01 – 0.48
San Francisco, CA (7)	1.4 – 2.8	−0.03 – 0.60
Riverside, CA (4)	1.3 – 3.2	−0.06 – 0.15
Los Angeles, CA (5)	1.4 – 4.9	−0.16 – 0.31

In Steubenville, OH (Figure 2-12), the area of highest SO_2 concentrations of all 12 CMSAs with more than four monitors, all monthly mean SO_2 concentrations (a) were substantially < 30 ppb, though max daily means in some months were often > 60 ppb, or even > 90 ppb. Sulfate data (b) at Steubenville were insufficient to make meaningful comparisons, though the 12 months of available SO_4^{2-} data suggest no correlation with SO_2 (c).

Next, consider Philadelphia, PA (Figure 2-13). SO_2 in Philadelphia, PA (a) is present at roughly one-half the monthly mean concentrations in Steubenville, OH, and demonstrates a strong seasonality with SO_2 concentrations peaking in winter. By contrast, SO_4^{2-} concentrations in Philadelphia peak in the three summer seasons, with pronounced wintertime minima. This seasonal anticorrelation still contains considerable monthly scatter, however.

Los Angeles, CA (Figure 2-14) presents a special case, since its size and power requirements place a larger number of SO_2 emitters near it than would otherwise be expected on the West Coast. Concentrations of SO_2 demonstrate weak seasonality in these 3 years, with summertime means of ~3 to 4 ppb, and maxima generally higher than wintertime ones, though the highest means and maxima occur during the winter of 2004–2005. SO_4^{2-} at Los Angeles shows stronger seasonality, most likely because the longer summer days of sunny weather allow for additional oxidation of SO_2 to SO_4^{2-} than would be available in winter. Weak seasonal effects in SO_2 likely explain the complete lack of correlation between SO_2 and SO_4^{2-} here.

The Riverside, CA CMSA (Figure 2-15) presents the strongest example among the 12 examined for this study of correlation between SO_2 and SO_4^{2-}, though even here the R^2 value is merely 0.3. Seasonal peaks are obvious in summertime for SO_2 and SO_4^{2-}, both at roughly one-half the ambient concentrations seen in Los Angeles. This is very likely due to Riverside's geographic location just downwind of the regionally large electric generating utility sources near Los Angeles and the prevailing westerly winds in summer. Again, as with Los Angeles, the summertime peaks in SO_4^{2-} are most likely due to the combination of peaking SO_2 and favorable meteorological conditions allowing more complete oxidation.

Phoenix, AZ was the CMSA with the lowest monthly mean SO_2 and SO_4^{2-} concentrations examined here (Figure 2-16). In Phoenix, nearly all monthly mean SO_2 values were at or below the regulatory monitors' operating LOD of ~3 ppb. SO_4^{2-} concentrations were equivalently low, roughly one-half the concentrations seen in Riverside, CA, for example. The monthly mean data show strong summertime peaks for even these very low-level SO_4^{2-} observations, which, at ~1 to

3 $\mu g/m^3$, were generally one-half of those in Philadelphia. This suggests some seasonality in SO_2, though anticorrelated with SO_4^{2-}; however, the trend is very weak, as the correlation scatterplot shows.

2.4.5. 5-Minute Sample Data in the Monitoring Network

Although the number of monitors across the CONUS varies somewhat each year, in 2006 there were ~500 SO_2 monitors in the NAAQS monitoring network (http://www.epa.gov/air/data). The state and local agencies responsible for these monitors are required to report 1-h avg concentrations to the EPA AQS. In addition, a very small number of sites—only 108 total from 1997 to 2006, and not the same sites in all years—voluntarily reported 5-min block avg to AQS. Of these, 104 reported only the max 5-minute average, 15 reported all 12 5-minute avg in each hour, and 11 of those 15 reported all 12 values each hour and maximum values for some fraction of time between 1997 and 2006. See Table 2-6 and Table 2-7 for a breakdown of these monitor locations and sampling periods, and Figure 2-17 for the geospatial distribution of these monitors across the CONUS.

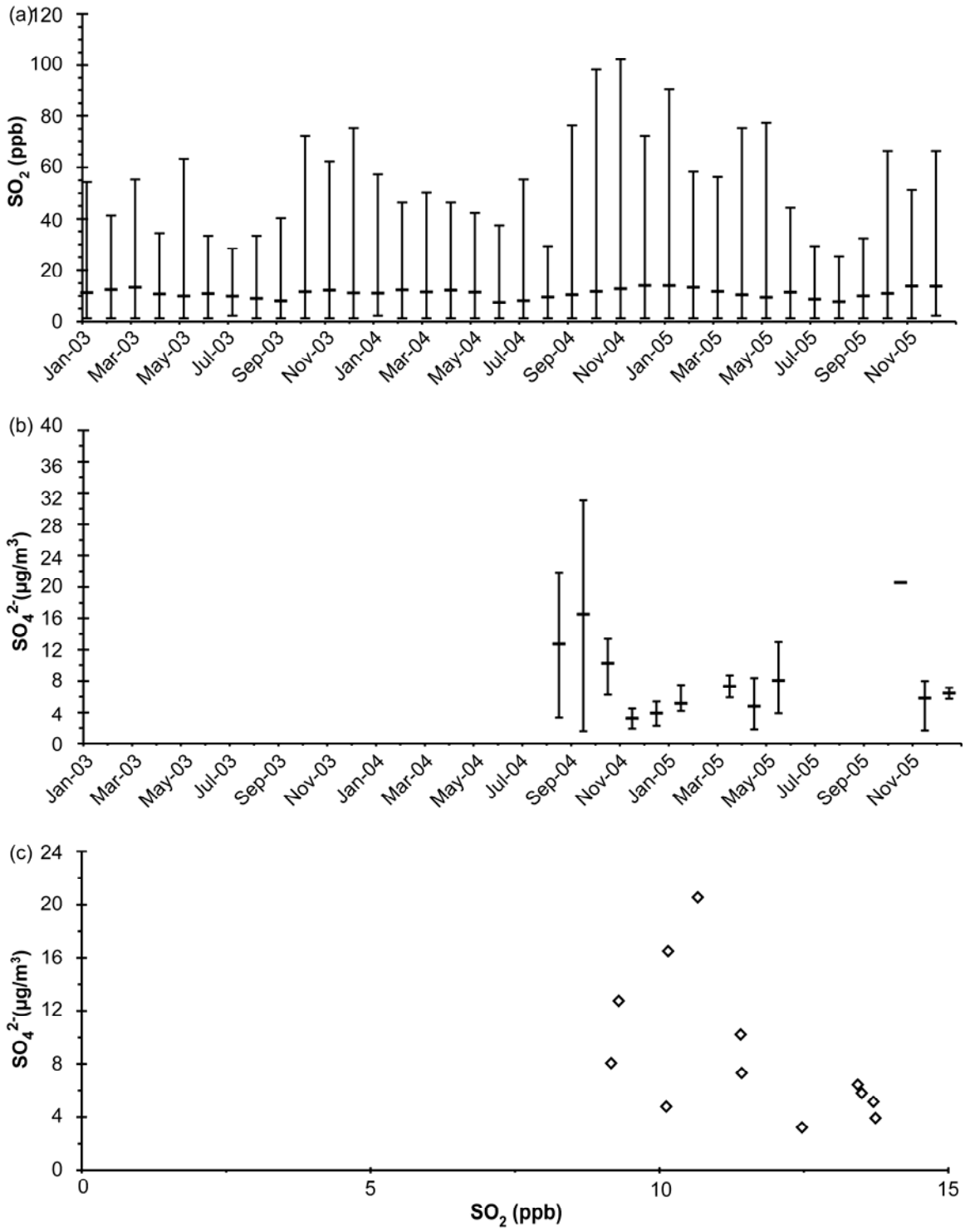

Figure 2-12. Steubenville, OH, 2003–2005. (a) Monthly mean, minimum, and maximum SO_2 concentrations. (b) Monthly mean, minimum, and maximum SO_4^{2-} concentrations. (c) Monthly mean SO_4^{2-} concentrations as a function of SO_2 concentrations.

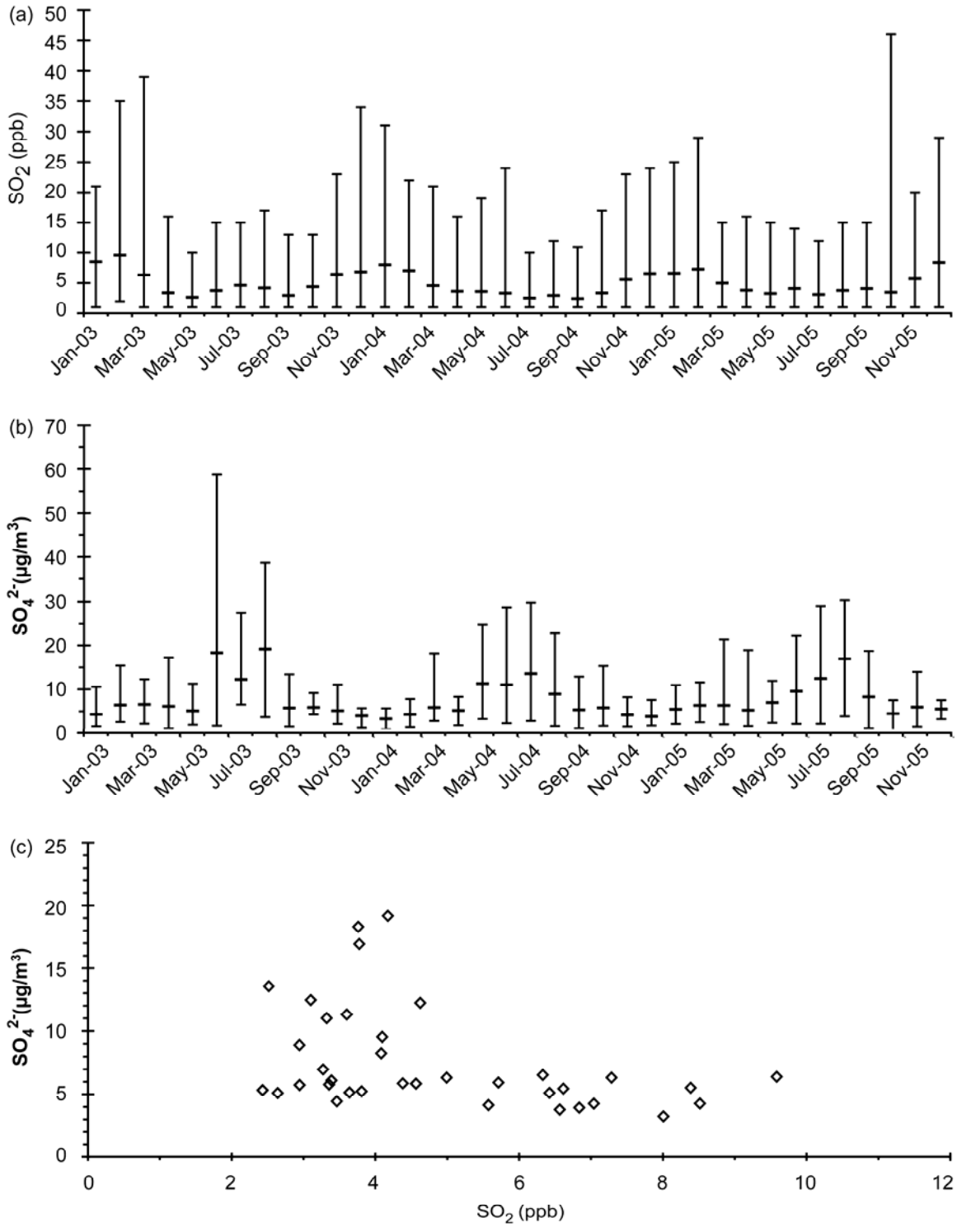

Figure 2-13. Philadelphia, 2003–2005. (a) Monthly mean, minimum, and maximum SO_2 concentrations. (b) Monthly mean, minimum, and maximum SO_4^{2-} concentrations. (c) Monthly mean SO_4^{2-} concentrations as a function of SO_2 concentrations.

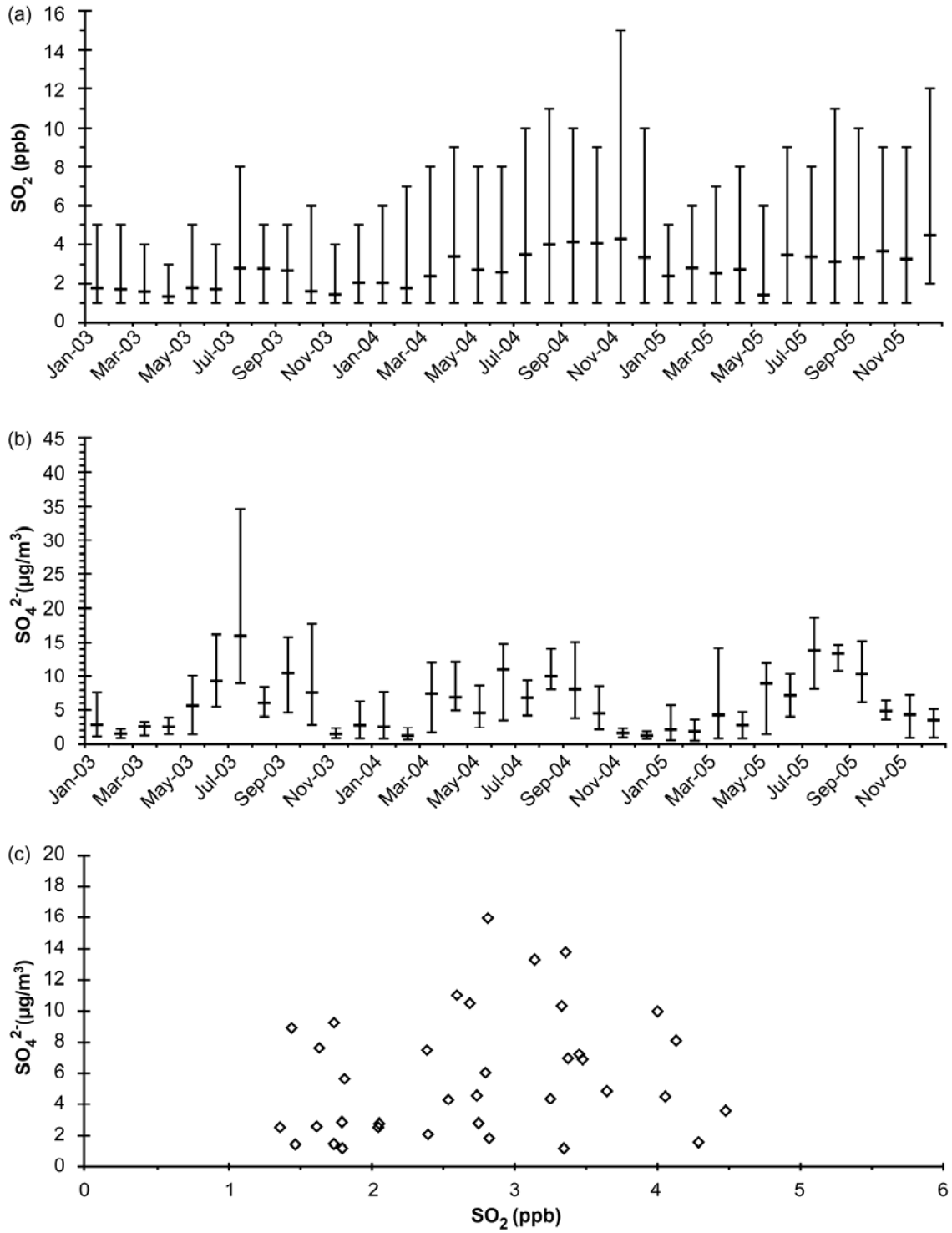

Figure 2-14. Los Angeles, 2003–2005. (a) Monthly mean, minimum, and maximum SO_2 concentrations. (b) Monthly mean, minimum, and maximum SO_4^{2-} concentrations. (c) Monthly mean SO_4^{2-} concentrations as a function of SO_2 concentrations.

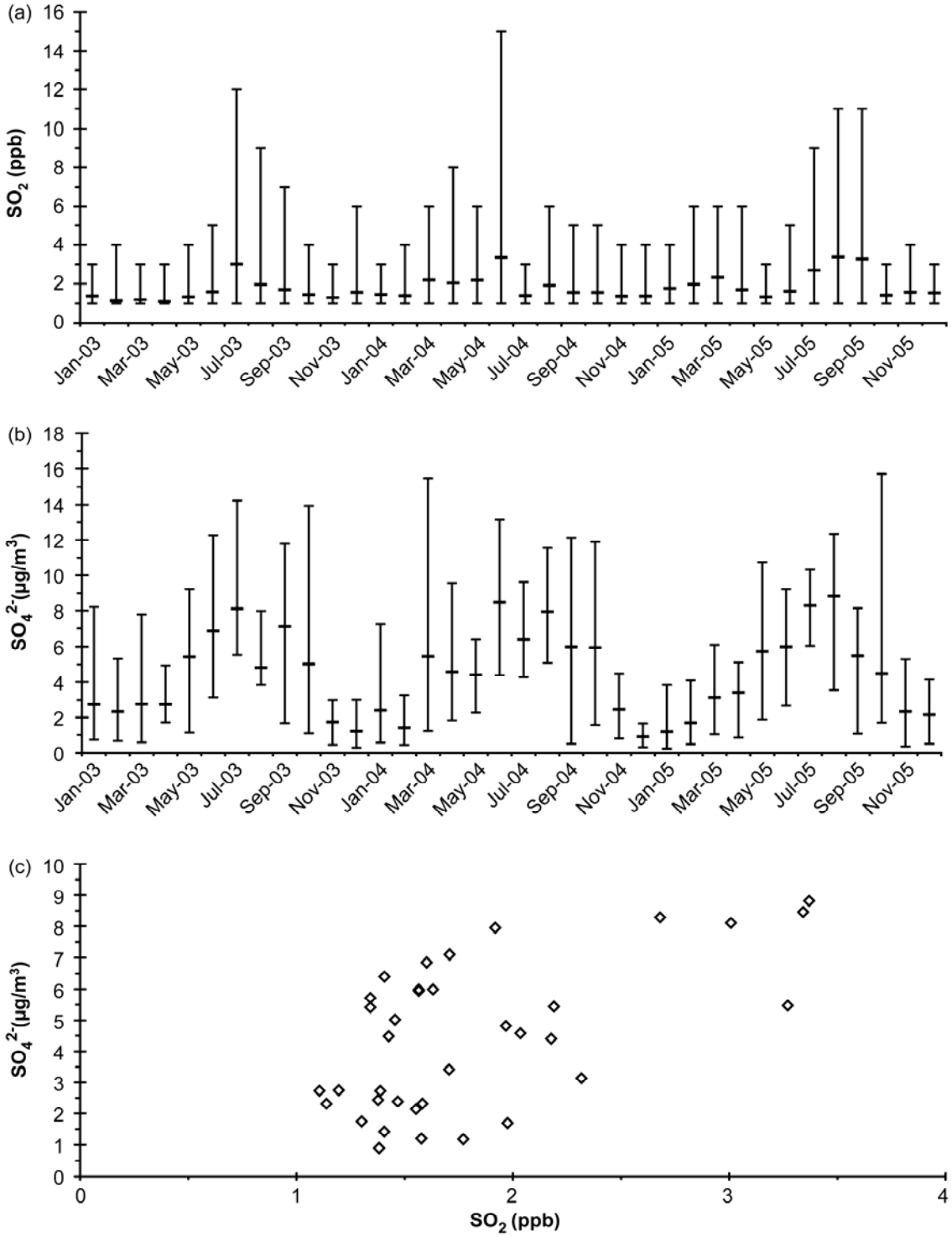

Figure 2-15. Riverside, CA, 2003–2005. (a) Monthly mean, minimum, and maximum SO_2 concentrations. (b) Monthly mean, minimum, and maximum SO_4^{2-} concentrations. (c) Monthly mean SO_4^{2-} concentrations as a function of SO_2 concentrations.

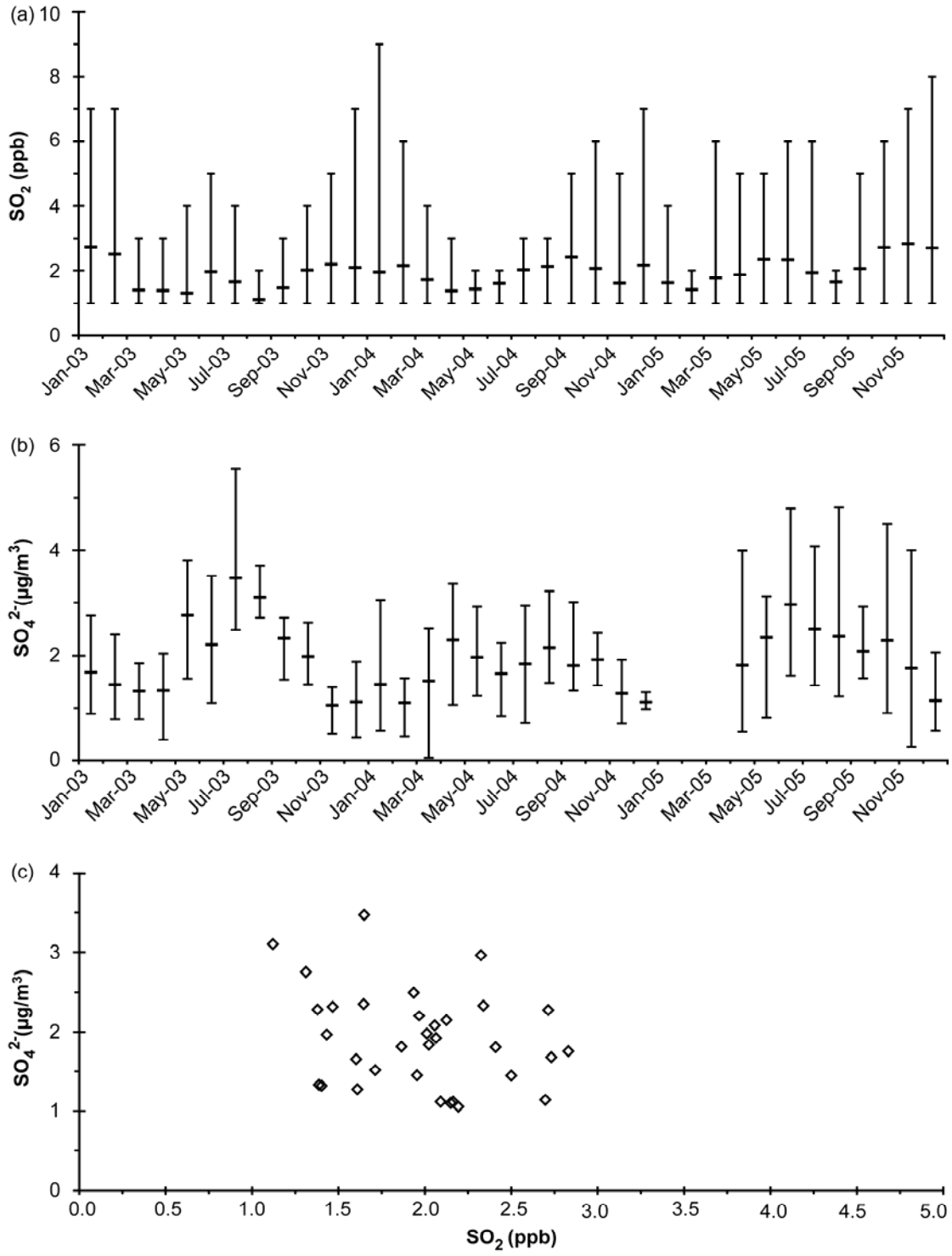

Figure 2-16. Phoenix, 2003–2005. (a) Monthly mean, minimum, and maximum SO_2 concentrations. (b) Monthly mean, minimum, and maximum SO_4^{2-} concentrations. (c) Monthly mean SO_4^{2-} concentrations as a function of SO_2 concentrations.

Although these 5-minute data meet AQS minimum quality assurance requirements, the voluntary nature of this reporting and the high variability across space and time make these data very difficult to use precisely.

Table 2-6. Locations, counts, and sampling periods of monitors reporting 5-minute maximum SO_2 values, 1997–2006.

STATE	NUMBER OF COUNTIES	NUMBER OF MONITORS	NUMBER OF YEARS	YEARS OPERATING
Arkansas	2	3	10	1997-2006
Colorado	1	1	10	1997-2006
Delaware	1	1	2	1997-1998
D.C.	1	1	5	2000-2004
Iowa	6	9	5	2001-2005
Louisiana	1	1	4	1997-2000
Missouri	7	14	10	1997-2006
Montana	1	7	10	1997-2006
North Carolina	1	1	8	1997-2004
North Dakota	11	19	10	1997-2006
Pennsylvania	8	23	7	1997-2003

Table 2-7. Locations, counts, and sampling periods of monitors reporting all 12 5-minute SO_2 values in each hour, 1997–2006.

STATE	NUMBER OF COUNTIES	NUMBER OF MONITORS	NUMBER OF YEARS	YEARS OPERATING
D.C.	1	1	1	2007
Florida	1	1	4	2002-2005
Missouri	1	2	4	2003-2006
Montana	1	4	1	2002
North Carolina	1	1	4	1999-2002
Pennsylvania	2	5	5	2002-2006
West Virginia	2	2	5	2001-2005

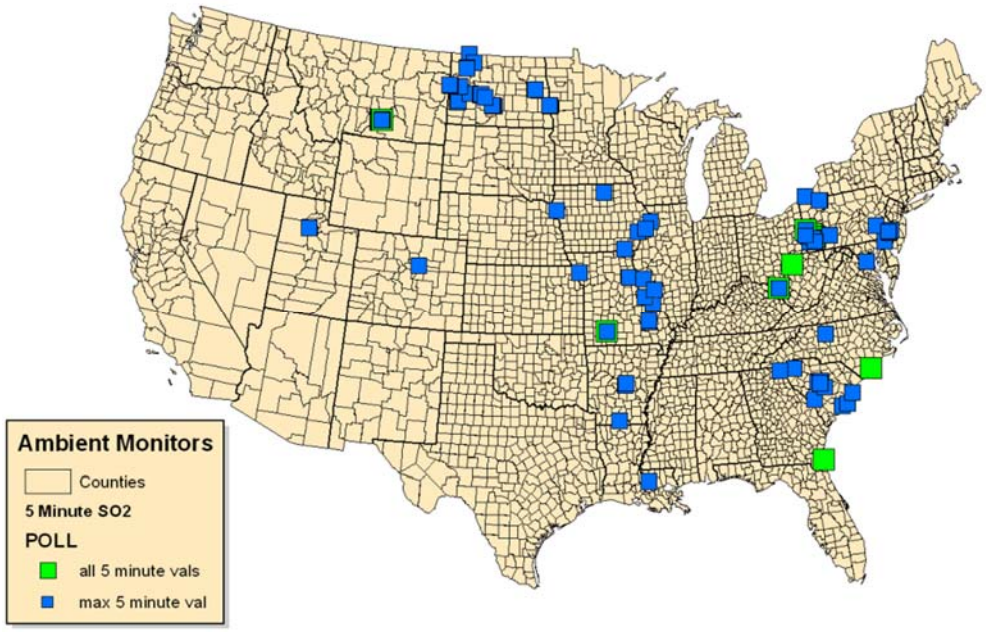

Figure 2-17. SO_2 monitors reporting maximum or continuous 5-minute average values for any period, 1997–2006.

2.4.6. Policy Relevant Background Contributions to SO_2 Concentrations

Background concentrations used for purposes of informing decisions about the NAAQS are referred to as Policy Relevant Background (PRB) concentrations. PRB concentrations are those concentrations that would occur in the United States in the absence of anthropogenic emissions in continental North America (defined here as the United States, Canada, and Mexico). PRB concentrations include contributions from natural sources everywhere in the world, and from anthropogenic sources outside these three countries. Background levels so defined facilitate separation of cases where pollution levels can be controlled by U.S. regulations (or through international agreements with neighboring countries), from cases where pollution is generally uncontrollable by the United States. EPA assesses risks to human health and environmental effects from SO_2 levels in excess of PRB concentrations.

Contributions to PRB concentrations include natural emissions of SO_2 and photochemical reactions involving reduced sulfur compounds of natural origin, as well as their long-range transport from outside of North America from any source. As an example, transport of SO_2 from Eurasia across the Pacific Ocean or the Arctic Ocean would carry PRB SO_2 into the U.S.

Annex B contains a schematic diagram showing the major photochemical processes involved in the sulfur cycle, including natural sources of reduced sulfur species from anaerobic microbial activity in wetlands and volcanic activity. Volcanoes and wildfires are the major natural source of SO_2. Biogenic emissions from agricultural activities are not considered in the formation of PRB concentrations. Discussions of the sources and estimates of emissions are given in Annex Section B.6.

The MOZART-2 global model of tropospheric chemistry (Horowitz et al., 2003) is used to estimate the PRB contribution to SO_2 concentrations. The model setup for the present-day simulation, i.e., including all sources in the U.S. Canada and Mexico, was published in a series of papers from a recent model intercomparison (Dentener et al., 2006; van Noije et al., 2006). MOZART-2 is driven by the National Oceanic and Atmospheric Administration's National Center for Environmental Prediction (NOAA/NCEP) meteorological fields and the International Institute for Applied Systems Analysis (IIASA) 2000 emissions at a resolution of $1.9° \times 1.9°$ with 28 σ (sigma) levels in the vertical, and includes gas- and aerosol-phase chemistry. Results shown in Figure 2-18 are for the meteorological year 2001. An additional PRB simulation was conducted in which continental North American anthropogenic emissions were set to zero.

The role of PRB in contributing to SO_2 concentrations in surface air is examined first. Figure 2-18 shows the annual mean predicted SO_2 concentrations in surface air in the simulation including all sources, or the "base case" (top panel); the PRB simulation (middle panel); and the percentage contribution of the background to the total base case SO_2 (bottom panel). Maximum concentrations in the base case simulation, > 5 ppb, occur along the Ohio River Valley (upper panel). Background SO_2 concentrations are orders of magnitude smaller, below 10 parts per trillion (ppt) over much of the United States (middle panel). Maximum PRB concentrations of SO_2 are 30 ppt. In the Northwest where there are geothermal sources of SO_2, the contribution of PRB to total SO_2 is 70 to 80%; however absolute SO_2 concentrations are still of the order of a couple of ppb or less. With the exception of the West Coast where volcanic SO_2 emissions cause high PRB concentrations, PRB contributes < 1% to present-day SO_2 concentrations in surface air (bottom panel).

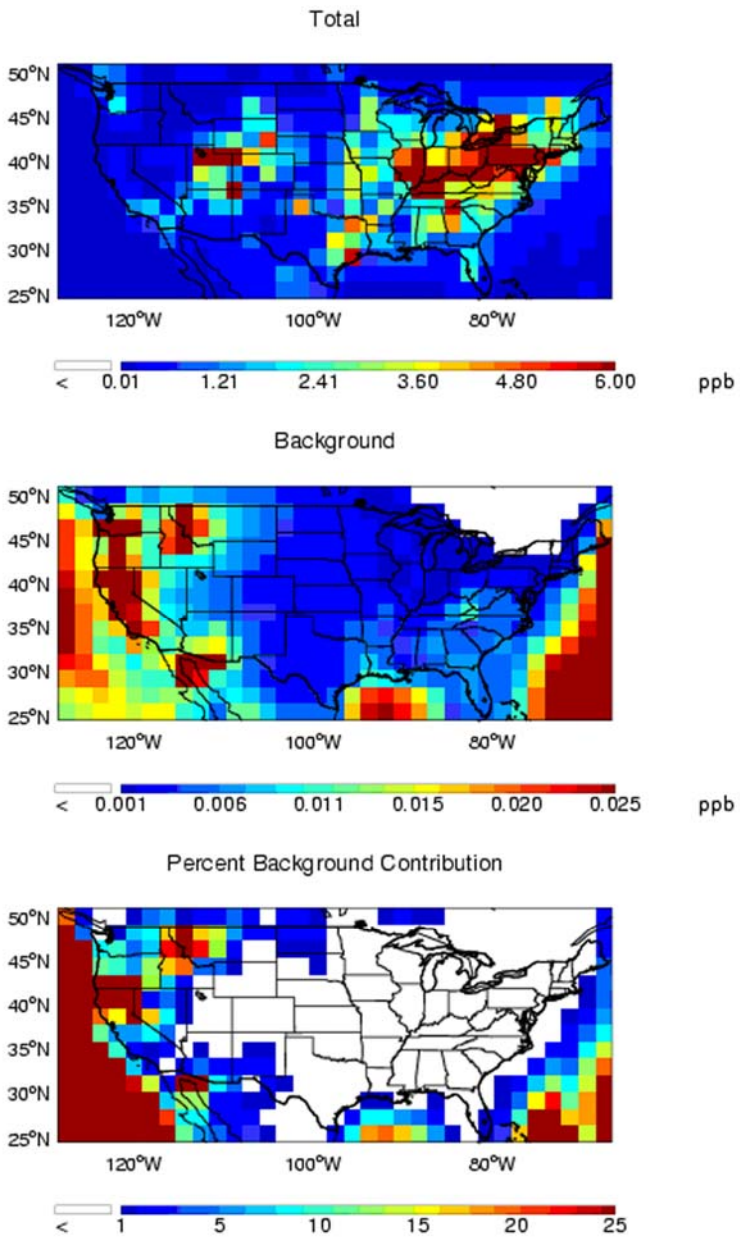

Figure 2-18. Annual mean model-predicted concentrations of SO_2 (ppb).

When estimating background concentrations it is instructive to consider measurements of SO_2 at relatively remote monitoring sites, i.e., sites located in sparsely populated areas not subject to obvious local sources of pollution. Berresheim et al. (1993) used a type of atmospheric pressure ionization mass spectrometer (APIMS) at Cheeka Peak, WA (48.30°N 124.62°W, 480 m asl), in April 1991 during a field study for DMS oxidation products. SO_2 concentrations ranged between 20 and 40 ppt. Thornton et al. (2002) have also used an APIMS with an

isotopically labeled internal standard to determine background SO_2 levels. SO_2 concentrations of 25 to 40 ppt were observed in northwestern Nebraska in October, 1999 at 150 m above ground using the National Center for Atmospheric Research (NCAR)'s C-130 research aircraft. These data are comparable to remote central South Pacific convective boundary layer SO_2 data (Thornton, 1999).

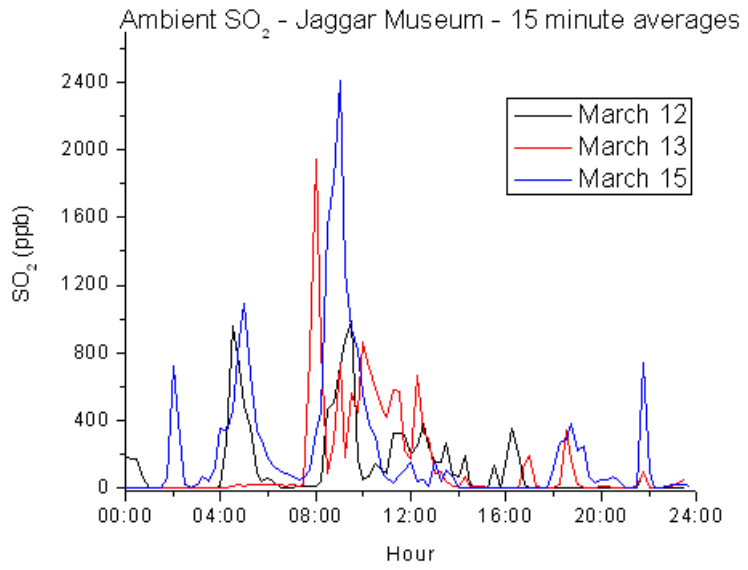

Figure 2-19. 15-minute average ambient SO_2 concentrations measured at Hawaii Volcanoes National Park monitoring sites, March 12, 13, and 15, 2007.

Source: National Park Service

As noted earlier, volcanic sources of SO_2 in the United States are found in the Pacific Northwest, Alaska, and Hawaii. The greatest potential domestic effects from volcanic SO_2 occurs on the island of Hawaii. Nearly continuous venting of SO_2 from Mauna Loa and Kilauea produces SO_2 in high concentrations (see Figure 2-19 and Figure 2-20) at two National Park sites near the Kilauea caldera and the nearby east rift zone. The latter emits several times as much SO_2 as the Kilauea caldera. The two measurement sites within the National Park are < 3 km from the summit emission source and ~10 km from the east rift source and are affected by the two sources during southerly and easterly winds. A number of communities and population centers are within the same distance from the east rift gas source that affects these two monitoring sites. When the

normal trade wind flows are disrupted, emissions from the sources can be brought directly to these various communities. Since these communities are located at a similar distance from the large east rift emission source as the Park monitoring stations, it is probable that these communities experience SO_2 concentrations as high as those measured within Hawaii Volcanoes National Park.

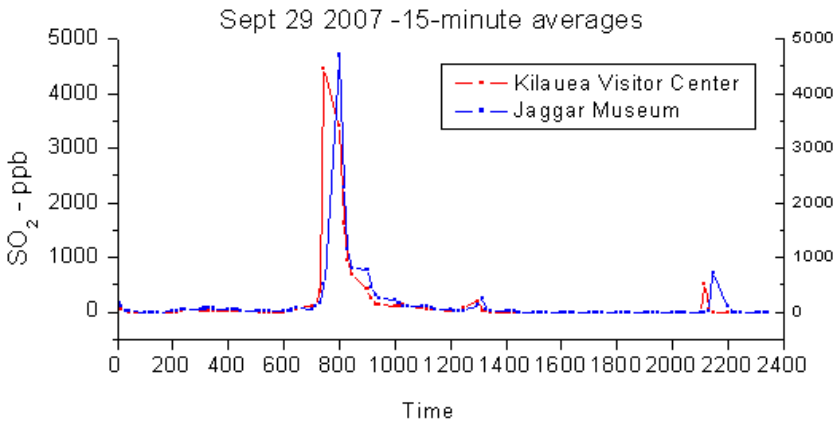

Figure 2-20. 15-minute average ambient SO_2 concentrations measured at the two National Park monitoring sites at Hawaii Volcanoes NP, Hawaii on September 29, 2007.

Source: National Park Service

Since 1980, the Mount St. Helens volcano (46.20°N, 122.18°W, summit 2549 m asl) in the Washington Cascade range has been a variable source of SO_2. Its major effects came in the explosive eruptions of 1980, which primarily affected the northwestern United States. The Augustine volcano near the mouth of the Cook Inlet in southwestern Alaska (59.363°N, 153.43°W, summit 1252 m asl) has emitted variable quantities of SO_2 since its last major eruptions in 1986. Volcanoes in the Kamchatka peninsula in far eastern Siberia do not particularly affect the surface concentrations in northwestern North America.

Overall, the background contribution to SO_2 over the United States is relatively small, with a max PRB of 0.030 ppb SO_2, except for areas with volcanic activity.

2.5. Issues Associated with Evaluating SO_2 Exposure

2.5.1. General Considerations for Personal Exposure

Human exposure to an airborne pollutant consists of contact between the human and the pollutant at a specific concentration for a specified period of time. People spend various amounts of time in different microenvironments characterized by different pollutant concentrations. The integrated exposure of a person to a given pollutant is the sum of the exposures over all time intervals for all microenvironments. Figure 2-21 represents a composite average of activity patterns across all age groups in the United States, based on data collected in the National Human Activity Pattern Survey (NHAPS) (Klepeis et al., 2001). The demographic distribution of the respondents was designed to be similar to that of overall U.S. Census data. Different cohorts, e.g., the elderly, young and middle-aged working adults, and children exhibit different activity patterns.

A person's exposure to a pollutant, such as SO_2, can be represented by:

$$E_T = \sum_{i=l}^{n} C_i t_i \tag{2-7}$$

where E_T is an individual's total personal exposure for a specific time period, n is the total number of microenvironments encountered, C_i is the average concentration, and t_i is the time spent in the *ith* microenvironment. The exposure a person experiences can be characterized as: an instantaneous exposure; a peak exposure such as might occur during cooking; an average exposure; or an integrated exposure over all environments encountered. These distinctions are important because health effects caused by long-term low-level exposures may differ from those caused by short-term peak exposures.

An individual's total exposure (E_T) can also be represented by:

$$E_T = E_a + E_{na} = \{y_o + \sum_i y_i \, [P_i a_i/(a_i + k_i)] \, \} C_a + E_{na} = \{y_o + \sum_i y_i F_{inf_i}\} C_a + E_{na} \tag{2-8}$$

subject to the constraint

$$y_o + \sum_i y_i = 1 \tag{2-9}$$

where E_a is the ambient component of personal exposure, E_{na} is the nonambient component of personal exposure, y_o is the fraction of time spent outdoors, and y_i is the fraction of time spent in microenvironment i. F_{inf_i}, P_i, a_i, and k_i are the infiltration factor, penetration coefficient, air exchange rate, and decay rate, respectively for microenvironment i. In the case where an exposure occurs mainly in one microenvironment, Equation 2-8 may be approximated by Equation 2-10 where y is the fraction of time spent outdoors, and α is the ratio of personal exposure from a pollutant of ambient origin to the pollutant's ambient concentration (or the ambient exposure factor). Other symbols have the same definitions as in Equations 2-8 and 2-9.

$$E_T = E_a + E_{na} = \{y + (1-y)[Pa/(a+k)]\}C_a + E_{na} = \alpha C_a + E_{na} \quad (2\text{-}10)$$

If concentrations in a single microenvironment are considered, then Equation 2-10 can be recast as

$$C_{me} = C_a + C_{na} = [Pa/(a+k)]C_a + S/[V(a+k)] \quad (2\text{-}11)$$

where C_{me} is the concentration in a microenvironment, C_a and C_{na} are the contributions to C_{me} from ambient and nonambient sources, S is the microenvironmental source strength, and V is the volume of the microenvironment. (Bracketed symbols are same as Equation 2-8.) In this equation, it is assumed that microenvironments do not exchange air with each other, but only with the ambient environment.

Microenvironments in which people are exposed to air pollutants such as SO_2 typically include residential indoor environments, other indoor locations, near-traffic outdoor environments, other outdoor locations, and in vehicles, as shown in Figure 2-21. Indoor combustion sources such as gas stoves and space heaters need to be considered when evaluating exposures to SO_2. Exposure misclassification may result when total human exposure is not disaggregated between various microenvironments, and this may obscure the true relationship between ambient air pollutant exposures and health outcomes.

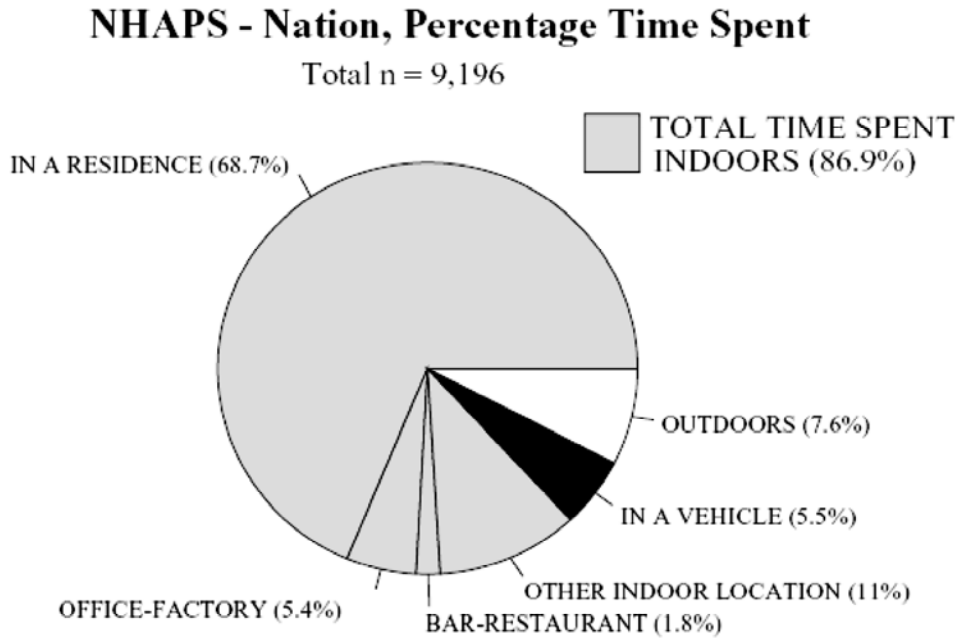

Figure 2-21. Percentage of time spent in various environments in the United States.[1]

Source: Klepeis et al. (2001).

In a given microenvironment, the ambient component of a person's microenvironmental exposure to a pollutant is determined by the following physical factors:

- ambient concentration C_a
- air exchange rate a_i
- pollutant specific penetration coefficient P_i
- pollutant specific decay rate k_i
- fraction of time an individual spends in the microenvironment y_i

These factors are in turn affected by the following exposure factors:

- environmental conditions, such as weather and season

[1] For example, the cohort of working adults between the ages of 18 and 65 represents ~50% of the population. Of this total, about 60% work outside the home, spending ~24% (40 h/168 h) of their time in factory/office environments. Thus, this cohort is likely to spend considerably more time in offices and factories than shown in the figure (5.4%), which reflects the entire population, and is also likely to spend less time in a residence than small children or the elderly.

- dwelling conditions, such as the location of the house which determines proximity to sources and geographical features that can modify transport from sources, the amount of natural ventilation (e.g., open windows and doors, and the "draftiness" of the dwelling) and ventilation system (e.g., removal efficiency and operation cycle)
- personal activities (e.g., the time spent cooking or commuting)
- indoor sources and sinks of a pollutant

Microenvironmental exposures can also be influenced by the individual-specific factors such as age, gender, health or socioeconomic status.

Time-activity diaries, completed by study participants, are used to compile activity patterns for input to exposure models and assessments. The EPA's National Exposure Research Laboratory (NERL) has consolidated the majority of the most significant human activity databases into one comprehensive database called the Consolidated Human Activity Database (CHAD). Eleven different human activity pattern studies were evaluated to obtain over 22,000 person-days of 24-h human activities in CHAD (McCurdy et al., 2000). These data can be useful in assembling population cohorts to be used in exposure modeling and analysis.

In general, the relationship between personal exposures and ambient concentrations can be modified by microenvironments. During infiltration, ambient pollutants can be lost through chemical and physical loss processes, and therefore, the ambient component of a pollutant's concentration in a microenvironment is not the same as its ambient concentration but the product of the ambient concentration and the infiltration factor (F_{inf} or α if people spend 100% of their time indoors). In addition, exposure to nonambient, microenvironmental sources modifies the relationship between personal exposures and ambient concentrations.

In practice, it is extremely difficult to characterize community exposures by measurements of each individual's personal exposures. Instead, the distribution of personal exposures in a community, or the population exposure, is simulated by extrapolating measurements of personal exposure using various techniques or by stochastic, deterministic or hybrid exposure modeling approaches such as APEX, SHEDS, and MENTOR (see Annex Section C.2 for a description of modeling methods). Variations in community-level personal exposures are determined by cross-community variations in ambient pollutant concentrations and the physical and exposure factors mentioned above. These factors also determine the strength of the association between population exposure to SO_2 of ambient origin and ambient SO_2 concentrations.

Of major concern is the ability of SO_2, measured by ambient monitors, to serve as a reliable indicator of personal exposure to SO_2 of ambient origin. The key question is what errors are associated with using SO_2 measured by ambient monitors as a surrogate for personal exposure to ambient SO_2 and/or its oxidation products in epidemiological studies. There are three aspects to this issue: (1) ambient and personal sampling issues; (2) the spatial variability of ambient SO_2 concentrations; (3) the associations between ambient concentrations and personal exposures as influenced by exposure factors, e.g., indoor sources and time spent indoors and outdoors. Items (1) and (3) are treated individually in the following sections; item (2) was treated previously in Section 2.4.2.

2.5.2. Methods Used for Monitoring Personal Exposure

Three basic methods of analysis have been used as personal exposure monitors (PEMs) to measure personal exposure to SO_2. The Harvard-EPA annular denuder system (HEADS) was initially developed to measure particles and acid gases simultaneously (Brauer et al., 1999; Koutrakis et al., 1988). The aerosol is initially sampled at 10 L/min through an impactor that is attached to an annular denuder to remove particles. Subsequently, the aerosol is sampled through an annular denuder coated with sodium carbonate (Na_2CO_3). This denuder is used to trap SO_2, nitric acid (HNO_3), and nitrous acid (HNO_2). Following sampling, the denuder is extracted with ultrapure water and analyzed by ion chromatography. Collection efficiencies of SO_2 in the denuder are typically around 0.993, which compares well with predicted values.

For a study conducted in Baltimore, MD, Chang et al. (2000) developed and employed a personal roll-around system (RAS, an active sampling system designed to measure short-term exposure) to measure personal exposure concentrations of several atmospherically relevant species, including SO_2. For the measurement of SO_2, the RAS employed an NO_2/SO_2 sorbent denuder worn on a vest by the study participant. The hollow glass denuder, encased in an aluminum jacket, is coated with triethanolamine (TEA) for the collection of SO_2 and NO_2, and aerosol is sampled through the denuder at 100 cc/min. Following sampling, the denuder can be extracted and analyzed for SO_2 concentrations by ion chromatography. The detection limit for 1-h sampling of SO_2 was reported to be 62 ppb, which resulted in many of the 1-h samples being below the LOD.

The most commonly employed SO_2 PEM method for personal exposure studies is the passive badge sampler. A personal multipollutant sampler has been developed to measure particulate and gaseous pollutants simultaneously (Demokritou et al., 2001). A single elutriator, operating at 5.2 L/min, is employed to sample particulate pollutants. A passive SO_2 badge is attached diametrically to the elutriator, which has been coated with Teflon to minimize reactive gas losses. The passive badge sample is coated with TEA for the collection of SO_2 and NO_2. Because wind speed can affect the collection rate of the passive badge sampler, this system employs a constant face velocity across the passive badge sampler. For 24-h sampling times, the estimated limit of detection (LOD) for SO_2 is 5 ppb.

Currently, limits exist for using PEM systems to measure personal exposure to SO_2. Because SO_2 concentrations have been declining annually in the United States, little focus has been placed on improving the methods of analysis. LODs for SO_2 PEMs (~5-10 ppb for 24 hr sampling) are often greater than the concentrations of SO_2 that are typically observed in urban ambient environments. However, much lower detection limits can be achieved by extending the sampling time (Kasper-Giebl et al., 1999). Personal exposure monitoring studies often suffer from having many of the daily SO_2 samples (e.g., 30 to 70%) collected below the sampler's LOD (see Tables 2-10 and 2-11). Because of these issues, current methods can not characterize hourly or shorter exposures unless these values are in the range of several tens to hundreds of ppb.

2.5.3. Relationship between Personal Exposure and Ambient Concentration

Because SO_2 concentrations have declined markedly over the past few decades, relatively few studies have focused on SO_2. Another consideration is that current indoor and outdoor levels in many areas are often beneath detection limits for passive personal SO_2 monitors.

2.5.3.1. Indoor Versus Outdoor SO_2 Concentrations

Several studies in the United States, Canada, Europe, and Asia have examined the relationships of indoor, outdoor, and personal concentrations of SO_2 to ambient SO_2 concentrations. Perhaps the most comprehensive set of indoor-outdoor data was obtained by Spengler et al. (1979) during the Harvard Six Cities Study. These data are shown in Figure 2-22.

Twenty-four-hour ambient and indoor SO_2 concentrations were measured every sixth day for 1 year in a minimum of 10 homes or public facilities for each of the cities studied.

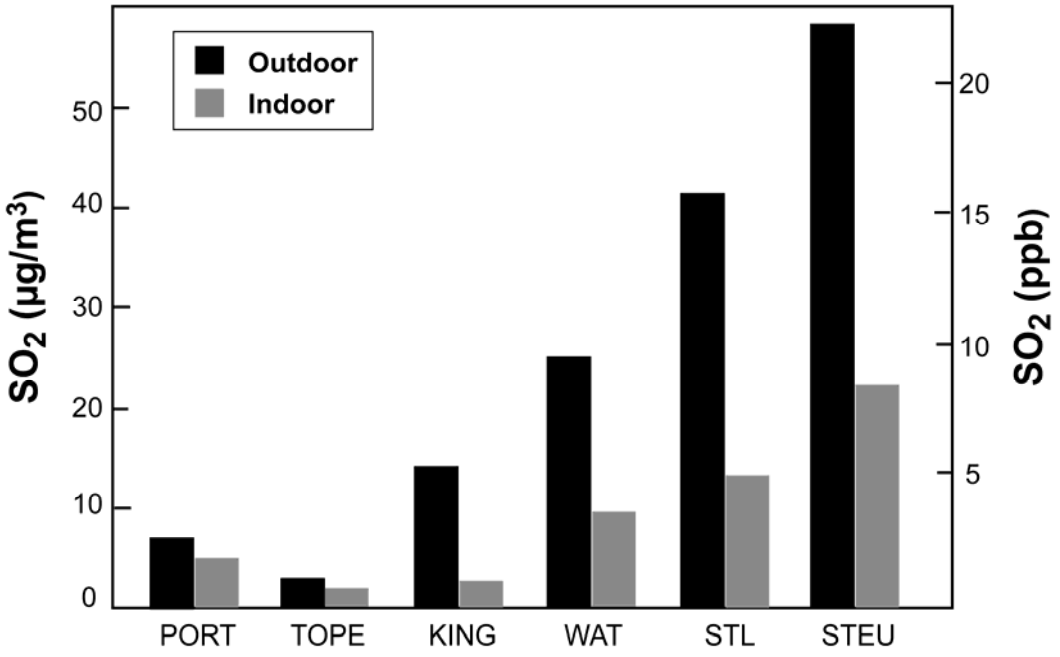

Figure 2-22. Average annual indoor and outdoor SO_2 concentrations for each of the six cities included in the analysis.

PORT = Portage, WI TOPE = Topeka, KS KING = Kingston, TN
WAT = Watertown, MA STL = St. Louis, MO STEU = Steubenville, OH.

Source: Adapted from Spengler et al. (1979).

As can be seen from Table 2-8, a wide range is found in the ratio of indoor to outdoor concentrations among the different studies. These differences among studies could be due in part to differences in building characteristics (e.g., residences versus schools or other public buildings), in activities affecting air exchange rates, and in analytical capabilities. In several studies, high values for R^2 were found, suggesting that indoor levels were largely driven by outdoor levels. A few studies found higher levels of SO_2 indoors than outdoors in some samples. This situation could have arisen if there were indoor sources or because of analytical measurement issues. One would expect to find lower concentrations indoors than outdoors, because SO_2 is consumed by reactions on indoor surfaces, especially those that are moist. Chao acknowledged this point but could not account for the findings of this study. It was noted that

two samples had unusually high indoor to outdoor ratios and that the mean ratios would have been much lower otherwise. Winter-summer differences in the indoor:outdoor ratio are consistent with seasonal differences in air exchange rates, as noted by Brauer et al. (1991).

Table 2-8. Relationships of indoor to outdoor SO_2 concentrations.

REFERENCE	LOCATION	INDOOR TO OUTDOOR RATIO V(# SAMPLES)	NOTES
Spengler et al. (1979)	Portage, WI	0.67 (349)	One year during Harvard Six Cities Study. West-Gaeke method.
	Topeka, KS	0.50 (389)	
	Kingston, TN	0.08 (425)	
	Watertown, MA	0.33 (486)	
	St. Louis. MO	0.31 (543)	
	Steubenville, OH	0.39 (499)	
Stock et al. (1985)	Houston, TX	0.54 (2425)	May to October, continuous FRM for indoor and outdoor.
Meranger and Brule (1987)	Antigonish, NS, Canada	0.84 (8)	Early spring, 1 wk avg in 1 house with oil furnace, FPD-TA
Brauer et al. (1989)	Boston, MA	0.23 (24)	Summer, HEADS
Li and Harrison (1990)	Essex, UK	0.22	Summer
Brauer et al. (1991)	Boston, MA	0.39 (geom. mean) (29), R^2 = 0.89	Summer, HEADS
		0.05 (geom. mean) (23), R^2 = 0.73	Winter, HEADS
Chan et al. (1994)	Taipei, Taiwan	0.24 (15)	Summer, PS
		0.23 (37)	Winter, PS
Lee et al. (1999)	Hong Kong	0.92, R_2 = 0.56	Winter, PF
Patterson and Eatough (2000)	Lindon, UT	0.027 ± 0.0023, R^2 = 0.73	Winter, ADS, all samples
Kindzierski and Sembaluk (2001)	Boyle, Alberta, Canada	0.12 (12)	Late Fall, PS
	Sherwood Park, Alberta, Canada	0.14 (13)	
Chao (2001)	Hong Kong	1.01 ± 0.78 (10)	Summer. Windows mainly kept closed, PS
Kindzierski and Ranganathan (2006)	Fort McKay, Alberta, Canada	0.35 (30)	Fall. All indoor levels < LOD and set =1/2 LOD, PS

FPD-TA = Flame Photometric Detection-Thermal Analysis
HEADS = Harvard-EPA Annular Denuder System
PS = passive sampler
PF = pulsed fluorescence
FRM = Federal Reference Method
ADS = Annular Denuder System

Indoor, or nonambient, sources of SO_2 could complicate the interpretation of associations between personal exposure to ambient SO_2 in exposure studies. Possible sources of indoor SO_2 are associated with the use of sulfur-containing fuels, with higher levels expected when emissions are poorly vented. Brauer et al. (2002) noted that only one study (Biersteker et al., 1965) conducted inferential analyses of potential determinants of exposure to indoor SO_2 levels.

In the Biersteker et al. study, conducted in the Netherlands, indoor levels increased with oil, coal, and gas heating, as well as smoking in homes and increased outdoor levels.

Triche et al. (2005) measured SO_2 levels in homes in which secondary heating sources (fireplaces, kerosene heaters, gas space heaters, and wood stoves) were used. They found elevated indoor levels of SO_2 when kerosene heaters were in use. Median levels of SO_2 when kerosene heaters were used (6.4 ppb) were much higher than when they were not in use (0.22 ppb). The maximum SO_2 level associated with kerosene heater use was 90.5 ppb. They did not find elevated SO_2 levels when the other secondary heating sources were in use.

2.5.3.2. Relationship of Personal Exposure to Ambient Concentration

A few studies evaluated the association of personal exposure to SO_2 to ambient concentrations (Brauer et al., 1989; Chang et al., 2000; Sarnat et al., 2000; 2001; 2005; 2006). Some of these studies fall under the umbrella of the Health Effects Institute's Characterization of Particulate and Gas Exposures of Sensitive Subpopulations Living in Baltimore and Boston research plan (Koutrakis et al., 2005). However, the focus of many of these studies has been exposure to particles, with acid gases included to evaluate confounder or surrogate issues.

Table 2-9 summarizes the longitudinal correlation coefficients between personal SO_2 exposures and ambient concentrations of SO_2, and Table 2-10 the pooled correlation coefficients. Most of the studies examined lack the ability to quantify 24-h averaged personal SO_2 exposures due to the low ambient SO_2 concentrations and the limitations of passive sampling, except two studies conducted by Brauer et al. (1989) and Sarnat et al (2006).

Brauer et al. (1989) determined the slope of the regression line between personal and ambient concentrations to be 0.13 ± 0.02, $R^2 = 0.43$, based on 44 measurements made in Boston, MA during the summer of 1988. Most if not all of the data points obtained using the HEADS appeared to be above the working detection limits as defined by the authors in their publications (Brauer et al., 1989; Koutrakis et al., 1988). Note that calculating detection limits in this way could result in lower detection limits than if field blanks were used. The authors reported significance at the $p < 0.001$ level, but the intercept was not significant at the $p < 0.001$ level. Since the stationary monitoring site was located at an elevation of 250 m above street level, the use of data from this ambient monitoring site will overestimate personal exposure, as the concentration of SO_2 increases with height because it is emitted mainly by elevated point

sources. Indeed, the ambient concentrations are about a factor of two higher than the outdoor concentrations. Sarnat et al. (2006) reported that ambient SO_2 was observed to be significantly associated with personal SO_2 exposures during the fall (slope = 0.08 for overall population) in a study in Steubenville, OH. The authors also observed the effect of ventilation on the association between personal exposures and ambient concentrations (slope = 0.07 for subjects in buildings with low ventilation rates, and 0.13 for subjects in buildings with high ventilation rates).

Table 2-9. Association between personal exposure and ambient concentration (longitudinal correlations coefficients).

REFERENCE	STUDY DESIGN	SEASON	MEAN CONC. (ppb)	SLOPE	INTERCEPT	r, R^2	COMMENTS
Sarnat et al. (2000)	Longitudinal, Baltimore, 20 senior, healthy, nonsmoking people (average age 75), summer of 1998 and winter of 1999, 1 day averaged sample, for 12 consecutive days for each subject; four to six subjects were measured concurrently during each 12-day monitoring period.	Winter	Ambient: 6.6 – 10.2 Personal: -0.8 – 1.2	NR	NR	-0.75 to 0.65 (r) with a median of 0.02 (14 subjects)	The LOD for 24-h sampling was 6.5 ppb. All personal samples were below LOD.
Sarnat et al. (2001)	Longitudinal, Baltimore, 56 seniors, schoolchildren, and people with COPD, summer of 1998 and winter of 1999, 14 of 56 subjects participated in both sampling seasons; all subjects were monitored for 12 consecutive days (24-h avg samples) in each of the one or two seasons, with the exception of children who were measured for 8 consecutive days during the summer.	Winter	Ambient: 4 – 17 Personal: -2 – 3	-0.05* (N = 487 with 45 subjects)	0.54* (N = 487 with 45 subjects)	-0.75 to 0.6 (r) with a median of -0.1 (44 subjects)	1) Concentrations are estimated from Figure 1 in the paper. 2) Correlation coefficients are estimated from Figure 2 in the paper. 3) LOD was referred to Sarnat et al (2000), which was 6.5 ppb. Therefore, all personal samples were below LOD.
Sarnat et al. (2005)	Longitudinal, Boston, 43 seniors and schoolchildren, summer of 1999 and winter of 2000, Similar study design as Sarnat et al. (2001).	Summer	Ambient: 2.8 – 4.5 Personal: 0.3 – 0.5	0.00 (N = 335)	NR	–0.60 to 0.70 (r) with a median of 0.00 (Sample size NR)	1) Correlation coefficients are estimated from Figure 1 in the paper. 2) LOD was 2.3 ppb, and 96.5% of personal samples were below LOD.
		Winter	Ambient: 4.9 – 10.7 Personal: -0.3 – 1.9	-0.02 (N = 299)	NR	-0.55 to 0.60 (r) with a median of 0.10 (Sample size NR)	1) Correlation coefficients are estimated from Figure 1 in the paper. 2) LOD was 3.2 ppb, and 95.4% of personal samples were below LOD.

* significant at α = 0.05 level

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The associations between personal exposure and ambient concentration cannot be examined in the other studies because almost all the personal exposure concentrations were beneath

detection limits. For example, Chang et al. (2000) tested a new personal active sampling device (a RAS with a TEA-based denuder) on volunteer participants to measure hourly personal exposure to SO_2. However, the method detection limit was too high for SO_2 (62 ppb for 1-h sampling) to generate a robust SO_2 exposure dataset to perform further analysis, and so the authors did not use the SO_2 data.

Table 2-10. Association between personal exposure and ambient concentration (pooled correlations coefficients).

REFERENCE	STUDY DESIGN	SEASON	MEAN CONC. (ppb)	SLOPE	INTERCEPT	r, R^2	COMMENTS
Brauer et al. (1989)	Pooled, Boston, study population was NR, the number of participants was estimated to be 48, July and August of 1988 for 24 days, 1 day averaged sample, two subjects were monitored each day.	Summer	Ambient: 2.5 – 9.5 Personal: 0.4 – 1.8	0.13* (N = 44)	Not significant	0.43 (R^2)	1) Concentrations estimated from Figure 2 in the paper. 2) Central site monitor was 250 m above the ground level. 3) LOD for personal samples was ~0.19 ppb based on the way to determine the LOD for an active sampling system.
Sarnat et al. (2006)	Steubenville, 15 senior subjects, summer and fall of 2000, two consecutive 24-h samples were collected for each subject for each wk, 23 wks total. Correlation coefficients were calculated in the pooled data set.	Summer	Ambient: 2.7 ± 3.9 Personal: 1.5 ± 3.3	0.03 (N = 106)	NR	0.00 (R^2)	LOD was 5.5 ppb; 53.5% of personal samples were below LOD.
		Fall	Ambient: 5.4 ± 9.6 Personal: 0.7 ± 1.9	0.08* (N = 152)	NR	0.15 (R^2)	LOD was 3.8 ppb, and 31.6% of personal samples were below LOD.

* significant at α = 0.05 level

In the context of determining the effects of ambient pollutants on human health, the association between the ambient component of personal exposures and ambient concentrations is more relevant than the association between personal total exposures (ambient component + nonambient component) and ambient concentrations. As described in Equations 2-8 and 2-10, personal total exposure can be decomposed into two parts; an ambient and a nonambient component. Usually, the ambient component of personal exposure is not directly measureable, but it can be estimated by exposure models, or the personal total exposure can be regarded as the personal exposure of ambient origin if there are no indoor or nonambient sources. It is expected that the association between ambient concentrations and the ambient component of personal exposures would be stronger than the association between ambient concentrations and personal total exposures as long as the ambient and nonambient component of personal total exposure are independent. None of the studies examined indoor sources, however, indoor sources are not

expected to be present. The correlation coefficients between personal ambient SO_2 exposures and ambient SO_2 concentrations in different types of exposure studies are relevant to different types of epidemiologic studies.

There are three types of correlations generated from different study designs and ways to analyze the data from exposure studies: longitudinal, "pooled," and daily-average correlations (EPA, 2004). Longitudinal correlations[1] are calculated when data from a study includes measurements over multiple days for each subject (longitudinal study design). Longitudinal correlations describe the temporal relationship between daily personal SO_2 exposure or microenvironment concentration and daily ambient SO_2 concentration for the same subject. The longitudinal correlation coefficient can differ between subjects (i.e., each person may have a different correlation coefficient). The distribution of correlations for each subject across a population could be obtained with this type of data (e.g., Sarnat et al., 2000; 2001; 2005). A longitudinal correlation coefficient between the ambient component of personal exposures and ambient concentrations is relevant to the panel epidemiological study design. In Table 2-9, most longitudinal studies reported the association between personal total exposures and ambient concentrations for each subject; for some subjects the associations were strong and for some subjects the associations were weak. The weak personal and ambient associations do not necessarily mean that ambient concentrations are not a good surrogate for personal exposures, because the weak associations could have resulted from the day-to-day variation in the nonambient component of total personal exposure. The type of correlation analysis can have a substantial effect on the value of the resultant correlation coefficient.

Mage (1999) showed that very low correlations between personal exposure and ambient concentrations could be obtained when people with very different nonambient exposures are pooled, even though their individual longitudinal correlations are high.

[1] $$r_{ax_i} = \frac{\sum_j \left(x_{ij} - \overline{x_i}\right)\left(a_j - \overline{a}\right)}{(n-1)s_{x_i}s_a}$$ where "r" is the longitudinal correlation coefficient between personal exposure and ambient concentration, "a" represents the ambient concentration, "x" represents exposure, "i" represents the ith subject, "j" represents the jth measurement (with the averaging time ranging from two days to two weeks for SO2 measurement), "s" represents the standard deviation, and "n" in the longitudinal studies is the number of measurements for each subject. The ambient concentration aj could be measured by one ambient monitor or the average of several ambient monitors.

Pooled correlations[1] are calculated when a study involves one or only a few measurements per subject and when different subjects are studied on subsequent days. Pooled correlations combine individual-subject/individual-day data for the calculation of correlations. Pooled correlations describe the relationship between daily personal NO_2 exposure and daily ambient SO_2 concentration across all subjects in the study (e.g., Brauer et al., 1989; Sarnat et al., 2006).

Daily-average correlations[2] are calculated by averaging exposure across subjects for each day. Daily-average correlations then describe the relationship between the daily average exposure and daily ambient pollutant concentration. This type of correlation (i.e., the association between community average exposures (ambient component) and ambient concentrations) is more directly relevant to community time-series and long-term cohort epidemiologic studies, in which ambient concentrations are used as a surrogate for community average exposure to pollutants of ambient origin. However, exposure of the population to SO_2 of ambient origin has not been reported in any of the studies examined.

Not only does the exposure study design determine the meaning of the correlation coefficients in the context of exposure assessment in epidemiologic studies, but it also affects the strength of the association between personal exposures and ambient concentrations. The strength of the association between personal exposures and ambient and/or outdoor concentrations for a population is determined by variations in several physical factors: indoor or other local sources, air exchange rate, penetration, and decay rate of the pollutant in different microenvironments and the time people spend in different microenvironments with different pollutant concentrations. For different types of correlation coefficients, the components of the variance of these physical factors are different, and therefore the strength of different types of correlation coefficients is different. Longitudinal correlation coefficients reflect the *inter-personal* variations of these physical factors; pooled correlation coefficient reflect both *inter-* and *intra-* personal variations of these physical factors; and for the association between community average exposures and ambient concentrations, *inter-personal* variations of these physical factors are reduced by

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[1] $r_{ax} = \frac{\sum_{i,j}(x_{ij} - \bar{x})(a_j - \bar{a})}{(n-1)s_x s_a}$ where "n" is the number of paired measurements of exposure and ambient concentration, and all other symbols are defined the same way as those in the longitudinal correlation coefficient.

[2] $r_{a\bar{x}} = \frac{\sum_{j}(\overline{x_j} - \bar{x})(a_j - \bar{a})}{(n-1)s_{\overline{x_j}} s_a}$, where n is the number of measurement period, during each of which the exposure for all subjects are measured, and all other symbols are defined the same way as those in the longitudinal correlation coefficient.

averaging personal exposures across a community. Therefore, the strength of the associations between personal exposures and ambient concentrations may not be comparable directly, although these associations are determined by the same set of physical factors (but affected in different ways).

Since correlations are standardized quantities that depend on multiple features of the data, in a correlation, not only is the linear "relatedness" (covariance) of the two quantities important, but so is the variability of each, which can be affected by exposure factors in various ways. In the following assessments, the effects of these physical factors on the strength of correlation coefficients are primarily examined *within* a study, and the purpose of the inter-study comparison is to examine the consistency of the effects across different types of studies.

The strength of the associations between personal exposures and ambient concentrations could also be affected by the quality of the data collected during the exposure studies. There are at least six aspects associated with the quality of the data: method precision, method accuracy (compared with FRM), percent of data above method detection limits (based on field blanks), completeness of the data collection, sample size, and soundness of the quality assurance/quality control procedures. Unfortunately, not all studies reported the SIX aspects of the data quality issue. The fraction of data below the detection limit might be a concern for some studies (see Sarnat et al., 2000; 2001; 2005). Correlation coefficients would be biased low if data used in their calculation are below detection limits. Sampling interferences associated with both ambient (see Section 2.3) and personal sampling (see Section 2.5.2) could also affect data quality. Therefore, caution must be exercised when interpreting the results in Table 2-9 and Table 2-10. Sarnat et al. (2001; 2005; 2006) examined the associations between ambient SO_2 concentrations and ambient or personal co-pollutant concentrations. Sarnat et al. (2001) reported that during the winter of 1999, ambient SO_2 was significantly associated (at 5% significance level) with personal exposure to fine particulate matter ($PM_{2.5}$) (slope = − 0.24), personal exposure to SO_4^{2-} (slope = − 0.03), and personal exposure to $PM_{2.5}$ of ambient origin (slope = − 0.16). However, it should be noted that all the slopes are negative perhaps as the result of measurement error. Sarnat et al. (2005) reported that significant associations between ambient SO_2 and either personal exposures or ambient concentrations of other pollutants were found for personal SO_4^{2-} (winter, slope = 0.06), personal SO_4^{2-} (summer, slope = 0.39), personal $PM_{2.5}$ (summer, slope = 1.68), ambient SO_4^{2-} (winter, slope = 0.19), and ambient $PM_{2.5}$ (winter, slope = 0.80). In Sarnat et al.

(2006), ambient SO_2 was observed to be significantly associated with ambient $PM_{2.5}$, ambient SO_4^{2-} and ambient EC during the fall (R^2 = 0.22, 0.33, and 0.34 respectively), and was significantly associated with personal $PM_{2.5}$ during the summer, personal SO_4^{2-} and personal EC during the fall (R^2 = 0.07, 0.06, and 0.05 respectively).

Of significant concern is the ability of currently available techniques for monitoring either personal exposures or ambient concentrations to measure SO_2 concentrations that are typically found in most urban environments. In some studies, most data, especially data for monitoring personal exposure and indoor concentrations, might be beneath detection limits. Indeed, in one study (Chang et al., 2000), the investigators had to discard data for SO_2, because the values were mostly beneath detection limits. In the study of Kindzierski and Ranganathan (2006), all indoor concentration data were beneath detection limits. In Sarnat et al. (2000), ~70% of personal measurements were beneath detection limits, and ~33% of personal measurements returned apparent negative concentration values. In such situations, associations between ambient concentrations and personal exposure are inadequately characterized. When personal exposure concentrations are above detection limits, a reasonably strong association is observed between personal exposures and ambient concentrations.

2.5.4. Exposure Measurement Errors in Epidemiological Studies

For the purposes of this draft, the effects of exposure error on epidemiological study results refers to changes in the health effects estimate expressed as the relative risk factor, β, and in the related standard error that results from using the ambient concentration of an air pollutant as an exposure indicator rather than using the actual personal exposure in the epidemiological statistical analysis. There are many assumptions made in going from the available measurement of a pollution indicator to an estimate of the personal exposure. The importance of these assumptions and their effect on β depend on the type of epidemiological study.

The considerations of exposure error for SO_2 are simplified compared to those for NO_2 and PM. The only experimental measure available is the ambient concentration of SO_2. In addition, indoor and other non-ambient sources of SO_2 are not thought to be important in population studies, lessening concerns about the possible influence of exposures other than to ambient SO_2.

2.5.4.1. Community Time-Series Studies

This section applies primarily to studies on the association of daily average SO_2 concentrations with daily measures of mortality or morbidity in a community. The following three exposure issues are of primary concern with respect to SO_2 time-series epidemiological analysis: (1) the relationship of the measured concentration of SO_2 to the true concentration; (2) the relationship of day-to-day variations in the concentrations of SO_2, as measured at a central monitoring site, with the corresponding variations in the average concentration of SO_2 over the geographic area from which the health measurements are drawn; and (3) the relationship of the community average concentration of SO_2 to the average personal exposure to ambient SO_2. These three issues are described below.

2.5.4.1.1. Relationship of Measured SO_2 to the True Concentration

Since there is always a random component to instrumental measurement error, the correlation of the measured SO_2 with the true SO_2, on either a 24-h or 1-h basis, will be less than 1. Sheppard et al. (2005) indicate that instrument error in the individual or daily average concentrations have "the effect of attenuating the estimate of α." Zeger et al. (2000) suggest that instrument error has both Berkson and non-Berkson error components; however, the authors state that the "instrument error in the ambient levels is close to the Berkson type," and in order for this error to cause substantial bias in β, the error term (the difference between the true concentrations and the measured concentrations) must be strongly correlated with the measured concentrations. Zeger et al. (2000) suggest that, "further investigations of this correlation in cities with many monitors are warranted." Averaging across multiple unbiased ambient monitors in a region should reduce the instrument measurement error (Sheppard et al., 2005; Wilson and Brauer, 2006; Zeger et al., 2000). There are concerns about the precision and accuracy of the ambient concentration measurements, because SO_2 concentrations are much lower now than when the SO_2 standards were first promulgated. Typical ambient concentrations of SO_2 in the contiguous United States are nearly all at or beneath the detection limit of the monitors currently used in the regulatory network. Thus, greater relative error is most often observed at the lower ambient concentrations compared to the less frequent higher concentration exposures, as might occur because of plume downwash near local point sources or entrainment of plumes downwind from

large power plants or smelters. It is unclear how uncertainties in the true concentrations of SO_2, i.e., instrument measurement error, will change β.

2.5.4.1.2. Relationship of Day-to-day Variations in the Ambient Concentration of SO_2 to Variations in the Community Average

There has been little analysis of the spatial variation of SO_2 across communities. SO_2 emissions arise mainly from coal fired power plants (see Annex Table B-4). Newer power plants and smelters in the United States are no longer located within urban areas. However, some older power plants and industrial facilities are located in many urban areas, especially in the Midwest and Northeast. Downwash from the plumes emitted from these facilities can contribute to elevated levels of SO_2 at the surface in these cities. However, it is anticipated that SO_2 will behave largely as a regional pollutant in most areas. Site-to-site correlations of SO_2 concentrations, as shown for several cities in Table 2-3 vary from very low to very high values. This suggests the concentration of SO_2, measured at any given monitoring site, may not be highly correlated with the average community concentration in some areas. There are a number of possible reasons for these findings: local sources that cause the SO_2 to be unevenly distributed spatially; a monitoring site being chosen to represent a nearby source; terrain features that divide the community into several sub-communities that differ in the temporal pattern of pollution; and errors in the measurement of the low concentrations of SO_2 present at most sites. To the extent that the correlation of the ambient concentration with the community average concentration is < 1, β will be reduced. Similarly, β will be reduced if there are subareas of the community where the correlation of the subarea average concentrations with the concentrations measured at the ambient monitoring site is < 1. If concentrations in an area of a community impacted by plumes from local SO_2 sources might be higher than, and not well-correlated with, the concentrations at the ambient monitor, and if such high concentrations affected a sizable portion of the population affected by a local source, that community might not be suitable for time-series epidemiological analyses. On the other hand, if the plume impacts the ambient monitor, the high concentration of SO_2 not accompanied by a corresponding high effect in the entire community will bias β toward the null.

2.5.4.1.3. Relationship of Community Average Concentration of SO_2 to Average Personal Exposure to Ambient SO_2

People spend much of their time indoors and, in the absence of indoor sources, indoor concentrations are lower than outdoor concentrations. This is very likely the case with SO_2, since the only known significant indoor source of SO_2 in the United States is the use of kerosene heaters, not thought to be widespread enough to influence population studies. Differences in infiltration factors among homes can also result in differences among individuals' personal exposures. It is necessary to consider how this difference between the ambient concentration, which is used in epidemiological analyses, and the personal ambient source exposure concentration (which includes exposure to the full outdoor concentration while outdoors, and exposure of only a fraction of the outdoor concentrations while indoors) will affect the calculated β. The contribution of the ambient concentration of SO_2 to the personal exposure to ambient SO_2 is given by $Ea = \alpha \bullet Ca$ where *Ea* is exposure to ambient SO_2, α is the ambient exposure factor with values between 0 and 1, and *Ca* is the ambient SO_2 concentration as measured at a community monitoring site. Zeger et al. (2000) noted that for community time-series epidemiology, which analyzes the association between health effects and potential causal factors at the community scale rather than the individual scale, it is the correlation of the daily average ambient concentrations with the daily *community average* personal exposures that is important, not the correlation between the daily average ambient concentrations and *the individual* personal exposures. Thus, as mentioned in Section 2.5.3, the low correlation between daily average ambient concentrations and individual personal exposures, as frequently found in pooled panel exposure studies, is not relevant to community time-series epidemiological analysis. Unfortunately, no studies provide adequate information about the community average personal exposure to SO_2.

There has also been concern with the variation of α. Zeger et al. (2000) suggested (for PM) that variations in the individual daily values of α would be a Berkson error and would not change the point estimate of β. Sheppard et al. (2005) used simulations to confirm this for nonreactive pollutants. However, such variations increase the standard error. Day-to-day variations in the population average fraction of ambient exposure will not change the point estimate of β unless the population average fraction of ambient exposure is correlated with seasonal trends in ambient concentration, according to Sheppard et al.

Both Zeger et al. (2000) and Sheppard et al. (2005) show that if βA is the health effect parameter that would be obtained with a time-series analysis using the ambient exposure and βC is the health effect parameter that would be obtained with a time-series analysis using the ambient concentration, then $\beta C = \alpha \bullet \beta A$. Thus, time-series studies yield different parameters depending on whether they use concentration or exposure. However, the two parameters are related by α. Overestimation of exposure by substitution of the ambient concentration for the ambient exposure leads to underestimation of the effect estimate, or generally bias toward the null.

2.5.4.2. Short-Term Panel Studies

Panel epidemiology refers to time series studies that follow a relatively smaller number of subjects for a relatively short time. Each subject must be considered individually. Panel studies typically examine the association between symptoms or health outcomes and either ambient concentrations or personal exposures. Personal exposures to SO_2 are not measured; rather, ambient concentrations are used in panel studies. Similar types of exposure error as discussed for community time series apply to panel studies.

The ambient exposure factor (α) may differ for each person and each day leading to error in the exposure estimate. If a panel is composed of subjects who live in similar housing and have similar activity pattern, and the study is limited to a single season, the variation in α over time and individual subjects may be small. However, if the panels are composed of more diverse subjects or extend or more than one season, values of α may be quite variable. Such variability will cause error in the estimate of exposure for each subject.

2.5.4.3. Long-Term Cohort Studies

For long-term exposure epidemiological studies, concentrations are integrated over time periods of a year or more, and usually for spatial areas the size of a city, county, or metropolitan statistical area (MSA), although integration over smaller areas may be feasible. Health effects are then regressed, in a statistical model, against the average concentrations in the series of cities (or other areas). In time-series studies, a constant difference between the measured and the true concentration (instrument offset) will not affect β, nor will variations in the daily average α or

the daily average nonambient exposure, unless the variations are correlated with the daily variations in concentrations. However, in long-term exposure epidemiological studies, if instrument measurement errors, long-term average values of α, or long-term averages of nonambient exposure differ for different cities (or other areas used in the analysis), the city-to-city long-term ambient SO_2 concentrations will not be perfectly correlated with the long-term average exposure to either ambient or total SO_2. This lack of correlation would be expected to bias the point estimate of β.

2.5.4.4. Summary of Evaluation of Exposure Measurement Error in Epidemiological Studies

Exposure error caused by using ambient concentrations of SO_2 as a surrogate for exposure to ambient SO_2 affect β in different ways, dependent upon the type of epidemiological study. In community time-series and short-term panel epidemiological studies, in general, the nonambient source component of personal exposure and the variation in the ambient exposure factor caused by building ventilation practices and personal behaviors, will not change the estimate of β; but the spatial variation of SO_2 or the representativeness of the ambient monitor might bias the estimate of β toward null. Therefore, β observed in SO_2 community time-series or panel epidemiological studies would be stronger and less uncertain if exposure errors had been adjusted and/or controlled for. In long-term cohort epidemiological studies, instrument measurement errors, factors that influence exposure to ambient SO_2, or long-term averages of nonambient exposure may differ for different cities, which may bias the estimate of β, but the extent and direction of this bias is unclear.

2.6. Dosimetry of Inhaled Sulfur Oxides

This section is intended to present an overview of general concepts related to the dosimetry of SO_2 in the respiratory tract. Dosimetry of SO_2 refers to the measurement or estimation of the amount of SO_2 or its reaction products reaching and persisting at specific respiratory tract and systemic sites after exposure. One of the principal effects of inhaled SO_2 is that it stimulates bronchial epithelial irritant receptors and initiates a reflexive contraction of smooth muscles in the bronchial airway. The compound most directly responsible for health effects may be the inhaled SO_2, or perhaps its chemical reaction products. Complete identification of the causative

agents and their integration into SO_2 dosimetry is a complex issue that has not been thoroughly evaluated. Few studies have investigated SO_2 dosimetry in the interval since the 1982 AQCD and the 1986 Second Addendum.

2.6.1. Gas Deposition

The major factors affecting the transport and fate of gases and aerosols in the respiratory tract are: the morphology of the respiratory tract; the physiochemical properties of the mucous and surfactant layers; respiratory functional parameters such as tidal volume, flow rate, and route of breathing; physicochemical properties of the gas; and the physical processes that govern gas transport. Physicochemical properties of SO_2 relevant to respiratory tract uptake include its solubility and diffusivity in epithelial lining fluid (ELF), as well as its reaction-rate with ELF constituents. Henry's law relates the gas phase and liquid phase interfacial concentrations at equilibrium, and is a function of temperature and pressure. Henry's law shows that the amount of SO_2 in the aqueous phase is directly proportional to the partial pressure or concentration of SO_2 in the gas phase. Although the solubility of most gases in mucus and surfactant is not known, the Henry's law constant is known for many gases in water. The Henry's law constant for SO_2 is 0.048 (mole/liter) air / (mole/liter) water at 37° C and 1 atm; for comparison, the value for O_3 is 6.4 under the same conditions (Kimbell and Miller, 1999). In general, the more soluble a gas is in biological fluids, the more rapid, and proximal its absorption will be in the respiratory tract. When the partial pressure of SO_2 on mucosal surfaces exceeds that of the gas phase, such as during expiration, some desorption of SO_2 from the ELF may be expected.

Because SO_2 is highly soluble in water, it is expected to be almost completely absorbed in the nasal passages of both humans and laboratory animals under resting conditions. The dosimetry of SO_2 can be contrasted with the lower solubility gas, O_3, for which the predicted tissue doses (O_3 flux to liquid-tissue interface) are very low in the trachea and increase to a maximum in the terminal bronchioles or first airway generation in the pulmonary region (see Chapter 4, EPA, 2006c). Similar to O_3, the nasal passages remove SO_2 more efficiently than the oral pathway (Brain, 1970). With exercise, the pattern of SO_2 absorption shifts from the upper airway to the tracheobronchial airway in conjunction with a shift from nasal to oronasal breathing and increased ventilatory rates. Due to its effect on delivery and uptake, mode of breathing is also recognized as an important determinant of the severity of SO_2-induced

bronchoconstriction, with the greatest responses occurring during oral breathing followed by oronasal breathing and the smallest responses observed during nasal breathing.

Melville (1970) measured the absorption of SO_2 (1.5 to 3.4 ppm) during nasal and oral breathing in 12 healthy volunteers. Total respiratory tract absorption of SO_2 was significantly greater ($p < 0.01$) during nasal than oral breathing (85 versus 70%, respectively) and was independent of the inspired concentration. Respired flows were NR. Andersen et al. (1974) measured the nasal absorption of SO_2 (25 ppm) in 7 volunteers at an average inspired flow of 23 L/min (i.e., eucapnic hyperpnea [presumably] to simulate light exertion). These investigators reported that the oropharyngeal SO_2 concentration was below their limit of detection (0.25 ppm), implying that at least 99% of SO_2 was absorbed in the nose of subjects during inspiration. Speizer and Frank (1966) also measured the absorption of SO_2 (16.1 ppm) in 7 healthy subjects at an average ventilation of 8.5 L/min (i.e., at rest). They reported that 14% of the inhaled SO_2 was absorbed within the first 2 cm into nose. The concentration of SO_2 reaching the pharynx was below the limit of detection, suggesting that at least 99% was absorbed during inspiration.

Frank et al. (1969) and Brain (1970) investigated the oral and nasal absorption of SO_2 in the surgically isolated upper respiratory tract of anesthetized dogs. Radiolabeled SO_2 ($^{35}SO_2$) at the concentrations of 1, 10, and 50 ppm was passed separately through the nose and mouth at the steady flows of 3.5 and 35 L/min for 5 min. The nasal absorption of SO_2 (1 ppm) was 99.9% at 3.5 L/min and 96.8% at 35 L/min. The oral absorption of SO_2 (1 ppm) was 99.56% at 3.5 L/min, but only 34% at 35 L/min. The nasal absorption of SO_2 at 3.5 L/min increased with concentration at 1, 10, and 50 ppm and was reported to be 99.9, 99.99, and 99.999%, respectively. This increase in absorption with concentration was hypothesized to be due to increased mucous secretion and increased nasal resistance at the higher SO_2 concentrations. The increased mucus was thought to provide a larger reservoir for SO_2 uptake. The increased nasal resistance may increase turbulence in the airflow and, thereby, decrease the boundary layer between the gas and liquid phases. Dissimilar to the nose, SO_2 absorption in the mouth decreased from 99.56 to 96.3% when the concentration was increased from 1 to 10 ppm at 3.5 L/min. Frank et al. (1969) noted that the aperture of the mouth may vary considerably, and that this variation may affect SO_2 uptake in the mouth. Although SO_2 absorption was dependent on inhaled concentration, the rate and route of flow had a greater effect on the magnitude of SO_2 absorption in the upper airway.

Strandberg (1964) studied the uptake of SO_2 in the respiratory tract of rabbits. A tracheal cannula with two outlets was utilized to allow sampling of inspired and expired air, and SO_2 absorption was observed to depend on inhaled concentration. The absorption during maximal inspiration was 95% at high concentrations (100 to 700 ppm), reflecting an increased SO_2 removal in the extrathoracic (ET) airway, whereas it was only 40% at low concentrations (0.05 to 0.1 ppm). On expiration, the total SO_2 absorbed (i.e., inspiratory removal in the ET airway plus removal in the lower airway) was 98% at high concentrations and only 80% at the lower concentrations.

Amdur (1966) examined changes in airway resistance in guinea pigs due to SO_2 exposure. Guinea pigs were exposed for 1-h to 0.1- to 800 ppm SO_2 during natural unencumbered breathing or to 0.4 to 100 ppm while breathing through a tracheal cannula. At concentrations of 0.4- to 0.5 ppm SO_2, route of administration did not affect the airway resistance response, whereas at concentrations of > 2 ppm, the responses were greater in animals exposed by tracheal cannula. Based on the concentration-dependent absorption of SO_2 in the ET airway observed by Strandberg (1964), Amdur (1966) concluded that the airway resistance responses at low-exposure concentrations were independent of method of administration, because the lung received nearly the same concentration with or without the cannula as evidenced by minimal ET absorption.

More recently, Ben-Jebria et al. (1990) investigated the absorption of SO_2 in excised porcine tracheae. Absorption was monitored over a 30-min period following the introduction of SO_2 (0.1 to 0.6 ppm, inlet concentration) at a constant flow (2.7 to 11 L/min). The data were analyzed using diffusion-reactor theory. An overall mass transfer coefficient (KSO_2) was determined and separated into its contributions due to gas (convection and diffusion) and tissue phase (diffusivity, solubility, and reaction rates) resistances. SO_2 in the liquid phase was assumed to form HSO_3^- rapidly, in proportion with the gas phase SO_2 concentration, HSO_3^- then diffused down the concentration gradient into the tissues where it reacted irreversibly with biochemical substrates. Initially, KSO_2 was limited only by gas phase resistance, but decreased exponentially over the first 5 to 10 min of SO_2 exposure to a smaller steady-state value because of tissue resistance to SO_2 absorption. The initial and steady-state KSO_2 values were found to be independent of inlet SO_2 concentration, i.e., for a given flow, the fractional absorption of SO_2 did not depend on SO_2 concentration. An increased KSO_2 (initial and steady-state) was observed with

an increasing flow that was thought to be due to a decrease in the boundary layer near the walls of the trachea for radial SO_2 transport. This is in agreement with Aharonson et al. (1974), who also reported that the transfer rate coefficient for SO_2 increases with increasing flow. However, the initial molar flux of SO_2 across the gas-tissue interface appears to increase purely as a function of the increase in mass transport occurring with increasing flow (see Figure 5 in Ben-Jebria et al., 1990). Given that the steady-state KSO_2 remained stable during the 10 to 30 min of exposure and that no SO_2 leakage through the tissue was identified, the authors concluded that there was an irreversible sink for SO_2 within the tissue.

Mathematical modeling specific to the regional respiratory uptake of SO_2 is unavailable for humans and laboratory animals. More generally, the influence of age on gas dosimetry in humans during light activity (on average) was examined by Ginsberg et al. (2005) using the U.S. EPA reference concentration methodology (EPA, 1994a). For a highly soluble gas, such as SO_2, they predicted that the majority of gas uptake would occur in the extrathoracic airway and that uptake in these airways would be modestly greater in a 3-month-old infant than an adult. The rate of gas uptake per surface, however, in the extrathoracic airway and large bronchial airway was not markedly different between infants and adults. The smaller bronchial airway of adults were predicted to receive a greater dose (i.e., uptake per unit time and surface area) relative to infants, although the majority of the inhaled SO_2 would be removed proximal to these airways.

In summary, inhaled SO_2 is readily absorbed in the upper airway of both humans and laboratory animals. During nasal breathing, the majority of available data suggests 95% or greater SO_2 absorption occurs in the nasal passages, even under ventilation levels comparable to exercise. Somewhat less SO_2 is absorbed in the oral passage than in the nasal passages. The difference in SO_2 absorption between the mouth and the nose is highly dependent on respired flow rates. With an increase in flow from 3.5 to 35 L/min, nasal absorption is relatively unaffected, whereas, oral absorption is reduced from 100 to 34%. Thus, the rate and route of breathing have a great effect on the magnitude of SO_2 absorption in the upper airway and so the penetration of SO_2 to the lower airway. Overall, the available data clearly show that the pattern of SO_2 absorption which shifts from the upper airway to the tracheobronchial airway in conjunction a shift from nasal to oronasal breathing and associated increased ventilatory rates in exercising humans. Mode of breathing is also recognized as an important determinant of the severity of

SO_2-induced bronchoconstriction, with the greatest responses occurring during oral breathing followed by oronasal breathing and the smallest responses observed during nasal breathing.

2.6.2. Particles and Sulfur Oxide Mixtures

As already discussed, inhaled SO_2 is readily absorbed in the upper airway, particularly during nasal breathing. It has been suggested that sulfur oxides may become absorbed to particles and subsequently transported to more distal lung regions. Depending on atmospheric conditions, SO_2 can be transformed to secondary sulfate particles and acid aerosols (H_2SO_4) and can adsorb onto particulate matter. Jakab et al. (1996) observed that the conversion of SO_2 to SO_4^{2-} on the surface of carbon black aerosols was dependent on high relative humidity (85%) and SO_2 concentration. These investigators suggested that fine carbon black particles can be an effective vector for delivery of SO_4^{2-} to the peripheral lung. Other studies investigating the effects of SO_2 coated aerosols are briefly discussed in Section 3.1.5.

Sulfate aerosols are hygroscopic and grow in the respiratory tract. The implications of hygroscopic growth on deposition have been reviewed extensively by Morrow (1986) and Hiller (1991). In general, compared to nonhygroscopic particles of the same initial size, the deposition of hygroscopic aerosols in different regions of the lung may be higher or lower, depending on the initial size. For particles with initial sizes larger than 0.5 μm (aerodynamic diameter), the influence of hygroscopicity would be to increase total deposition with a shift in regional deposition from the distal to larger proximal airway; for smaller particles deposition would tend to be decreased. A thorough review of respiratory deposition and clearance of particulate matter is available elsewhere (EPA, 2004; 2006b). The intent herein was to briefly mention some issues specific to sulfur oxides.

2.6.3. Distribution and Elimination of Sulfur Oxides

When SO_2 contacts the fluids lining the airway, it dissolves into the aqueous fluid and forms hydrogen (H^+) ions and bisulfite (HSO_3^-) and sulfite (SO_3^{2-}) anions (Bascom et al., 1996). The majority of anions are expected to be present as HSO_3^- at a concentration proportional to the gas phase concentration of SO_2 (Ben-Jebria et al., 1990). Because of the chemical reactivity of these anions, various reactions are possible, leading to the oxidation of SO_3^{2-} to SO_4^{2-} (see Section 12.2.1, EPA, 1982). Clearance of SO_3^{2-} from the respiratory tract may involve several

intermediate chemical reactions and transformations. Gunnison and Benton (1971) identified *S*-sulfonate in blood as a reaction product of inhaled SO_2. Following inhalation of SO_2, the clearance half-time of 4.1 days for *S*-sulfonate in rabbits has been reported (Gunnison and Palmes, 1973).

Some SO_2 is also removed by desorption of from the respiratory tract. Desorption is expected when the partial pressure of SO_2 in airway lining fluids exceeds that of the air. Speizer and Frank (1966) found that on expiration, 12% of the SO_2 absorbed during inspiration was desorbed into the expired air. During the first 15 min after the 25- to 30-min SO_2 exposure, another 3% was desorbed. In total, 15% of the amount originally inspired and absorbed SO_2 was desorbed from the nasal mucosa. Frank et al. (1969) reported that up to 18% of the SO_2 was desorbed within ~10 min after exposure.

Chapter 3. Integrated Health Effects

This integrated discussion is structured to provide a coherent framework for the assessment of health risks associated with human exposure to ambient SO_2 in the United States. The main goals of this chapter are: (1) to integrate newly available epidemiological, human clinical, and animal toxicological evidence with consideration of key findings and conclusions from the 1982 AQCD for Sulfur Oxides and First Addendum (EPA, 1982), 1986 Second Addendum (EPA, 1986c), and 1994 Supplement to the Second Addendum, (EPA, 1994c); and (2) to draw conclusions about the causal nature of SO_2 in relation to a variety of health effects. These causal determinations utilize the framework outlined in Chapter 1.

This chapter is organized to present morbidity and mortality associated with short-term exposures to SO_2, followed by morbidity and mortality associated with long-term exposures. Human clinical studies examining the effect of peak exposures (less than 1-h, generally 5-10 min) of SO_2 on respiratory symptoms and lung function are discussed first. Later sections describe the findings of epidemiological studies that examine the association between short-term (generally 24-h avg) and long-term (generally months to years) ambient SO_2 exposure and heath outcomes, such as respiratory symptoms in children and asthmatics, emergency department (ED) visits and hospital admissions for respiratory and cardiovascular diseases, and premature mortality. The human clinical and epidemiological evidence are presented with relevant animal toxicological data, when available.

Considerations in the Interpretation of Health Evidence

Human clinical studies are conducted in a controlled laboratory setting using fixed concentrations of air pollutants under carefully regulated environmental conditions and subject activity levels. Results of human clinical studies provide evidence of potential mechanisms for observed effects and a direct quantitative assessment of the SO_2 exposure-health response relationship among asthmatic individuals. Observed effects in these studies may underestimate the response in certain sensitive subpopulations for a number of reasons. First, study subjects must either be healthy, or have a level of illness which does not preclude them from participating in the study. Second, asthmatics who are unable to withhold the use of bronchodilators for at

least 6 hours prior to exposure and subjects with a recent history of upper respiratory tract infections are typically excluded from clinical studies of exposure to SO_2. While human clinical studies provide important information on the biological plausibility of associations observed between SO_2 exposure and health outcomes in epidemiological studies, the concentration-response relationships cannot necessarily be directly extrapolated to concentrations below those administered in the laboratory. Further, human clinical studies are normally conducted on a relatively small number of subjects, which reduces the power of the study to detect significant differences in the health outcomes of interest between exposure to varying concentrations of SO_2 and clean air.

Epidemiological studies provide important information on the associations between health effects and exposure of human populations to ambient levels of SO_2. These studies also help to identify susceptible subgroups and associated risk factors. However, associations observed between specific air pollutants and health outcomes in epidemiological studies may be confounded by copollutants or meteorological conditions, and influenced by model specifications in the analytical methods. Extensive discussion of these issues is provided in the 2004 AQCD for PM (EPA, 2004) and the 2006 AQCD for O_3 and Related Photochemical Oxidants (EPA, 2006c), and therefore presented only briefly below.

The use of multipollutant regression models has been the prevailing approach for controlling potential confounding by copollutants in air pollution health effects studies. Finding the likely causal pollutant from multipollutant regression models is made difficult by the possibility that one or more air pollutants may be acting as a surrogate for an unmeasured or poorly-measured pollutant or for a particular mixture of pollutants. SO_2 presents an especially interesting test of multipollutant effects models: correlations with sulfate, the principal atmospheric oxidation product of SO_2, show temporal and spatial discongruities that can influence exposures and health effects. Short-term, mostly time-series epidemiological studies generally use intracity ambient concentration data which show very little or no correlation between emitted SO_2 and transformed sulfate. In contrast, long-term epidemiological studies using intercity data can show correlations between SO_2 and sulfate on the order of 0.8 or higher. In these studies the fine-scale spatiotemporal variations in the intracity data are significantly reduced, since sulfate has sufficient time for production from SO_2, dispersed over a wide spatial area, and mixed down to ground level. Layered over these spatial and fine-scale temporal

differences are seasonal and regional dissimilarities driven by cities' various SO_2 emissions profiles and differing available time and sunlight conditions for oxidation. Thus, attempts to distinguish gaseous and particle effects related to SO_2 using multipollutant epidemiological models must be interpreted with caution. Despite these limitations, the use of multipollutant models is still the prevailing approach employed in most studies of SO_2 and health effects, and may provide some insight into the potential for confounding or interaction among pollutants.

Model specification and model selection also need to be considered in the interpretation of the epidemiological evidence. The studies presented in this chapter investigated the association between various measures of SO_2 (e.g., multiple lags and different exposure metrics) and various health outcomes using different model specifications. The summary of health effects in this chapter is vulnerable to the errors of publication bias and multiple testing. Efforts have been made to reduce the impact of multiple testing errors. For example, although many studies examined multiple single-day lag models, priority was given to effects observed at 0- or 1-day lags, rather than at longer lags. Additional focus was placed on results from distributed and moving average lags as they are able to take into consideration multiday effects. Both single- and multiple-pollutant models were considered and examined for robustness of results. Additional analyses of multiple model specifications for adjustment of temporal or meteorological trends are considered to be sensitivity analyses.

In addition to issues related to confounding by copollutants and model selection, the evaluation of the epidemiological evidence also considers study population and sample size, with particular emphasis placed on multicity studies. Other factors considered are study location (North America versus other regions), meaningfulness and reliability of the health endpoint measurements, and appropriateness of the statistical analyses methods used. These considerations in the interpretation of the epidemiological evidence lead to emphasis of certain studies in the chapter text, tables, and figures.

Animal toxicological studies may provide further evidence for the potential mechanism of an observed effect; however, most of these studies have been conducted at concentrations vastly exceeding current ambient conditions. In discussing the mechanisms of SO_x toxicity, studies conducted under atmospherically relevant conditions are emphasized whenever possible; studies at higher levels are also considered, due to species-to-species differences and potential differences in sensitivity between study subjects and especially susceptible human populations.

This chapter focuses on important new scientific studies, with emphasis on those conducted at or near current ambient concentrations. Given their respective strengths and limitations, evidence from human clinical, epidemiological and animal toxicological studies are considered in order to evaluate the causality of SO_x–health effects associations. The annexes supplement the information included here by presenting a more details of the literature.

3.1. Respiratory Morbidity Associated with Short-Term Exposure

3.1.1. Summary of Findings from the Previous Review

The majority of the SO_2 human clinical studies in the 1982 AQCD for Sulfur Oxides evaluated respiratory effects of SO_2 exposure in healthy adults, with some limited data from clinical studies of adults with asthma. SO_2-related respiratory effects such as increased airway resistance and decreased forced expiratory volume in 1 s (FEV_1) were observed in healthy individuals at concentrations > 1.0-5.0 ppm, and in asthmatics at concentrations < 1.0 ppm. The 1986 Second Addendum (EPA) and 1994 Supplement to the Second Addendum (EPA) reviewed several additional controlled studies involving both healthy and asthmatic individuals. In general, these studies found no pulmonary effects of SO_2 exposure in healthy subjects exposed to concentrations < 1.0 ppm (Bedi et al., 1984; Folinsbee et al., 1985; Kulle et al., 1984; Stacy et al., 1983). However, in exposures of asthmatic adults, respiratory effects were observed following short-term exposures (5-10 min) to levels < 1.0 ppm (Balmes et al., 1987; Horstman et al., 1988; Linn et al., 1987).

Only a few epidemiological studies reviewed in the 1982 AQCD were useful in determining the concentration-response relationship of respiratory health effects from short-term exposure to SO_2. The most notable study was by Lawther (1970), which examined the association between air pollution and worsening health status in bronchitic patients residing in London, England. It was concluded in the 1982 AQCD that worsening of health status among chronic bronchitic patients was associated with daily black smoke (BS) levels of 250-500 $\mu g/m^3$ in the presence of SO_2 levels in the range of 191-229 ppb. In the 1986 Second Addendum, additional studies investigated morbidity associated with short-term exposure to SO_2. The most relevant study was by Dockery (1982), which examined pulmonary function in school children in

Steubenville, OH, as part of the Harvard Six Cities Study. This study found that small but statistically significant reversible decrements in forced vital capacity (FVC) and forced expiratory volume in 0.75 s ($FEV_{0.75}$) were associated with increases in 24-h avg concentrations of total suspended particles (TSP) at levels ranging up to 220-420 $\mu g/m^3$ and SO_2 at levels ranging up to 107-176 ppb. However, it was impossible to separate the relative contributions of TSP and SO_2, and no threshold level for the observed effects could be discerned from the wide range of exposure levels.

Epidemiological evidence for an association between SO_2 and respiratory morbidity, as indicated by increased use of ED facilities or increased hospital admissions for respiratory diseases, was also reported in the 1982 AQCD. Overall, these results suggested increased upper respiratory tract morbidity during episodic marked elevations of PM or SO_2 (400-500 ppb), especially among older adults. The 1982 AQCD further concluded that the studies reviewed provided essentially no evidence for an association between asthma attacks and acute exposures at typical ambient PM or SO_2 levels in the United States (the mean annual average SO_2 concentrations from 1972 to 1977 was approximately 6 ppb, with 90th percentile values ranging from 15 to 20 ppb).

The 1982 AQCD for Sulfur Oxides (EPA, 1982) reported numerous effects on the respiratory system in animals exposed to SO_2. Effects were generally observed at levels exceeding those found in the ambient environment, and included morphological changes, altered pulmonary function, lipid peroxidation, and changes in host lung defenses. The immediate effect of acute SO_2 exposure in animals was increased pulmonary resistance to airflow, a measure of bronchoconstriction. Bronchoconstriction was reported to be the most sensitive indicator of lung function effects in acute SO_2 exposure.

Collectively, the human clinical, epidemiological and animal toxicological, studies provided biological plausibility and coherent evidence of an adverse effect of ambient SO_2 on respiratory health. Since the 1982 AQCD, 1986 Second Addendum, and 1994 Supplement to the Second Addendum, additional studies have been conducted to determine the relationship between short-term exposures to ambient SO_2 and adverse respiratory health effects, including respiratory symptoms, lung function, airway inflammation, airway hyperresponsiveness, lung host defenses, and ED visits and hospitalizations for respiratory causes. The epidemiological, human clinical, and animal toxicological evidence on the effects of SO_2 on these various

endpoints are discussed below. The finding of the previous review are integrated below with the current literature.

3.1.2. Potential Mode of Action for Respiratory Health Effects

The 1982 AQCD (EPA, 1982) gave background information on the biochemistry of SO_2, chemical reactions of bisulfite (HSO_3^-), metabolism of SO_2, and the activating or inhibiting effects of bisulfite on various enzymes. SO_2 readily dissolves in water, rapidly becoming hydrated to form sulfurous acid, which at physiological pH substantially dissociates to form bisulfite and sulfite (SO_3^{2-}) ions. Studies in vitro have shown that SO_2 and/or bisulfite readily react with nucleic acids, proteins, lipids, and other classes of biomolecules. Bisulfite participates in three important types of reactions with biomolecules: sulfonation (sulfitolysis), autooxidation with generation of free radicals, and addition to cytosine. Products of sulfonation reactions have been shown to be long-lived in vivo and may be highly reactive. Products of autooxidation may be responsible for the initiation of lipid peroxidation, which, among other effects, could damage plasma membranes. In contrast, studies have shown that bisulfite can react with nucleic acids to convert cytosine to uracil, thus resulting in mutational events. A principal mechanism of detoxification of SO_2 (and sulfite/bisulfite) occurs through the enzymatic activity of sulfite oxidase, resulting in the production of sulfate. Sulfite oxidase is a molybdenum-containing enzyme, and the 1982 AQCD noted that depleting its activity through a low-molybdenum diet supplemented with the competitive inhibitor tungsten resulted in a significant lowering of the LD_{50} for intraperitoneally injected bisulfite. It was also noted that while in vitro exposure to SO_2 or sulfite/bisulfite had been shown to either activate or inhibit a variety of enzymes, no such effects had yet been demonstrated for in vivo exposure.

As discussed in the 1982 AQCD, the immediate effect of acute SO_2 exposure in animals was bronchoconstriction. Reactions of SO_2 with respiratory tract fluids can result in the production of bisulfite, sulfite, and a lowering of the pH, which may be involved in the bronchoconstrictive response. It is now widely appreciated that bronchoconstriction following SO_2 exposure is mediated by chemosensitive receptors in the tracheobronchial tree. Rapidly activating receptors (RARs) and sensory C-fiber receptors found at all levels of the respiratory tract are sensitive to irritant gases such as SO_2 (Coleridge and Coleridge, 1994; Widdicombe, 2006). Activation of these vagal afferents causes central nervous system reflexes resulting in

bronchoconstriction, mucus secretion, mucosal vasodilation, cough, or apnea, followed by rapid shallow breathing and effects on the cardiovascular system such as bradycardia and hypotension or hypertension (Coleridge and Coleridge, 1994; Widdicombe and Lee, 2001; Widdicombe, 2003).

Early experiments demonstrated that SO_2-induced reflexes were mediated by cholinergic parasympathetic pathways involving the vagus nerve and inhibited by atropine (Grunstein et al., 1977; Nadel et al., 1965a; 1965b). Bronchoconstriction was found to involve smooth muscle contraction since β-adrenergic agonists such as isoproterenol reversed the effects (Nadel et al., 1965a; 1965b). Acetylcholine and histamine were also thought to be involved in SO_2-induced bronchoconstriction (EPA, 1982).

More recent experiments in animal models conducted since 1982 have demonstrated that both cholinergic and noncholinergic mechanisms may be involved in SO_2-induced effects. In two studies utilizing bilateral vagotomy, vagal afferents were found to mediate the immediate ventilatory responses to SO_2 (Wang et al., 1996), but not the prolonged bronchoconstrictor response (Barthelemy et al., 1988). Other studies showed that atropine failed to block SO_2-induced bronchoconstriction, and that a local axon reflex resulting in C-fiber secretion of neuropeptides (i.e.., neurogenic inflammation) was responsible for the effect (Atzori et al., 1992a; Hajj et al., 1996). Neurogenic inflammation has been shown to play a key role in animal models of airway inflammatory disease (Groneberg et al., 2004).

In humans, the mechanisms responsible for SO_2-induced bronchoconstriction are not fully understood. In non-asthmatics, near complete attenuation of bronchoconstriction has been demonstrated using the anticholinergic agents atropine and ipratropium bromide (Snashall and Baldwin, 1982; Tan et al., 1982; Yildirim et al., 2005). However, in asthmatics, these same anticholinergic agents (Field et al., 1996; Myers et al., 1986a), as well as short- and long-acting *β2*-adrenergic agonists (Gong et al., 1996; Linn et al., 1988), theophylline (Koenig et al., 1992), cromolyn sodium (Myers et al., 1986), nedocromil sodium (Bigby and Boushey, 1993) and leukotriene receptor antagonists (Gong et al., 2001; Lazarus et al., 1997) only partially blocked SO_2-induced bronchoconstriction. That none of these therapies have been shown to completely attenuate the effects of SO_2 implies the involvement of both parasympathetic pathways and inflammatory mediators in asthmatics. Strong evidence of this is borne out in a study by Myers et al. (1986), in which asthmatic adults were exposed to SO_2 following pretreatment with

cromolyn sodium (a mast cell stabilizer), atropine (a muscarinic receptor antagonist), and the two medications together. While both treatments individually provided some protection against the bronchoconstrictive effects of SO_2, there was a much stronger and statistically significant effect following concurrent administration of the two medications.

It has been proposed that inflammation contributes to the enhanced sensitivity to SO_2 seen in asthmatics by altering autonomic responses (Tunnicliffe et al., 2001), enhancing mediator release (Tan et al., 1982) and/or sensitizing C-fibers and RARs (Widdicombe and Lee, 2001). Whether local axon reflexes also play a role in SO_2-induced bronchoconstriction in asthmatics is not known (Widdicombe and Lee, 2001; Widdicombe, 2003; Groneberg et al., 2004). However, differences in respiratory tract innervation between rodents and humans suggest that C-fiber mediated neurogenic inflammation may be unimportant in humans (Groneberg et al., 2004; Widdicombe and Lee, 2001; Widdicombe, 2003).

3.1.3. Respiratory Effects Associated with Peak Exposure

SO_2-induced respiratory effects among exercising asthmatics are well-documented, and have been consistently observed following peak exposures (defined here as 5-10 min exposures to relatively higher concentrations, e.g., 0.4-1.0 ppm) (Balmes et al., 1987; Bethel et al., 1985; Horstman et al., 1986; 1988; Linn et al., 1984b; 1987; 1990; Schachter et al., 1984; Sheppard et al., 1981). Similar respiratory effects have been observed in some sensitive asthmatics at concentrations as low as 0.2-0.3 ppm; however, these effects have not reached statistical significance (Horstman et al., 1986; Linn et al., 1987; 1988; 1990). Since the publication of the 1994 Supplement, several additional human clinical studies have been published that provide supportive evidence of SO_2-induced decrements in lung function and increases in respiratory symptoms among exercising asthmatics (see Annex Table D-2). Descriptions of older studies are presented in the 1994 Supplement, and will not be described in great detail in this document. However, based on recent guidance from the American Thoracic Society (ATS) regarding what constitutes an adverse health effect of air pollution (ATS, 2000a), some key older studies were reviewed and analyzed along with studies published since 1994. In its official statement, the ATS recommended that transient loss in lung function with accompanying respiratory symptoms attributable to air pollution should be considered adverse. In addition, ATS concluded that a decrease in health-related quality of life, which refers to an individual's perception of well being,

should also be considered to represent an adverse effect of air pollution. Therefore, whereas the conclusions in the 1994 Supplement were based on SO_2 exposure concentrations which resulted in large decrements in lung function along with moderate to severe respiratory symptoms, the current review of data from human clinical studies focuses on moderate to large SO_2-induced decrements in lung function combined with respiratory symptoms ranging from mild (perceptible wheeze or chest tightness) to severe (breathing distress requiring the use of a bronchodilator).

3.1.3.1. Respiratory Symptoms

The 1994 Supplement to the Second Addendum described in detail several studies that evaluated respiratory symptoms following controlled human exposures to SO_2. Briefly, following 5-min exposures to 0, 0.2, 0.4, and 0.6 ppm SO_2 during moderate to heavy levels of exercise (48 L/min), Linn et al. (1983) reported that the severity of respiratory symptoms (i.e., cough, chest tightness, throat irritation) among asthmatics increased with increasing SO_2 concentration. Relative to clean air exposures, exposures to SO_2 resulted in statistically significant increases in respiratory symptoms at concentrations of 0.4 and 0.6 ppm. In a subsequent study, Linn et al. (1987) observed a significant effect of SO_2 on respiratory symptoms in asthmatics who were engaged in slightly lower levels of exercise (40 L/min) for a duration of 10 min. Clear increases in respiratory symptoms were observed at concentrations of 0.6 ppm, with 43% of subjects experiencing SO_2-induced symptoms. Some evidence of SO_2-induced increases in respiratory symptoms was also demonstrated at concentrations as low as 0.4 ppm, with 15% of subjects experiencing symptoms (Smith, 1994). It was also observed that these symptoms abated < 1 h after exposure. Balmes et al. reported that 7 out of 8 asthmatic adults developed respiratory symptoms, including wheezing and chest tightness, following 3-min exposures to 0.5 ppm SO_2 during eucapnic hyperpnea ($\dot{V}_E$ = 60 L/min).

Additional human clinical studies published since the 1994 Supplement to the Second Addendum have provided support for previous conclusions regarding the effect of peak exposures to SO_2 on respiratory symptoms. In a human clinical study with SO_2-sensitive asthmatics, Gong et al. (1995) reported that respiratory symptoms (i.e., shortness of breath, wheeze, and chest tightness) increased with increasing SO_2 concentration (0, 0.5, and 1.0 ppm SO_2) following exposures of 10 min with varying levels of exercise. It was also observed that exposure to 0.5 ppm SO_2 during light exercise evoked a more severe symptomatic response than

heavy exercise in clean air. Trenga et al. (1999) observed a significant correlation between decreases in FEV_1 and increases in respiratory symptoms following 10 min exposures to 0.5 ppm SO_2.

3.1.3.2. Lung Function

In controlled exposures of healthy human subjects to SO_2, respiratory effects including increased respiration rates, decrements in peak flow, bronchoconstriction, and increased airway resistance have been observed at concentrations > 1 ppm (Abe, 1967; Amdur et al., 1953; Andersen et al., 1974; Frank et al., 1962; Lawther, 1955; Lawther et al., 1975; Sim and Pattle, 1957; Snell and Luchsinger, 1969). SO_2-induced decrements in lung function can be potentiated by increasing ventilation rate, either through eucapnic hyperpnea or by performing exercise during exposure. This effect is likely due to an increased uptake of SO_2 resulting from both the increase in $\dot{V}_E$ as well as a shift from nasal breathing to oronasal breathing.

It has been clearly established that subjects with asthma are more sensitive to the respiratory effects of SO_2 exposure than healthy individuals without asthma. Asthmatic individuals exposed to SO_2 concentrations as low as 0.4-0.6 ppm for 5-10 min during exercise have been shown to experience moderate or greater bronchoconstriction, measured as an increase in sRaw ($\geq$ 100%) or decrease in FEV_1 ($\geq$ 15%) after correction for exercise-induced responses in clean air (Linn et al., 1983; 1984; 1987; 1988; 1990; Magnussen et al., 1990; Roger et al., 1985). Asthmatic subjects who are most sensitive to the respiratory effects of SO_2 have been observed to experience significant decrements in lung function following exposure to SO_2 at concentrations $\leq$ 0.3 ppm (Horstman et al., 1986; Sheppard et al., 1981). In some cases, bronchoconstrictive responses to SO_2 can occur in as little as 2 min after the start of exposure (Balmes et al., 1987; Horstman et al., 1988). Gong et al. (1995) demonstrated an exposure-response relationship between SO_2 and lung function by exposing 14 unmedicated, SO_2-sensitive asthmatics to 0, 0.5, and 1 ppm SO_2 under 3 different levels of exercise. It was shown that increasing SO_2 concentration had a greater effect on sRaw and FEV_1 than increasing exercise level. Trenga et al. (1999) observed that 25 out of 47 adult asthmatics experienced a drop in FEV_1 versus baseline of between 8 and 44% (mean = 17.2%) following a 10 min exposure to 0.5 ppm SO_2 during moderate exercise.

Since some of the studies involving asthmatic subjects have used change in sRaw as the endpoint of interest while others measured changes in FEV_1 or both, a comparison of FEV_1 and sRaw based on data from Linn et al. (1987; 1990) was provided in the 1994 Supplement to the Second Addendum. Based on simple linear interpolation of the data from these two studies, a 100% increase in sRaw corresponded to a 12 to 15% decrease in FEV_1 and a 200% increase in sRaw corresponded to a 25 to 30% decrease in FEV_1.

One of the aims of the Linn et al. (1987) study was to determine how the intensity of response varied with asthma severity or status. In this study, 24 normal, 21 atopic (but not asthmatic), 16 mild asthmatic, and 24 moderate/severe asthmatic subjects were exposed to SO_2 concentrations between 0 and 0.6 ppm. While the moderate/severe asthmatics were more responsive than mild asthmatics following exposure to clean air during exercise, their increases in response to increasing SO_2 concentrations were similar to those of the mild asthmatic group. Thus, it was concluded that SO_2 response was not strongly dependent on the clinical severity of asthma. However, the apparent lack of correlation between SO_2 response and asthma severity should be interpreted with caution, since the SO_2 response may have been attenuated by medication usage or its persistence. Three of the moderate/severe asthmatics were unable to withhold medication usage during the exposure period. Conversely, a few of the asthmatics, including some in the moderate/severe group, did not react to 0.6 ppm SO_2.

One of the key studies discussed in the 1994 Supplement to the Second Addendum was by Horstman et al. (1986). In this study, 27 asthmatic subjects were exposed to concentrations of SO_2 between 0- and 2 ppm SO_2 for 10 min on different days under exercising conditions ($\dot{V}_E$ = 42 L/min). The authors reported that for 22% of the subjects, the concentration of SO_2 needed to produce a doubling of sRaw compared to clean air exposure [$PC(SO_2)$] was < 0.5 ppm, with 2 subjects (7.4%) experiencing moderate decrements in lung function following exposure to concentrations of SO_2 at or below 0.3 ppm (see Figure 3-1). For approximately 15% of the subjects, the $PC(SO_2)$ was > 2 ppm, with approximately 35% of asthmatic subjects experiencing a doubling in sRaw versus clean air at ≤ 0.6-ppm SO_2.

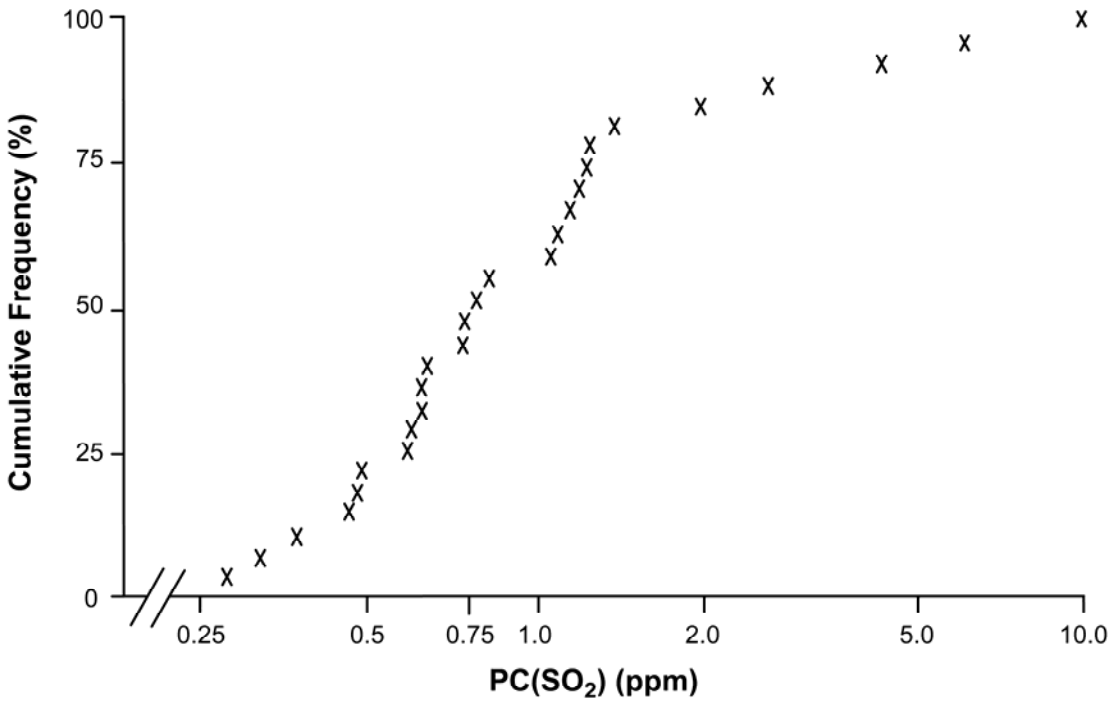

Figure 3-1. Distribution of individual airway sensitivity to SO_2. Each data point represents the value of $PC(SO_2)$ for an individual subject. $PC(SO_2)$ is defined as the concentration of SO_2 which resulted in a doubling of sRaw compared to clean air exposure.

Source: Horstman et al. (1986).

It is important to note that a transient decrement in lung function following exposure to an air pollutant is not automatically considered to represent an adverse effect. However, SO_2-induced decrements in lung function (increased sRaw and decreased FEV_1) have frequently been associated with increases in respiratory symptoms among asthmatics (Balmes et al., 1987; Gong et al., 1995; Linn et al., 1987; 1988; 1990; 1983; Roger et al., 1985), which together does constitute an adverse effect under the ATS guidelines. Linn et al. (1987) exposed 40 mild and moderate asthmatics during 10 min periods of exercise to 0, 0.2, 0.4, and 0.6 ppm SO_2. The effect of SO_2 on lung function and respiratory symptoms was assessed immediately following exposure, and the individual-specific results have been made available to the U.S. EPA by the study authors (Smith, 1994). Following exposure to 0.6 ppm SO_2 and after adjusting for effects of exercise in clean air, 21 of the 40 subjects demonstrated moderate or greater decrements in lung function, defined as a ≥15% decrease in FEV_1, a ≥100% increase in sRaw, or both. Of these

21 responders, 14 (67%) also experienced mild to severe respiratory symptoms (6 mild, 6 moderate, and 2 severe). In the same study, 14 asthmatics experienced moderate or greater decrements in lung function at 0.4 ppm SO_2, 5 of whom (36%) also experienced mild to moderate respiratory symptoms (2 mild, 3 moderate). Five asthmatics experienced moderate or greater decrements in lung function at the lowest SO_2 concentration tested (0.2 ppm), with 1 of the 5 (20%) also experiencing mild respiratory symptoms.

It has been proposed that, as in asthmatics, individuals with COPD may also be more susceptible to SO_2-induced respiratory health effects. However, this group has not been extensively studied in human clinical studies. Among a group of older adults with physician-diagnosed COPD, Linn et al. (1985) reported no significant effect on lung function following 15 min exposures to SO_2 at concentrations of 0.4 and 0.8 ppm. While it was concluded that older adults with COPD appear to be less sensitive to SO_2 when compared with younger adult asthmatics, the authors suggested that the lack of response may have been due in part to the very low levels of exercise used in the study ($\dot{V}_E$ = 18 L/min), which would result in a lower dose of SO_2 reaching the lower airway. In contrast to studies with asthmatics, most of the subjects in this study regularly used bronchodilators and were permitted their use up to 4 h prior to the study.

In summary, SO_2-induced decrements in lung function have been observed following peak exposures in humans. These effects are particularly evident in exercising asthmatic individuals, with significant decreases in sRaw and increases in FEV_1 consistently demonstrated following 5-10 min exposures to 0.4-0.6 ppm SO_2. SO_2-induced decrements in lung function have frequently been associated with respiratory symptoms, and with increasing SO_2 exposure concentration from 0.2-1.0 ppm, both the magnitude of response among asthmatics and the percentage of asthmatics significantly affected have been shown to increase.

3.1.3.3. Airway Inflammation

A very limited number of human clinical studies have investigated the role of airway inflammation in the asthmatic response following peak exposure to SO_2. Gong et al. (2001) observed an SO_2-induced increase in sputum eosinophil counts in exercising asthmatics 2 h after a 10 min exposure to 0.75 ppm SO_2. The results of this study provide some evidence that SO_2 may elicit an allergic inflammatory response in the airways of asthmatics which extends beyond the short time period typically associated with SO_2 effects.

3.1.3.4. Evidence of the Effect of Peak Exposure from Animal Studies

In addition to the findings of human clinical studies involving asthmatics, SO_2-induced decrements in lung function have been demonstrated following peak exposures to SO_2 in laboratory animals. The 1982 AQCD reported bronchoconstriction, as indicated by increased pulmonary resistance, as the most sensitive indicator of lung function effects of acute SO_2 exposure based on the observations of increased pulmonary resistance in guinea pigs that were acutely exposed to 0.16 ppm SO_2. Since 1982, a few new animal toxicological studies have demonstrated acute changes in lung function following SO_2 exposures of 45 min or less. These studies are summarized below and in Annex Table E-1.

Lewis and Kirchner (1984) measured lung function in dogs exposed for 5 min to two doses of SO_2 via an endotracheal tube. Increased pulmonary resistance and decreased compliance were observed in conscious dogs exposed to 30 ppm SO_2, but not to 10 ppm SO_2.

All other studies focused on the role of local nervous system reflexes and/or C-fiber receptors in mediating responses to SO_2. Barthelemy et al. (1988) measured lung function in anesthetized rabbits exposed for 45 min by endotracheal tube to two doses of SO_2. Airway resistance increased 16% and 50% following 0.5 and 5 ppm SO_2, respectively. Bivagal vagotomy had little effect on the response to 5 ppm, indicating that the prolonged bronchoconstriction response did not result from a vagal reflex. This study did not rule out the possibility that vagal reflexes were involved in immediate bronchoconstriction following SO_2 exposure.

In another study, Atzori et al. (1992a) demonstrated bronchoconstriction, as measured by changes in dynamic lung compliance and airway conductance, within the first 5 min following exposure of isolated and perfused guinea pig lungs to 100 and 250 ppm SO_2 via an endotracheal tube. This response was found to be due to a local nervous system reflex. However, this result does not preclude involvement of central nervous system reflexes in SO_2-induced bronchoconstriction under conditions of an intact vagus nerve. Furthermore, the formation of sulfite was observed in perfusate following SO_2 exposure. Using the same model, Atzori et al. (1992b) found that SO_2-induced bronchoconstriction was associated with the release of a sensory neuropeptide and was inhibited when C-fiber receptors were blocked.

Other animal toxicological studies examined immediate respiratory effects from exposure to very high SO_2 concentrations. Hajj et al. (1996) exposed anesthetized guinea pigs to six tidal breaths of 500–2,000 ppm SO_2. Increased total pulmonary resistance, decreased dynamic

compliance, and systemic hypotension were observed within seconds. Tachykinin antagonists blocked the changes in lung airway function, but not the changes in blood pressure in this model system. Atropine failed to block the airway response. These results suggest that a local nervous system reflex involving tachykinin release is an important mediator of bronchoconstriction following high concentrations of SO_2. Wang et al. (1996) exposed anesthetized rats to two tidal breaths of 0.5% SO_2 via an endotracheal tube. Immediate and transient bradypnea and bradycardia were observed. Selective block of the C-fiber receptors and bilateral vagotomy eliminated the SO_2-mediated effect on ventilation.

3.1.3.5. Summary of Evidence on the Effect of Peak Exposure on Respiratory Health

Collectively, evidence from earlier studies considered in the previous review, along with a limited number of new human clinical studies, consistently indicates that with elevated ventilation rates, asthmatic individuals experience moderate or greater decrements in lung function, as well as increased respiratory symptoms, following peak exposures to SO_2 at concentrations as low as 0.4-0.6 ppm (Balmes et al., 1987; Gong et al., 1995; Horstman et al., 1986; Linn et al., 1987; Linn et al., 1983). These findings are consistent with our understanding of the potential modes of action for respiratory health as described in Section 3.1.2. Some sensitive asthmatics have been shown to experience moderate decrements in lung function at concentrations below 0.3 ppm (Balmes et al., 1987; Linn et al., 1987; Sheppard et al., 1981), although there is limited evidence of a significant increase in respiratory symptoms at these exposure concentrations. Among asthmatics, both the magnitude of SO_2-induced decrements in lung function and the percent of individuals affected have consistently been shown to increase with increasing exposure to SO_2 concentrations between 0.2 and 1.0 ppm. This is summarized in Table 3-1 along with supporting evidence of SO_2-induced increases in respiratory symptoms at various exposure concentrations. The table includes data from all studies where individual data are presented or have been made available by the authors (Smith, 1994). Although the vast majority of human clinical studies involving controlled exposure to SO_2 have been conducted in adult asthmatics, there is a relatively strong body of evidence to suggest that adolescents may experience many of the same respiratory effects at similar SO_2 exposure concentrations (Koenig et al., 1981; 1983; 1987; 1988; 1990; 1992). It should be noted, however, that in all of these

studies involving adolescents, SO_2 was administered via inhalation through a mouthpiece rather than an exposure chamber. This exposure technique bypasses nasal absorption of SO_2, likely resulting in a relative increase of pulmonary SO_2 uptake (see Section 2.6.1).

Table 3-1. Percentage of asthmatic individuals in controlled human exposures experiencing SO_2-induced decrements in lung function.

SO_2 CONC (ppm)	EXPOSURE DURATION	NO. SUBJ	VENTILATION (L/MIN)	LUNG FUNCT	CUMULATIVE PERCENTAGE OF RESPONDERS (NUMBER OF SUBJECTS)[1]			REFERENCE	RESPIRATORY SYMPTOMS: SUPPORTING STUDIES
					sRaw ≥ 100% ↑	sRaw ≥ 200% ↑	sRaw ≥ 300% ↑		
					FEV_1 ≥ 15% ↓	FEV_1 ≥ 20% ↓	FEV_1 ≥ 30% ↓		
0.2	10 min	40	~40	sRaw	5% (2)	0	0	Linn et al. (1987)[2]	Some evidence of SO_2-induced increases in respiratory symptoms in the most sensitive individuals: Linn et al. (1987; 1988; 1990; 1984a; 1983), Schacter et al. (1984)
	10 min	40	~40	FEV_1	13% (5)	5% (2)	3% (1)	Linn et al. (1987)	
0.25	5 min	19	~50-60	sRaw	32% (6)	16% (3)	0	Bethel et al. (1985)	
	5 min	9	~80-90	sRaw	22% (2)	0	0		
	10 min	28	~40	sRaw	4% (1)	0	0	Roger et al. (1985)	
0.3	10 min	20	~50	sRaw	10% (2)	5% (1)	5% (1)	Linn et al. (1988)[3]	
	10 min	21	~50	sRaw	33% (7)	10% (2)	0	Linn et al. (1990)[3]	
	10 min	20	~50	FEV_1	15% (3)	0	0	Linn et al. (1988)	
	10 min	21	~50	FEV_1	24% (5)	14% (3)	10% (2)	Linn et al. (1990)	
0.4	10 min	40	~40	sRaw	23% (9)	8% (3)	3% (1)	Linn et al. (1987)	Stronger evidence with some statistically significant increases in respiratory symptoms: Balmes et al. (1987)[4], Gong et al. (1995), Linn et al. (1987; 1983), Roger et al. (1985)
	10 min	40	~40	FEV_1	30% (12)	23% (9)	13% (5)	Linn et al. (1987)	
0.5	5 min	10	~50-60	sRaw	60% (6)	40% (4)	20% (2)	Bethel et al. (1983)	
	10 min	28	~40	sRaw	21% (6)	4% (1)	4% (1)	Roger et al. (1985)	
	10 min	45	~30	sRaw	36% (16)	16% (7)	13% (6)	Magnussen et al. (1990)[4]	
0.6	10 min	40	~40	sRaw	35% (14)	28% (11)	18% (7)	Linn et al. (1987)	Clear and consistent increases in SO_2-induced respiratory symptoms: Linn et al.(1987; 1988; 1984a; 1990), Gong et al. (1995), Horstman et al. (1988)
	10 min	20	~50	sRaw	60% (12)	35% (7)	10% (2)	Linn et al. (1988)	
	10 min	21	~50	sRaw	57% (12)	33% (7)	14% (3)	Linn et al. (1990)	
	10 min	40	~40	FEV_1	53% (21)	45% (18)	20% (8)	Linn et al. (1987)	
	10 min	20	~50	FEV_1	55% (11)	55% (11)	5% (1)	Linn et al. (1988)	
	10 min	21	~50	FEV_1	45% (9)	35% (7)	19% (4)	Linn et al. (1990)	
1.0	10 min	28	~40	sRaw	54% (15)	25% (7)	14% (4)	Roger et al. (1985)	
	10 min	10	~40	sRaw	60% (6)	20% (2)	0	Kehrl et al. (1987)	

[1]Data presented from all references from which individual data were available. Percentage of individuals who experienced greater than or equal to a 100, 200, or 300% increase in specific airway resistance (sRaw), or a 15, 20, or 30% decrease in FEV_1. Lung function decrements are adjusted for effects of exercise in clean air.
[2]Responses of mild and moderate asthmatics reported in Linn et al. (1987) have been combined.
[3]Analysis includes data from only mild (1988) and moderate (1990) asthmatics who were not receiving supplemental medication.
[4]Indicates studies in which exposures were conducted using a mouthpiece rather than a chamber.

In laboratory animals, SO_2-induced decrements in lung function were observed following peak exposures in several studies conducted since the last review. Most of these experiments were designed to evaluate the mode of action underlying SO_2-mediated bronchoconstriction. They used high concentrations of administered SO_2, which in many cases were delivered using an endotracheal tube. As a result, these studies are of limited usefulness in understanding the effects of SO_2 at or near ambient levels or under conditions of nasal breathing.

3.1.4. Respiratory Effects Associated with Short-Term (≥ 1 h) Exposure

3.1.4.1. Respiratory Symptoms

Consideration of the mode of action suggests that SO_2 may contribute to respiratory symptoms by stimulating mucus secretion and cough through activating central nervous system reflexes. Recent studies in vitro have demonstrated increased expression of a gene encoding mucin protein, MUC5AC, in human bronchial epithelial cells following exposure to the SO_2 derivatives sulfite and bisulfite at concentrations of 1-10 μM (Li and Meng, 2007). Increased levels of MUC5AC protein were also reported. Sulfite and bisulfite were used, since SO_2 dissolves into the aqueous fluid and forms hydrogen ions and bisulfite and sulfite anions when it contacts the fluids lining the airway. These same investigators conducted a related in vivo study in which rats were exposed by inhalation to 2 ppm SO_2 for 1 h per day for 7 days. Rats which were sensitized and challenged with ovalbumin, as well as exposed to SO_2, had increased MUC5AC mRNA and protein levels compared with animals treated with ovalbumin or SO_2 alone (Li et al., 2007b). Further studies are required to determine the relevance of mucin gene expression to mucous secretion and respiratory symptoms in allergic and non-allergic animals at ambient levels of SO_2. However, evidence from toxicological studies such as these may provide biological plausibility for the effects of SO_2 on respiratory symptoms in humans.

Epidemiological studies have examined the association between ambient SO_2 concentrations and respiratory symptoms in both adults and children. In air pollution field studies, respiratory symptoms are usually assessed using questionnaire forms (or "daily diaries") completed by study subjects. Questions address the daily experience of coughing, wheezing, shortness of breath (or difficulty breathing), production of phlegm, and others.

3.1.4.1.1. Children

Epidemiological studies on respiratory symptoms published since the last review are summarized in Annex Table F-1; key studies are discussed in detail below.

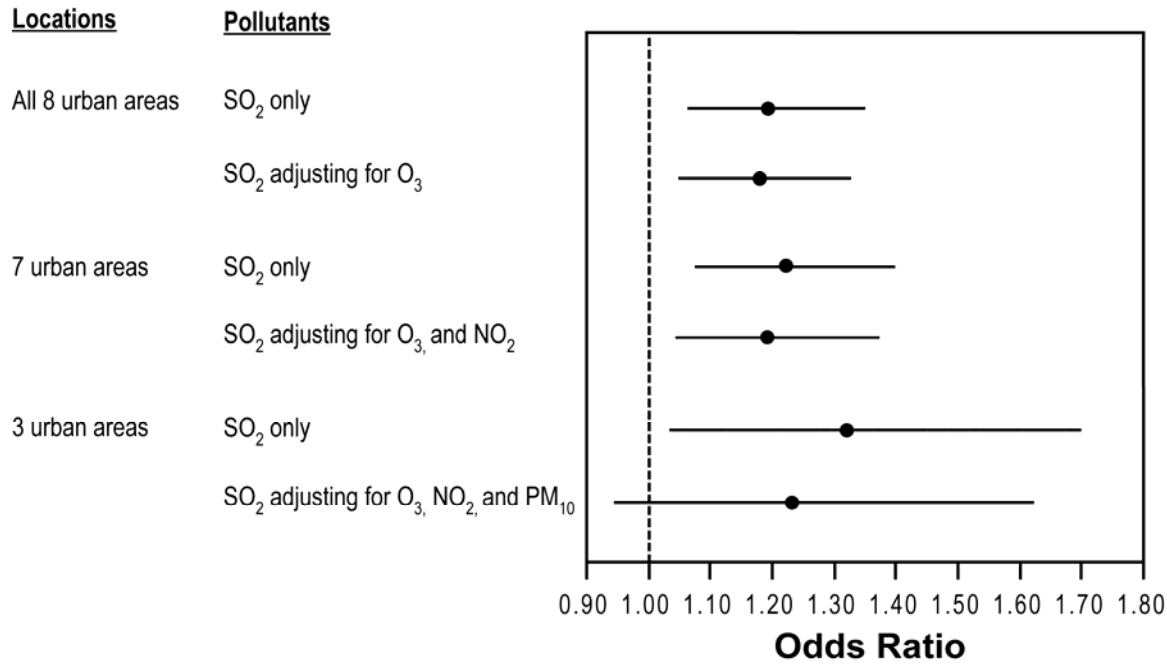

Figure 3-2. Odds ratios (95% CI) for incidence of morning asthma symptoms of 846 asthmatic children from the National Cooperative Inner-City Asthma Study. Effects associated with a 20 ppb increase in 3-h avg SO_2 with a lag of 1-2 day moving average are presented. SO_2 effect estimates from single- and multipollutant models are shown.

Source: Mortimer et al. (2002).

The strongest epidemiological evidence for an association between respiratory symptoms and exposure to ambient SO_2 comes from two large U.S. multicity studies (Mortimer et al., 2002; Schildcrout et al., 2006). Mortimer et al. examined 846 asthmatic children from eight U.S. urban areas in the National Cooperative Inner-City Asthma Study (NCICAS) for summertime air pollution-related respiratory symptoms. Median 3-h avg SO_2 (8 to 11 a.m.) levels ranged from 17 ppb in Detroit, MI to 37 ppb in East Harlem, NY. Morning symptoms were found to be most strongly associated with an average of a 1- to 2-day lag of SO_2 concentrations. In multipollutant models with O_3 and NO_2 (measured in seven cities), the SO_2 association remained robust (see

Figure 3-2). When particulate matter with an aerodynamic diameter of ≤ 10 μm (PM_{10}) was also included in the multipollutant models, the SO_2 effect estimate decreased only slightly; however, it became nonsignificant, possibly due to reduced statistical power (only three of eight cities were included in this analysis) or collinearity resulting from adjustment of multiple pollutants. A similar decline was observed in the effect estimate for PM_{10} in the multipollutant model compared to the single-pollutant model.

In the Childhood Asthma Management Program (CAMP) study, the association between ambient air pollution and asthma exacerbations in children (n = 990) from eight North American cities was investigated (Schildcrout et al., 2006). SO_2 measurements were available in seven of the eight cities. The median 24-h avg SO_2 concentrations ranged from 2.2 ppb (interquartile range [IQR]: 1.7, 3.1) in San Diego, CA to 7.4 ppb (IQR: 5.3, 10.7) in St. Louis, MO. Results for the associations between asthma symptoms and all pollutants are shown in Figure 3-3. Analyses indicate that although SO_2 was positively related to increased risk of asthma symptoms at all lags, only the 3-day moving average was statistically significant. No associations were observed between SO_2 and rescue inhaler use. Stronger associations were observed for CO and NO_2. The effect estimates appear to be slightly larger in joint-pollutant models with CO or NO_2, particularly at a 2-d lag, but did not change much when PM_{10} was jointly considered.

A longitudinal study of 1,844 schoolchildren during the summer from the Harvard Six Cities Study suggested that the association between SO_2 and respiratory symptoms could be confounded by PM_{10} (Schwartz et al., 1994). The median 24-h avg SO_2 concentration during this period was 4.1 ppb (10th–90th percentile: 0.8, 17.9; max 81.9). SO_2 concentrations were found to be associated with cough incidence and lower respiratory tract symptoms. Of the pollutants examined, PM_{10} had the strongest associations with respiratory symptoms. In two-pollutant models, the effect of PM_{10} was found to be robust to adjustment for other copollutants, while the effect of SO_2 was substantially reduced after adjustment for PM_{10}. Because the PM_{10} concentrations were correlated strongly to SO_2-derived sulfate particles (r = 0.80), the diminution of the SO_2 effect estimate may indicate that for PM_{10} dominated by fine sulfate particles, PM_{10} has a slightly stronger association than SO_2. This study further investigated the concentration-response function and observed a nonlinear relationship between SO_2 concentrations and respiratory symptoms. Though an increasing trend was observed at concentrations as low as

10 ppb, no statistically significant increase in the incidence of lower respiratory tract symptoms was seen until concentration exceeded a 24-h avg SO_2 of 22 ppb.

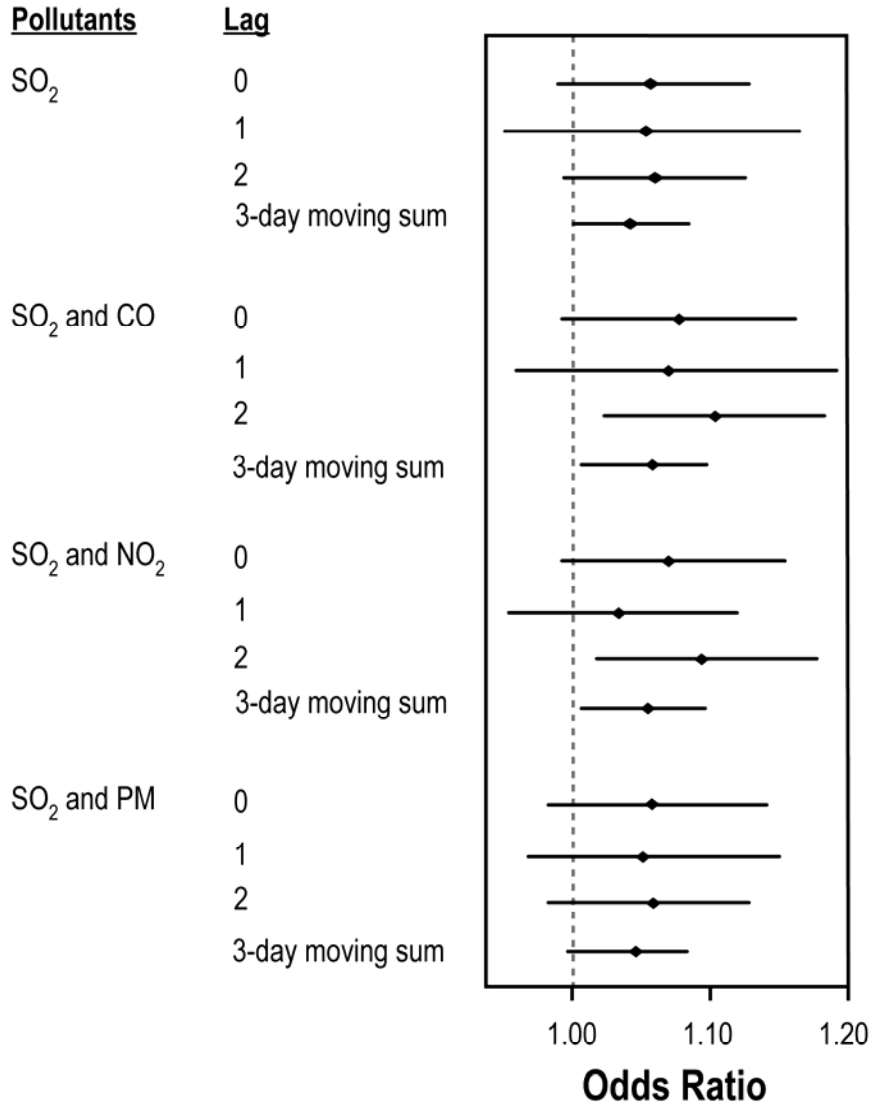

Figure 3-3. Odds ratios (95% CI) for daily asthma symptoms of 990 asthmatic children from the Childhood Asthma Management Program Study. Effects associated with a 10 ppb increase in within-subject concentrations of 24-h avg SO_2 are presented. Data collected from November 1993 to September 1995 were used. Results from single- and joint-pollutant models are shown.

Source: Schildcrout et al. (2006).

In the Pollution Effects on Asthmatic Children in Europe (PEACE) study, a multicenter study of 14 cities across Europe, the effects of acute exposure to various pollutants including SO_2 on the respiratory health of children with chronic respiratory symptoms (n = 2,010) was examined during the winter of 1993–1994 (Roemer et al., 1998). Mean 24-h avg SO_2 concentrations ranged from 1 ppb in the urban area of Umeå, Sweden, to 43 ppb in the urban area of Prague, Czech Republic. No associations were observed between SO_2 and daily prevalence of respiratory symptoms or bronchodilator use at any of the single- and multiday lags considered. In addition, no associations were observed for any of the other pollutants examined. It should be noted that during the study period, there were only two major air pollution episodes, at the beginning and end of the study period. In the epidemiological model, the control for time trend was accomplished through the use of linear and quadratic terms. Given the timing of the air pollution episodes, the quadratic trend term would have removed most of the air pollution effect. Other studies that participated in the PEACE study and analyzed results for longer periods of time have observed statistically significant associations between SO_2 and respiratory symptoms in children (van der Zee et al., 1999, presented below).

Additional studies have examined the relationship between respiratory symptoms and ambient SO_2 concentrations and generally found positive associations, including two U.S. studies (Delfino et al., 2003; Neas et al., 1995) and several European studies (Hoek and Brunekreef, 1994; Peters et al., 1996; Roemer et al., 1993; Segala et al., 1998; Timonen and Pekkanen, 1997; van der Zee et al., 1999). However, some did not find a consistent association between respiratory symptoms and SO_2 concentrations (e.g., Hoek and Brunekreef, 1993; 1995; Romieu et al., 1996). Only one of these studies examined possible confounding of the SO_2 effect by copollutants. Van der Zee et al. (1999) looked at the association between respiratory symptoms and SO_2 in 7- to 11-year-old children (n = 633) with and without chronic respiratory symptoms in the Netherlands. Significant associations with lower respiratory tract symptoms and increased bronchodilator use were observed for SO_2, as well as PM_{10}, BS, and sulfate, in symptomatic children living in urban areas (n = 142). In a two-pollutant model with PM_{10}, the results were robust for bronchodilator use, but slightly reduced for lower respiratory tract symptoms. A subgroup analysis of this cohort examining SO_2-related respiratory symptoms in children with airway hyperresponsiveness and atopy (Boezen et al., 1999) is discussed in Section 3.1.4.4.

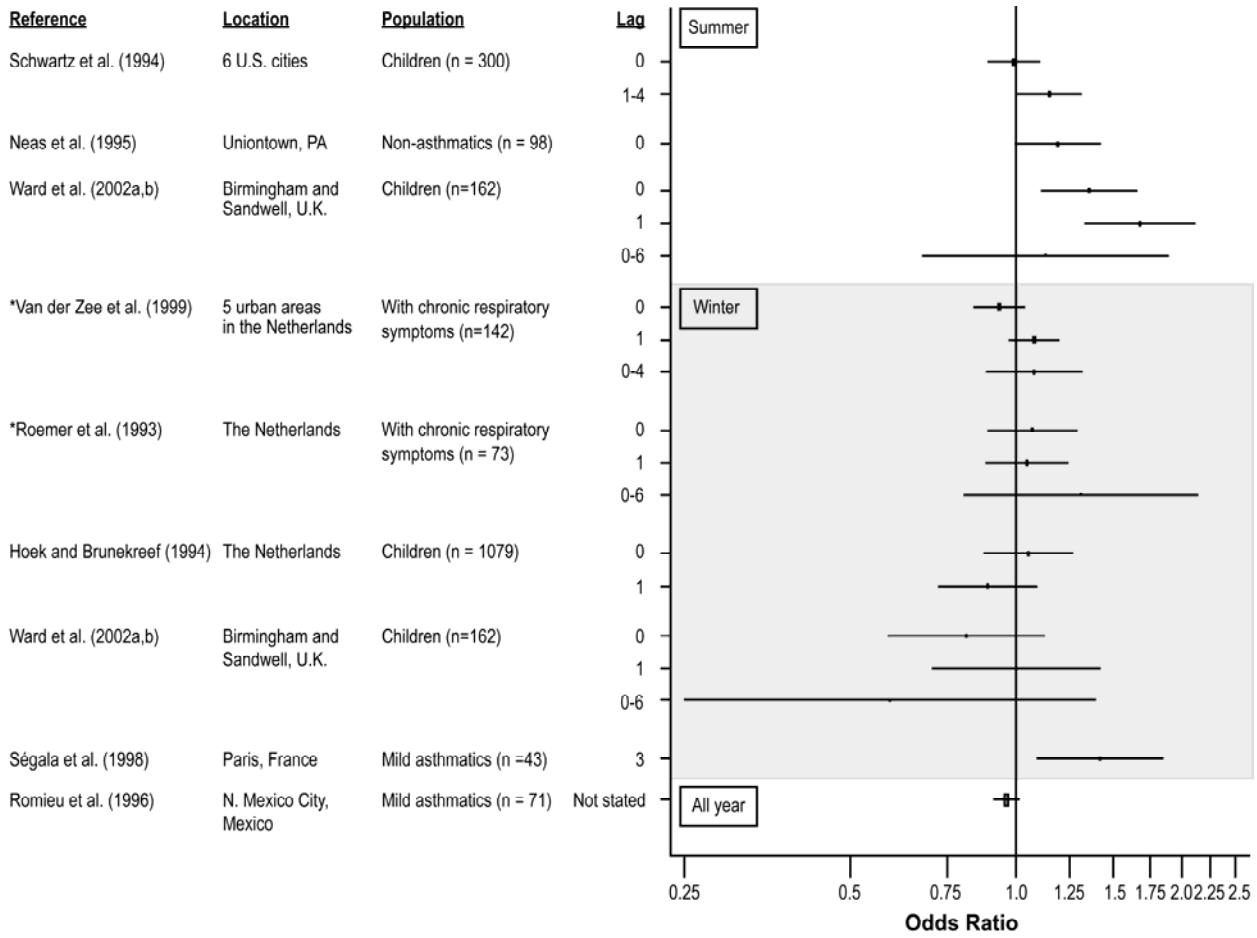

Figure 3-4. Odds ratios (95% CI) for incidence of cough among children, grouped by season. For single-day lag models, current day and/or previous day SO_2 effects are shown, except for Ségala et al. (1998), which only presented results for a 3-day lag. Multiday lag models represent the effect of the mean concentration from the range of days noted. Risk estimates are standardized per 10 ppb increase in 24-h avg SO_2 level. The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.

*Note that van der Zee et al. (1999) and Roemer et al.(1998) presented results for prevalence of cough.

Figure 3-4 and Figure 3-5 present the odds ratios for SO_2-related cough and lower respiratory tract or asthma symptoms, respectively, from several epidemiological studies with relevant data. The results for cough are somewhat variable with wide confidence intervals, as shown in Figure 3-4. The studies conducted in the summer generally indicate increased risk of cough from exposure to SO_2. A more consistent effect of SO_2 is observed on lower respiratory tract or asthma symptoms (Figure 3-5). Although there is some variability in the individual effect estimates, the majority of the odds ratios appear to be greater than one. As was the case with

cough, stronger associations with lower respiratory tract or asthma symptoms were observed in the summer, as opposed to the winter. There was some variability among the different lags of exposure; however, effects were generally observed with current day or previous day exposure and, in some cases, with a distributed lag of 2 to 3 days.

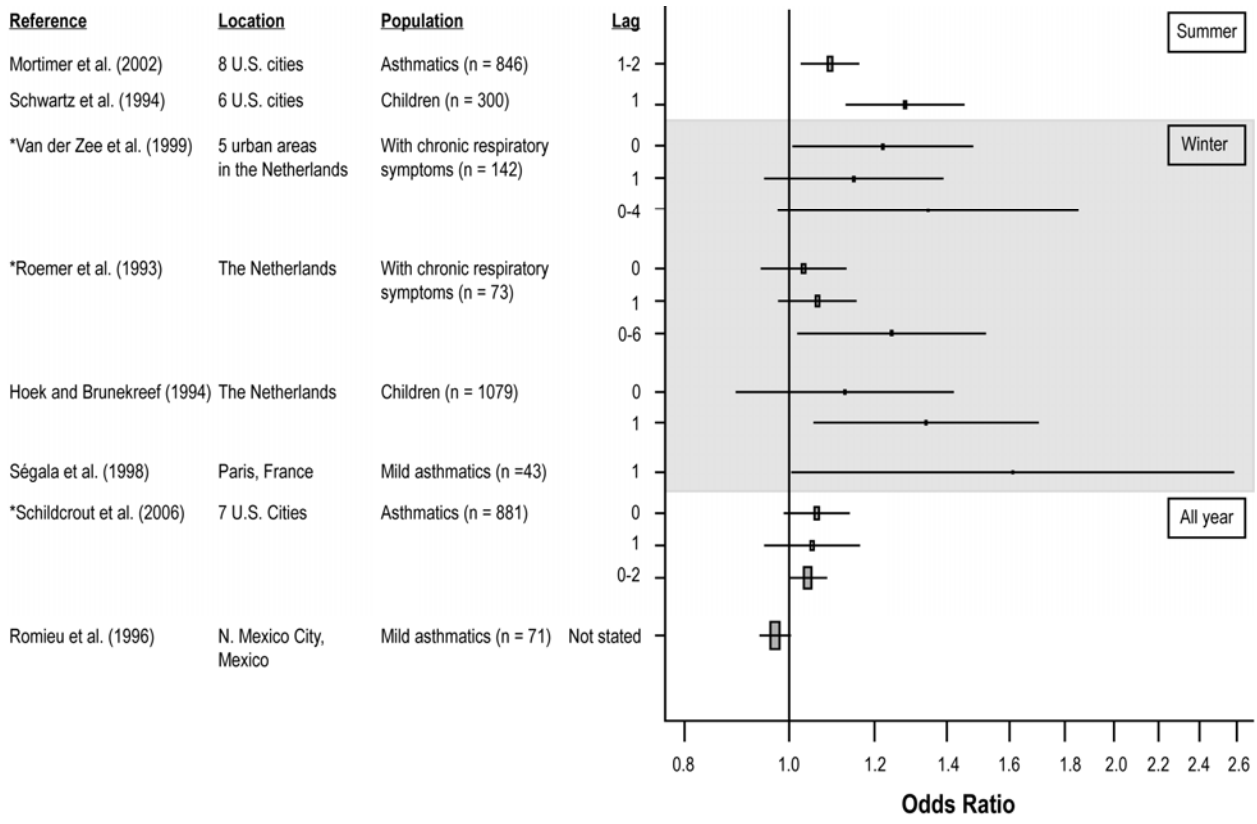

Figure 3-5. Odds ratios (95% CI) for the incidence of lower respiratory tract or asthma symptoms among children, grouped by season. Risk estimates are standardized per 10 ppb increase in 24-h avg SO_2 level. For single-day lag models, current day and/or previous day SO_2 effects are shown. Multiday lag models represent the effect of the moving average from the range of days noted. The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.

*Note that van der Zee et al. (1999), Roemer et al. (1998) and Schildcrout et al. (2006) presented results for prevalence of cough.

Overall, recent epidemiological studies provide evidence for an association between ambient SO_2 exposures and increased respiratory symptoms in children, particularly those with asthma or chronic respiratory symptoms. Recent U.S. multicity studies observed significant

associations between SO_2 and respiratory symptoms at a median range of 17 to 37 ppb (75th percentile: ~25 to 50) across cities for 3-h avg SO_2 (NCICAS, Mortimer et al., 2002) and 2.2 to 7.4 ppb (90th percentile: 4.4 to 14.2) for 24-h avg SO_2 (CAMP, Schildcrout et al., 2006). However, an earlier study that examined the concentration-response function found that a statistically significant increase in the incidence of lower respiratory tract symptoms was not observed until concentrations exceeded a 24-h avg SO_2 of 22 ppb, though an increasing trend was observed at concentrations as low as 10 ppb (Harvard Six Cities Study, Schwartz et al., 1994). In the limited number of studies that examined potential confounding by copollutants through multipollutant models, the SO_2 effect was generally found to be robust after adjusting for PM and other copollutants. More details of the literature published since the last review are found in Annex Table F-1.

3.1.4.1.2. Adults

Compared to the number of studies conducted with children, fewer epidemiological studies were performed that examined the effect of ambient SO_2 exposure on respiratory symptoms in adults. Most of these studies focused on potentially susceptible populations, i.e., those with asthma or COPD. One of the larger studies was conducted by van der Zee et al. (2000) in 50- to 70-year-old adults, with (n = 266) and without (n = 223) chronic respiratory symptoms in the Netherlands. In adults both with and without chronic respiratory symptoms, no consistent associations were observed between SO_2 levels and respiratory symptoms or medication use. A subgroup analysis of this cohort examining SO_2-related respiratory symptoms in individuals with airway hyperresponsiveness and atopy (Boezen et al., 2005) is discussed in Section 3.1.4.4.

Studies by Desqueyroux et al. (2002b; 2002a) examined the association between air pollution and respiratory symptoms in other potentially susceptible populations, i.e., those with severe asthma (n = 60, mean age 55 years) and COPD (n = 39, mean age 67 years), in Paris, France. The mean 24-h avg SO_2 concentration was 3 ppb (range: 1, 10) in the summer and 7 ppb (range: 1, 31) in the winter. No associations were observed between SO_2 concentrations and the incidence of asthma attacks or episodes of symptom exacerbation in severe asthmatics or individuals with COPD. O_3 was found to have the strongest effect in these studies.

Several other European studies did observe an association between ambient SO_2 concentrations and respiratory symptoms in adults with asthma or chronic bronchitis (Higgins et

al., 1995; Neukirch et al., 1998; Peters et al., 1996; Taggart et al., 1996). Only one of these studies examined possible confounding of the association by copollutants. Higgins et al. examined the effect of summertime air pollutant exposure on respiratory symptoms in 62 adults with either asthma, COPD, or both. The max 24-h avg SO_2 level was 45 ppb. An association was observed between SO_2 and symptoms of wheeze, and it remained robust after adjustment for O_3 and NO_2. The effects of PM were not examined in this study.

Results from the epidemiological studies examining the association between SO_2 and respiratory symptoms in adults are generally mixed, with some showing positive associations and others finding no relationship at current ambient levels. The overall epidemiological evidence that 24-h avg SO_2 exposures at or near ambient concentrations has an effect on adults is inconclusive. However, as discussed in Section 3.1.3.1, human clinical studies have observed an effect of peak exposures to SO_2 on respiratory symptoms, particularly among SO_2-sensitive asthmatics, with 10 min exposures to SO_2 concentrations as low as 0.4-0.6 ppm under exercise conditions. These effects in clinical studies are at levels that have sometimes been measured in ambient air for similarly short-time durations.

3.1.4.2. Lung Function

The 1982 AQCD reported bronchoconstriction, indicated by increased pulmonary resistance, as the most sensitive indicator of lung function effects of acute SO_2 exposure, based on the observations of increased pulmonary resistance in guinea pigs that were acutely exposed to 0.16 ppm SO_2. Since then, only a few new animal toxicological studies have measured lung function at or near ambient levels of SO_2. These studies, and those using higher concentrations of SO_2, are summarized in Annex Table E-4. Increased pulmonary resistance and decreased dynamic compliance were observed in conscious guinea pigs exposed to 1 ppm SO_2 for 1 h (Amdur et al., 1983). Effects were seen immediately after exposure and were not present 1 h post-exposure. No changes in tidal volume, minute volume or breathing frequency were found. These same investigators also exposed guinea pigs to 1 ppm SO_2 for 3 h/day for 6 days (Conner et al., 1985). No changes were observed in pulmonary function or respiratory parameters, i.e., diffusing capacity for carbon monoxide, functional reserve capacity, vital capacity, total lung capacity, respiratory frequency, tidal volume, pulmonary resistance or pulmonary compliance. In another study, Barthelemy et al. (1988) demonstrated a 16% increase in airway resistance

following a 45-min exposure of anesthetized rabbits to 0.5 ppm SO_2 via an endotracheal tube. This latter exposure is more relevant to oronasal than nasal breathing.

3.1.4.2.1. Children

Most epidemiological studies discussed in the previous section on respiratory symptoms also examined lung function. In these studies self-administered PEF meters were primarily used to assess lung function. PEF follows a circadian rhythm, with the highest values found during the afternoon and lowest values during the night and early morning (Borsboom et al., 1999). Therefore, these studies generally analyze PEF data stratified by time of day. The epidemiological studies on lung function are summarized in Annex Table F-1.

Mortimer et al. (2002) examined 846 asthmatic children from eight U.S. urban areas in the NCICAS for changes in PEF related to air pollution. The mean 3-h avg SO_2 was 22 ppb across the eight cities during the study period of June through August, 1993. No associations were observed between SO_2 concentrations and morning or evening PEF. Of all the pollutants examined, including PM_{10}, O_3, and NO_2, only O_3 was associated with changes in morning PEF.

In another U.S. study (Neas et al., 1995), 83 children from Uniontown, PA reported twice-daily PEF measurements during the summer of 1990. The mean daytime 12-h avg SO_2 concentration was 14.5 ppb (max 44.9). No associations were observed between daytime 12-h avg SO_2 concentrations and mean deviation in evening PEF, even after concentrations were weighted by the proportion of hours spent outdoors during the prior 12-h. Statistically significant associations were observed for O_3, total sulfate particles, and particle-strong acidity.

A study by van der Zee et al. (1999) observed associations between ambient SO_2 concentrations and daily PEF measurements in 7- to 11-year-old children (n = 142) with chronic respiratory symptoms living in urban areas of the Netherlands. The OR for a > 10% decrement in evening PEF per 10 ppb increase in 24-h avg SO_2 was 1.20 (95% CI: 0.97, 1.47) with same-day exposure. A greater effect was observed at a 2-day lag, OR = 1.40 (95% CI: 1.18, 1.67), and this effect remained robust in a two-pollutant model with PM_{10}, OR = 1.34 (95% CI: 1.08, 1.64).

Multipollutant analyses also were conducted in a study by Chen et al. (1999), which examined the effects of short-term exposure to air pollution on the pulmonary function of 895 children, ages 8 to 13 years, in three communities in Taiwan. The daytime 1-h max SO_2 the day before spirometry ranged from 0 to 72.4 ppb. In a single-pollutant model, 1-h max SO_2

concentration at a 2-day lag was significantly associated with FVC, -50.80 mL (95% CI: -97.06, -4.54), or a 2.6% decline, per 40 ppb 1-h max SO_2. However, in multipollutant models, authors noted that only O_3 remained significantly associated with FVC and FEV_1. Effect estimates for SO_2 in multipollutant models were not provided.

While additional studies have observed associations between ambient SO_2 concentrations and changes in lung function in children (Hoek and Brunekreef, 1993; Roemer et al., 1993; Peters et al., 1996; Segala et al., 1998; Timonen and Pekkanen, 1997), several other studies did not find a significant association between SO_2 and lung function parameters. In addition, in studies that did observe an association, the correlations between SO_2 and other pollutants, particularly PM indices, were high [for example, r = 0.8-0.9 in Peters et al. (1996), making it difficult to separate the contributions of individual pollutants.

In conclusion, while some epidemiological studies observed a positive association between short-term SO_2 exposure and lung function in children, several others, including a large U.S. multicity study, did not observe such an association. The limited evaluation of potential confounding by copollutants also indicated mixed results. Overall, the evidence is insufficient to conclude that short-term exposure to ambient SO_2 has an independent effect on lung function in children.

3.1.4.2.2. Adults

Only a limited number of epidemiological studies have been conducted examining the association between ambient SO_2 concentrations and lung function in adults, as in the case of respiratory symptoms. In a cross-sectional survey, Xu et al. (1991) investigated the effects of indoor and outdoor air pollutants on the respiratory health of 1,140 adults (aged 40 to 69 years) living in residential, industrial, and suburban areas of Beijing, China. The annual mean concentrations of SO_2 in residential, industrial, and suburban areas from 1981 to 1985 were 49 ppb, 22 ppb, and 7 ppb, respectively. Log-transformed SO_2 and TSP were significantly associated with reductions in FEV_1 and FVC. The authors cautioned that since SO_2 and TSP concentrations were strongly correlated, the effect of SO_2 could not be separated.

Van der Zee et al. (2000) observed an association between SO_2 and morning PEF in 50- to 70-year-old adults (n = 138) with chronic respiratory symptoms living in urban areas of the Netherlands. No associations were observed with evening PEF. The OR for a > 20% decrement

in PEF was 1.21 (95% CI: 0.76, 1.92) per 10 ppb increase in 24-h avg SO_2 with same-day exposure and 1.56 (95% CI: 1.02, 2.39) at a 1-day lag. No associations were observed for a > 10% decrement in PEF. The authors hypothesized that while SO_2 level did not have much effect on PEF in most subjects, a small subgroup of individuals experienced fairly large PEF decrements when SO_2 levels were high. No multipollutant analyses were conducted.

Higgins et al. (1995) examined the association between pulmonary function and air pollution in 75 adults with either asthma, COPD, or both. Exposure to SO_2 was associated with increased variation in PEF, but not with mean or minimum PEF. The SO_2 effects on PEF variation were robust to adjustment for O_3 and NO_2. Effects of PM were not considered. Neukirch et al. (1998) also observed associations between lung function and SO_2 concentrations in a study of asthmatic adults in Paris, France; however, significant associations were found for all pollutants examined, including BS, PM_{13}, and NO_2. Other epidemiological studies observed only weak relationships between ambient SO_2 concentrations and lung function in adults (Peters et al., 1996; Taggart et al., 1996).

Evidence from human clinical studies clearly indicates that asthmatic individuals experience moderate or greater decrements in lung function, as well as increased respiratory symptoms, following peak exposure (5-10 min) to SO_2 (Balmes et al., 1987; Gong et al., 1995; Horstman et al., 1986; Linn et al., 1987; 1983) These effects were seen at peak concentrations as low as 0.4-0.6 ppm. However, in a human clinical study by Tunnicliffe et al. (2003) that evaluated the effect of 1-h exposures to 0.2 ppm SO_2 in resting healthy and asthmatic subjects, no significant changes were observed in lung function as measured by FEV_1, FVC, and maximal midexpiratory flow (MMEF).

In summary, the epidemiological studies examining adults do not provide strong evidence for an association between short-term exposure to ambient SO_2 and lung function. While some studies did observe associations between SO_2 exposure and decrements in lung function parameters, the strong correlation between SO_2 and various copollutants in most studies, and the lack of evidence evaluating potential confounding by copollutants, limit interpretation of independent effects of SO_2 on lung function.

3.1.4.3. Airway Inflammation

The animal toxicological studies on airway inflammation are summarized in Annex Table E-1. In one study, guinea pigs were exposed to 1 ppm SO_2 for 3 h/day for 5 days and bronchoalveolar lavage was performed daily (Conner et al., 1985) No change in numbers of total cells or neutrophils was observed. However, in two models of allergic sensitization, SO_2 exposure increased airway inflammation. In one study (Park et al., 2001), guinea pigs were exposed to 0.1 ppm SO_2 for 5 h/day for 5 days and sensitized with 0.1% ovalbumin aerosols for 45 min on days 3-5. One week later, animals were subjected to bronchial challenge with 1.0% ovalbumin and bronchoalveolar lavage and histopathologic examination were performed 24 h later. Results demonstrated increased numbers of eosinophils in lavage fluid, and an infiltration of inflammatory cells, bronchiolar epithelial cell damage and plugging of the airway lumen with mucus and cells in the bronchial tissues of animals treated with both SO_2 and ovalbumin, but not in animals treated with ovalbumin or SO_2 alone.

In a second study, rats which were sensitized and challenged with ovalbumin and exposed to 2 ppm SO_2 for 1 h/day for 7 days had an increased number of inflammatory cells in bronchoalveolar lavage fluid and an enhanced histopathological response compared with those treated with ovalbumin or SO_2 alone (Li et al., 2007a). Similar responses were noted for ICAM-1, a protein involved in regulating inflammation. Further experiments are required to determine whether near ambient SO_2 also enhance inflammatory responses in non-allergic and allergic rats. Taken together, these animal experiments suggest that near-ambient levels of SO_2 may play a role in exacerbating allergic responses.

In a human clinical study, Tunnicliffe et al. (2003) measured levels of exhaled NO (eNO) in asthmatic and healthy adult subjects, before and after 1-h exposure to 0.2 ppm SO_2 under resting conditions. While eNO concentrations were higher in the asthmatic than in healthy subjects, no significant difference was observed between pre- and postexposure in either group.

One epidemiological study by Adamkiewicz et al. (2004) examined eNO as a biological marker for inflammation in 29 older adults (median age 70.7 years) in Steubenville, OH. The mean 24-h avg SO_2 concentration was 12.5 ppb (IQR 11.5). The authors reported that, while significant and robust associations were observed between increased daily levels of fine PM ($PM_{2.5}$) and increased eNO, no associations were observed with any of the other pollutants examined, including SO_2, NO_2, and O_3.

Overall, the very limited human clinical and epidemiological evidence does not indicate that exposure to SO_2 at current ambient concentrations is associated with inflammation in the airway. However, toxicological studies suggest that repeated exposures to SO_2, at concentrations as low as 0.1 ppm in guinea pigs, may exacerbate inflammatory responses in allergic animals.

3.1.4.4. Airway Hyperresponsiveness and Allergy

The toxicological studies describing SO_2-induced effects on airway obstruction, hypersensitivity and/or allergy in guinea pigs and sheep are summarized in Annex Table E-3. In one study, Amdur et al. (1988) exposed guinea pigs for 1 h to 1 ppm SO_2 and measured airway responsiveness to acetylcholine 2 h later. No airway hyperresponsiveness (AHR) was observed. In a second study, Douglas et al., (1994) found no AHR following a histamine challenge 24 h after exposure of rabbits to 5 ppm SO_2 for 2 h. In a third study, exposure of sheep for 4 h to 5 ppm SO_2 failed to result in AHR following carbachol (Gong et al., 2001). In a fourth study, a 5 min exposure to 30 ppm but not to 10 ppm SO_2 resulted in AHR in horses challenged with methacholine (Lewis and Kirchner, 1984). Collectively, these results show that a single exposure to SO_2 at a concentration of 10 ppm or less failed to induce AHR following challenge in 4 different animal models.

However, two other studies demonstrated increased airway responsiveness in guinea pigs exposed repeatedly to SO_2 and allergen. Riedel et al. (1988) studied the effect of SO_2 exposure on local bronchial sensitization to inhaled antigen. Guinea pigs were exposed by inhalation to 0.1, 4.3 and 16.6 ppm SO_2 for 8 h/d for 5 days. During the last 3 days, SO_2 exposure was followed by exposure to nebulized ovalbumin for 45 min. Following bronchial provocation with inhaled ovalbumin (0.1%) one week later, airway obstruction was measured by whole body plethysmography. In addition, specific antibodies against ovalbumin were measured in serum and bronchaolveolar fluids. Results show significantly higher bronchial obstruction in animals exposed to SO_2 (at all concentration levels) with ovalbumin compared with animals exposed only to ovalbumin. In addition, significant increases in anti-ovalbumin IgG antibodies were detected in bronchoalveolar lavage fluid of animals exposed to 0.1, 4.3 and 16.6 ppm SO_2 and in serum from animals exposed to 4.3 and 16.6 ppm SO_2 compared with controls exposed only to ovalbumin. These results demonstrate that repeated exposure to SO_2 can enhance allergic sensitization in the guinea pig at a concentration as low as 0.1 ppm. In a second study, guinea

pigs were exposed to 0.1 ppm SO_2 for 5 h/day for 5 days and sensitized with 0.1% ovalbumin aerosols for 45 min on days 3 to 5 (Park et al., 2001). One week later, animals were subjected to bronchial challenge with 1.0% ovalbumin and lung function was evaluated 24 h later by whole body plethysmography. Results demonstrated a significant increase in enhanced pause (P_{enh}), a measure of airway obstruction, in animals exposed to SO_2 with ovalbumin but not in animals treated with ovalbumin or SO_2 alone. These experiments also indicate that near ambient levels of SO_2 may play a role in exacerbating allergic responses in the guinea pig.

In a human clinical study evaluating SO_2-induced AHR to an inhaled allergen (house dust mite), Devalia et al. (1994) found that neither SO_2 (0.2 ppm) nor NO_2 (0.4 ppm) enhanced sensitization to the allergen in asthmatic individuals. However, following concurrent exposure (6 h) to SO_2 and NO_2 while at rest, subjects did exhibit increased sensitivity to the inhaled allergen. In a subsequent study, Rusznak et al. (1996) confirmed these findings and observed that the combination of SO_2 and NO_2 enhanced sensitization to house dust mite antigen up to 48 hours post-exposure.

A limited number of epidemiological studies also examined the association between SO_2 and AHR. Other studies considered individuals with AHR and atopy as a subgroup potentially susceptible to SO_2-related health effects. These studies are summarized in Annex Table F-1. Søyseth et al. (1995) investigated the effect of short-term exposure to SO_2 and fluoride on the number of capillary blood eosinophils, and the prevalence of AHR in schoolchildren, ages 7 to 13 years, (n = 620) from two regions in Norway, a valley containing an SO_2-emitting aluminum smelter and a similar but nonindustrialized valley. The median 24-h avg SO_2 concentration was 8 ppb (10th–90th percentile: 1, 33) in the exposed area and 1 ppb (10th–90th percentile: 0, 4) in the nonindustrialized valley. The mean number of eosinophils was significantly greater in children living near the aluminum smelter compared to the nonindustrialized area. However, within children in the exposed area, a negative concentration-response relationship was observed between mean eosinophils and previous-day 24-h avg SO_2. The observed association between SO_2 and eosinophils was limited to atopic children. In children living in the exposed area, a statistically significant positive association was observed between prevalence of AHR and previous-day 24-h avg SO_2 concentrations. Similar associations were observed for fluoride. The authors hypothesized that recent exposure to SO_2 may have induced changes in the airway

leading to AHR, in addition to recruitment of eosinophils to the airways in atopic subjects. Exposure to PM was not assessed in this study.

A study by Taggart et al. (1996) examined the effect of summertime air pollution levels in northwestern England on AHR in nonsmoking, asthmatic subjects (n = 38) aged 18 to 80 years who were determined to be methacholine (MCh) reactors. Subjects were tested multiple times, for a total of 109 evaluable challenge tests, with a range of two to four tests per subject. The max 24-h avg SO_2 concentration during the study period was 40 ppb. This study reported that 24-h avg SO_2 levels were marginally associated with a decreased dose of MCh required for a 20% drop in the postsaline FEV_1 ($PD20FEV_1$).

Other epidemiological studies investigated the effect of exposure to SO_2 on children and adults with AHR and atopy. Boezen et al. (1999) examined 7- to 11-year-old children (n = 459) in the Netherlands and tested them for AHR and atopy. These children were a subset of a larger cohort examined in van der Zee et al. (1999). It was hypothesized that children with AHR, as measured using a MCh challenge, and atopy, indicated by raised serum total IgE (> 60 kU/L, the median value), may be susceptible to the effects of air pollution. One of the strengths of this study was the use of AHR and serum IgE concentration to indicate susceptibility; these measurements would be less prone to error than self-reported chronic respiratory symptoms. A total of 121 children were found to have AHR and relatively high serum total IgE; 67 had AHR and relatively low serum total IgE, 104 had no AHR but had a relatively high serum total IgE concentration, and 167 were found to have neither AHR nor relatively high serum total IgE. For the subset of children with relatively low serum total IgE with or without AHR, no associations were observed between SO_2 and any respiratory symptoms. However, for children with relatively high serum total IgE either with or without AHR, the prevalence of lower respiratory tract symptoms increased with increasing SO_2 concentrations. For children with AHR and relatively high serum total IgE, the OR for the prevalence of lower respiratory tract symptoms was 1.70 (95% CI: 1.26, 2.29) with a 5-day moving average for every 10 ppb increase in SO_2. For children without AHR but with relatively high serum total IgE, the OR was 1.82 (95% CI: 1.33, 2.50) with a 5-day moving average.

Boezen et al. (2005) conducted a similar study in 50- to 70-year-old adults (n = 327) in the Netherlands. The subgroup of individuals with elevated serum total IgE, both with (n = 48) and without (n = 112) AHR, were found to be more susceptible to air pollutants when contrasted with

those who did not have elevated serum total IgE (n = 167). Significant associations were observed between previous-day 24-h avg SO_2 concentrations and the prevalence of upper respiratory tract symptoms in those with elevated serum total IgE. Stratified analyses by gender indicated that, among those with AHR and elevated IgE, only males (n = 25) were at a higher risk for respiratory symptoms. The OR for these males was 3.54 (95% CI: 1.79, 7.07) increase in 24-h avg SO_2 for a 5-day moving average, compared with 1.05 (95% CI: 0.59, 1.91) for the females.

In summary, the animal toxicological evidence suggests that repeated exposures to SO_2 at concentrations as low as 0.1 ppm in guinea pigs can exacerbate airway responsiveness following allergic sensitization. Two new human clinical studies have demonstrated an increase in sensitivity to an inhaled allergen in asthmatic subjects following exposures to a combination of 0.2-ppm SO_2 and 0.4-ppm NO_2. These findings are consistent with the very limited epidemiological evidence that suggests that exposure to SO_2 may lead to AHR in atopic individuals.

3.1.4.5. Respiratory Illness-Related Absences

An additional concern has been the potential for SO_2 exposure to enhance susceptibility to, or the severity of illness resulting from respiratory infections, especially in children. School absenteeism is an indicator of morbidity in children caused by acute conditions. Respiratory conditions are the most frequent cause, particularly influenza and the common childhood infectious diseases. Park et al. (2002) examined the association between air pollution and school absenteeism in 1,264 first- to sixth-grade students attending school in Seoul, Korea. The study period extended from March 1996 to December 1999, with a mean 24-h avg SO_2 concentration of 9.19 ppb (SD 4.61). Note that analyses were performed using Poisson Generalized Additive Model (GAM) with default convergence criteria. Same-day SO_2 concentrations were positively associated with illness-related absences (16% excess risk [95% CI: 13, 22] per 10 ppb increase in 24-h avg SO_2), but inversely associated with non-illness–related absences (9% decrease [95% CI: 2, 15]). PM_{10} and O_3 concentrations also were positively associated with illness-related absences. In two-pollutant models containing SO_2 and either PM_{10} or O_3, the SO_2 estimates were robust.

A study by Pönka (1990) observed results that were consistent with those from the Park et al. (2002) study. Pönka found that absenteeism due to febrile illnesses among children in day

care centers and schools and in adults was significantly higher on days of higher SO_2 concentrations (> 8.1 ppb weekly mean of 1-h avg), compared to days of lower SO_2 concentrations. In addition, on days of higher SO_2 concentrations, the mean weekly number of cases of upper respiratory tract infections and tonsillitis reported from health centers increased. Temperature, but not NO_2, was also found to be associated with febrile illnesses and respiratory tract infections. From these epidemiological studies, it is unknown whether SO_2 increases susceptibility to infection or whether its presence exacerbates preexisting morbidity following infection.

Pino et al. (2004) examined the association between air pollution and respiratory illnesses in a cohort of 504 infants recruited at 4 months of age from primary health care units in southeastern Santiago, Chile. The infants were followed through the first year of life. The mean 24-h avg SO_2 concentration was 11.6 ppb (5th–95th percentile: 3.0, 29.0). The most frequent diagnosis during follow-up was wheezing bronchitis. No associations were observed between current-day or previous-day SO_2 and wheezing bronchitis, but with a 7-day lag, a 21% (95% CI: 8, 39) excess risk in wheezing bronchitis was observed per 10 ppb increase in 24-h avg SO_2. However, it should be noted that stronger associations were observed with $PM_{2.5}$, which was well-correlated with SO_2 (r = 0.73). These epidemiologic studies are summarized in Annex Table F-1.

To summarize, very few studies have examined the association between ambient SO_2 concentrations and absences from school or work as a result of respiratory illnesses. The limited evidence suggests a possible association between exposure to SO_2 concentrations and increased respiratory illnesses, particularly among young children; however, this association was also seen with PM, which was correlated with SO_2.

3.1.4.6. Emergency Department Visits and Hospitalizations for Respiratory Diseases

Total respiratory causes for ED visits and hospital admissions typically include asthma, bronchitis and emphysema (collectively referred to as COPD), upper and lower respiratory tract infections, pneumonia, and other minor categories. Temporal associations between ED visits or hospital admissions for respiratory diseases and the ambient concentrations of SO_2 have been the subject of more than fifty peer-reviewed research publications since 1994. In addition to considerable statistical and analytical refinements, recent studies have examined responses of

morbidity in different age groups, the effect of seasons on ED and hospital usage, and multipollutant models to characterize the effects of copollutant mixtures. The epidemiological studies of ED visits and hospital admissions for respiratory causes are summarized in Annex Table F-2.

3.1.4.6.1. All Respiratory Diseases

There are relatively few studies of ED visits for all respiratory causes in contrast to the quantity of studies that examine hospital admissions for all respiratory causes. Collectively, studies of ED visits and hospitalizations provide suggestive evidence of an association between ambient SO_2 levels and ED visits and hospitalizations for all respiratory causes. When analyses were restricted by age, the results among children (0-14 years) and older adults (65+ years) were mainly positive, though not all statisticallly significant. The studies that examined the association of these outcomes and SO_2 levels among adults (15-64 years) reported a mix of positive and negative results. When all age groups were combined, the results of ED and hospitalization studies were mainly positive; however, the excess risk estimates were generally smaller compared to the children and older adults groups. It is possible that the effects observed in the combined age groups were driven by increases in the very young or older adult subpopulations. The results from the hospitalization and ED studies, separated by analyses among all ages and age-specific analyses, are shown in Figure 3-6. Overall, the effect estimates in this figure range from a -5% to 20% excess risk in ED visits or hospital admissions for respiratory causes per 10 ppb increase in 24-h avg SO_2, with the large majority of studies suggesting an increase in risk.

Wilson et al. (2005) examined ED visits for all respiratory causes in Portland, ME from 1996–2000 and in Manchester, NH from 1998–2000. The mean 1-h max SO_2 concentration in Portland was 11.1 ppb (SD 9.1), and was higher during the winter months (mean 17.1 ppb (SD 12.0]) and lower in the summer (mean 9.1 ppb [SD 8.0]). In Manchester, the mean 1-h max SO_2 concentration was 16.5 ppb (SD 14.7 ppb), and was higher in the winter months (mean 25.7 ppb [SD 15.8]) as opposed to the summer months (mean 10.6 ppb [SD 15.1]). Though the authors reported the 1-h max SO_2 concentrations, they used the 24-h avg SO_2 concentrations in their analyses. When all ages where included in analyses, Wilson et al. found positive associations between ED visits and SO_2, with an 8% (95% CI: 3.0, 11) and 11% (95% CI: 0.0, 20.0) excess

risk per 10 ppb increase in 24-h avg SO_2 at a 0-d lag in Portland, ME and Manchester, NH, respectively.

Peel et al. (2005) investigated ED visits for all respiratory causes in Atlanta, GA from 1993–2000. This study included 484,830 ED visits. The mean 1-h max SO_2 concentration was 16.5 ppb (SD 17.1). The researchers found a weak positive relationship between ED visits and SO_2, though the increased risk was not statistically significant (1.6% [95% CI: −0.6, 3.8] excess risk per 40 ppb increase in 1-h max SO_2). Tolbert et al. (2007) recently reanalyzed these data with four additional years of data and found similar results. An analysis by Dab et al. (1996) examined the association between SO_2 and hospital admissions for all respiratory causes in Paris, France, using both the 24-h avg and 1-h max. It should be noted that these researchers observed similar effect estimates for both exposure metrics; however, only the estimate using 24-h avg was statistically significant (1.1% [95% CI: 0.1, 2.0] excess risk per 10 ppb increase in 24-h avg SO_2 versus 1.9% [95% CI: −1.3, 5.0]) per 40 ppb increase in 1-h max SO_2).

When analyses were stratified to include only children (0-14 years), evidence of a modest association between SO_2 and ED visits or hospitalizations for all respiratory causes in children was reported in several Australian (Barnett et al., 2005; Petroeschevsky et al., 2001) and European (Anderson et al., 2001; Atkinson et al., 1999a; 1999b) studies. Excess risks ranging from 3% to 22% per 10 ppb increase in 24-h avg SO_2 were reported by these studies. In a multicity study spanning Australia and New Zealand, Barnett et al. (2005) compared hospital admission data collected from 1998–2001 with ambient SO_2 concentrations, where the mean 24-h avg SO_2 concentration ranged from 0.9 to 4.8 ppb. The authors found a 5% (95% CI: 1, 9) excess risk per 10 ppb increment in 24-h avg SO_2 among children (1-4 years) in these cities. However, some additional U.S. (Wilson et al., 2005), European (Fusco et al., 2001; Ponce de Leon et al., 1996), and Latin American (Braga et al., 1999; 2001) studies did not find statistically significant associations between ambient SO_2 concentrations and hospitalizations for all respiratory causes among children.

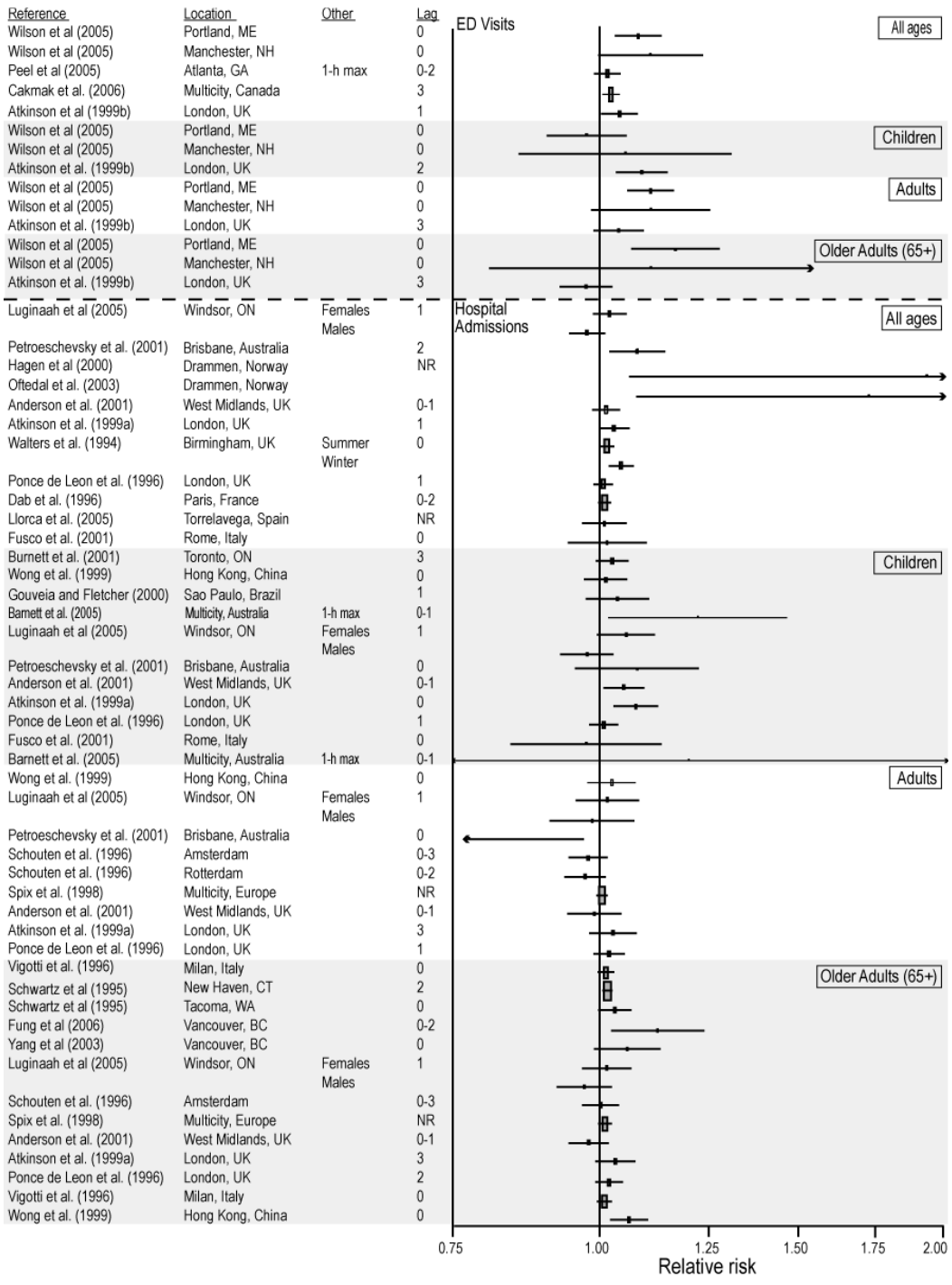

Figure 3-6. Relative risks (95% CI) of SO_2-associated emergency department visits and hospitalizations for all respiratory causes among all ages and separated by age group. Risk estimates are standardized per 10 ppb increase in 24-h avg SO_2 concentrations or 40 ppb increase in 1-h max SO_2. The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.

Wilson et al. (2005) found a positive association between ED visits and SO_2, with a 16% (95% CI: 8.0, 25.0) excess risk per 10 ppb increase in 24-h avg SO_2 at a 0-d lag, and no association in Manchester, NH when only older adults (65+ years) were considered. In another two-city study, Schwartz (1995) compared 13,740 hospital admission in New Haven, CT and Tacoma, WA from 1988–1990 with ambient SO_2 concentrations. The mean 24-h avg SO_2 concentration was 29.8 ppb (90^{th} percentile: 159) in New Haven and 16.8 ppb (90^{th} percentile: 74) in Tacoma. Schwartz found positive associations between hospitalizations and SO_2, with a 2% (95% CI: 1.0, 3.0) excess risk at a 2-d lag in New Haven and 3% (95% CI: 1.0, 6.0) excess risk at a 0-d lag in Tacoma per 10 ppb increase in 24-h avg SO_2. In two-pollutant models, the SO_2 effect estimate from New Haven, but not Tacoma, was found to be robust to adjustment for PM_{10}. Here, the term robust is used to indicate that there was little change in the magnitude of the central estimate, though statistical significance may have been lost. In Vancouver, BC, both Fung et al. (2006a) and Yang et al. (2003) also found positive associations between hospitalizations and SO_2. In a multipollutant model including coefficient of haze (CoH), NO_2, O_3, and CO, the SO_2 effect estimate diminished slightly (Jaffe et al., 2003).

Additional evidence of a positive association between ED visits or hospitalizations for all respiratory causes among older adults and SO_2 comes from several European (Spix et al., 1998; Sunyer et al., 2003; Vigotti et al., 1996) and Australian (Petroeschevsky et al., 2001) studies. Excess risks ranging from 1% to 12% per 10 ppb increase in 24-h avg SO_2 were reported by these studies. Petroeschevsky et al. (2001) examined 33,710 hospital admissions in Brisbane, Australia from 1987–1994. The mean 24-h avg SO_2 concentration was 4.1 ppb, and was highest in the winter months (4.8 ppb) and lowest in the spring (3.7 ppb). Petroeschevsky et al. found a 12% (95% CI: 2.0, 23.0) excess risk per 10 ppb increase in 24-h SO_2 at 0-d lag. Additional European studies did not find statistically significant associations between ambient SO_2 concentrations and hospitalizations for all respiratory causes among older adults (Anderson et al., 2001; Atkinson et al., 1999b; Ponce de Leon et al., 1996; Schouten et al., 1996).

In summary, many studies show a small, positive, though not statistically significant association between ambient SO_2 concentrations and ED visits and hospitalizations, particularly among children and older adults (65+ years). The positive evidence from these studies is supported by the results of panel, human clinical, and limited toxicological studies that also found a positive relationship between SO_2 levels and adverse respiratory outcomes.

3.1.4.6.2. Asthma

Studies of ED visits and hospitalizations provide suggestive evidence of an association between ambient SO_2 levels and ED visits and hospitalizations for asthma. The results from the hospitalization and ED studies, separated by analyses among all ages and age-specific analyses, are shown in Figure 3-7. Overall, central effect estimates in the figure range from a -10% to 40% excess risk in ED visits and hospitalizations for asthma per 10 ppb increase in 24-h avg SO_2. Most of the effect estimates are positive (suggesting an association with SO_2 and ED visits and hospitalizations for asthma), though few are statistically significant at the 95% confidence level. When all ages were included in the analyses, Wilson et al. (2005) found a positive association between ED visits and SO_2, with a 10% (95% CI: 2.0, 20.0) excess risk per 10 ppb increase in 24-h avg SO_2 at a 0-d lag in Portland, ME and a positive, though not statistically significant association in Manchester, NH. Ito et al. (2003) found a 36% (95% CI: 1.23, 1.51) excess risk in asthma ED visits per 10 ppb increase in 24-h avg SO_2, though this association was diminished once NO_2 was included in the model. A study conducted in (NY Dept of Health, 2006) found a 11% (95% CI: 6, 17) excess risk in asthma hospital admissions per 10 ppb increase in 24-h avg SO_2 for Bronx residents, but a null association for the residents of Manhattan. A study conducted in Atlanta (Peel et al., 2005) found a null relationship between asthma ED visits and 1-h max SO_2.

A study by Jaffe et al. (2003) examined the association between SO_2 and ED visits for asthma in three cities in Ohio – Cincinnati, Cleveland, and Columbus – in asthmatics aged 5 to 34 years. The mean 24-h avg SO_2 concentrations were 14 ppb (range: 1–50) in Cincinnati, 15 ppb (range: 1–64) in Cleveland, and 4 ppb (range: 0–22) in Columbus. A positive association was observed in the multicity analysis, with a 6.1% (95% CI: 0.5, 11.5) excess risk in asthma visits observed per 10 ppb increase in 24-h avg SO_2. In the city-stratified analyses, significant associations were only observed for Cincinnati (17.0% [95% CI: 4.6, 30.8]).

When analyses were stratified to include children (0-14 years) only, Wilson et al. (2005) found positive, but not statistically significant associations between ED visits and SO_2 in Portland, ME or Manchester, NH. Similarly, Lin et al. (2005) observed a weak positive association between hospitalizations for asthma and SO_2 among girls, and a null association for boys (Toronto, ON; mean 24-h avg SO_2 of 5.36 ppb [SD 5.90]). Stronger evidence comes from a study of childhood asthma hospitalizations conducted in Bronx County, New York (Lin et al.,

2003b). In this study, the authors conducted a case-control study of children aged 0-14 years and examined the association of daily ambient SO_2 concentrations (categorized into quartiles of both average and max levels) and cases admitted to the hospital for asthma or controls who were admitted for reasons other than asthma. The mean 24-h avg SO_2 was below 17 ppb for both cases and controls across all lag days examined. The authors found that cases were exposed to higher 24-h avg SO_2 than controls. When the highest exposure quartile was compared with the lowest, the ORs were strongest when a 3-day lag was employed (OR 2.16 [95% CI: 1.77, 2.65] for 24-h avg SO_2; OR 1.86 [95% CI: 1.52, 2.27] for 1-h max SO_2). The results were positive and statistically significant for all lag days examined. These results suggest a consistent positive association between SO_2 exposure and hospitalizations for childhood asthma.

Additional evidence of a positive association between ED visits or hospitalizations for asthma and SO_2 comes from several European (Anderson et al., 1998; Atkinson et al., 1999a; Hajat et al., 1999; Sunyer et al., 1997; 2003; Thompson et al., 2001) and Asian (Lee et al., 2002) studies. Excess risks ranging from 2% to 10% per 10 ppb increase in 24-h avg SO_2 were reported by these studies. Several of these studies observed that the SO_2 effect estimate was robust to adjustment for BS and NO_2 (Anderson et al., 1998; Sunyer et al., 1997), but one study observed that the SO_2 effect diminished considerably with adjustment for PM_{10} and benzene (Thompson et al., 2001). Atkinson et al. (1999b) compared 165,032 hospital admissions in London from 1992–1994 with ambient SO_2 levels (mean 24-h avg of 7.2 ppb [SD 4.7]). They found a 10% (95% CI: 4.0, 16.0) excess risk per 10 ppb increase in 24-h avg SO_2 at 1-d lag. Additional European (Fusco et al., 2001), Australian (Barnett et al., 2005; Petroeschevsky et al., 2001), Asian (Ko et al., 2007; Lee et al., 2006) and Latin American (Gouveia and Fletcher, 2000) studies did not find statistically significant associations between ambient SO_2 concentrations and hospitalizations for all respiratory causes among children.

In summary, small, positive associations were observed between ambient SO_2 concentrations and ED visits and asthma hospitalizations. Evidence from these studies is further supported by the results of panel and human clinical studies that have also found SO_2-related respiratory effects in asthmatics.

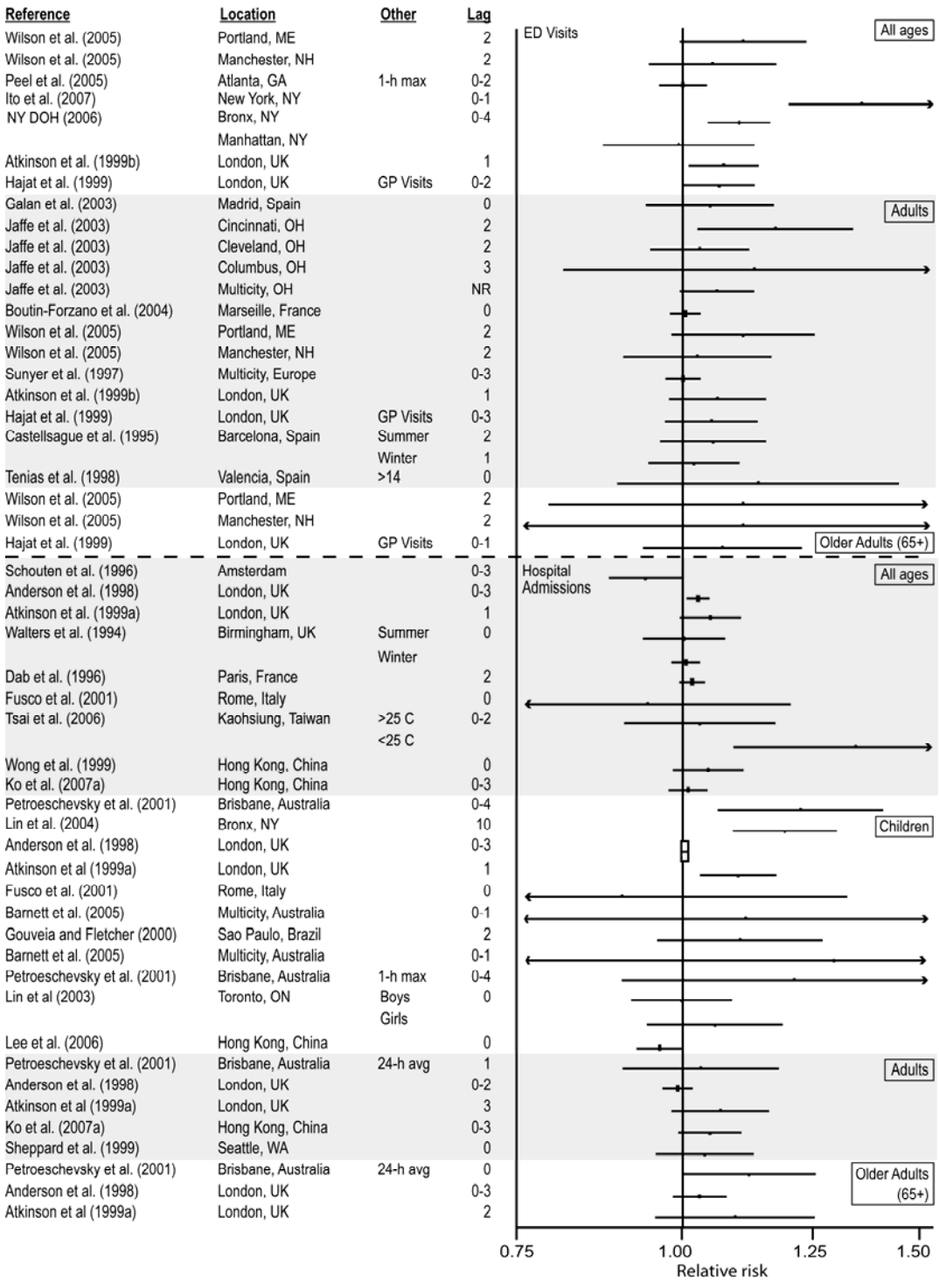

Figure 3-7. Relative risks (95% CI) of SO_2-associated emergency department visits and hospitalizations for asthma among all ages and age-specific groups. Risk estimates are standardized per 10 ppb increase in 24-h avg SO_2 concentrations or 40 ppb increase in 1-h max SO_2. The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.

3.1.4.6.3. Chronic Obstructive Pulmonary Disease

There are relatively few studies that have examined the association of ED visits and hospitalizations for COPD and ambient SO_2 levels, and very little evidence that an association exists. A recent study (Ko et al., 2007) found a significant association between hospital admissions for COPD (not including asthma) in Hong Kong (1.8% [95% CI: 0.3, 3.8]) excess risk per 10 ppb increase in 24-h avg SO_2 concentration). Three additional studies reported positive and statistically significant results for COPD and SO_2; all three studies included asthma in their diagnostic definition of COPD (Anderson et al., 2001; Moolgavkar, 2003; Sunyer et al., 2003). Anderson et al. (2001) reported a 12% (95% CI: 5.0, 20.0) excess risk per 10 ppb increase in 24-h avg SO_2 among children, while Moolgavkar (2003) and Sunyer et al. (2003) found 5% and 2% excess risks per 10 ppb increase in 24-h avg SO_2 among older adults populations, respectively. Other studies examining COPD did not find statistically significant results (Atkinson et al., 1999b; Burnett et al., 1999; Michaud et al., 2004).

Overall, this limited and inconsistent evidence does not support a relationship between ED visits and hospitalizations for COPD and ambient SO_2 levels.

3.1.4.6.4. Respiratory Diseases Other than Asthma or COPD

Studies of ED visits or hospital admissions for other respiratory diseases looked at several other specific outcomes. There are limited studies with mixed results for upper respiratory tract infections (Burnett et al., 1999; Hajat et al., 2002; Lin et al., 2005; Peel et al., 2005), pneumonia (Barnett et al., 2005; Moolgavkar et al., 1997; Peel et al., 2005), bronchitis (Barnett et al., 2005; Michaud et al., 2004), and allergic rhinitis (Hajat et al., 1999; Villeneuve et al., 2006). The limited evidence is suggestive of an association between SO_2 levels and ED visits for lower respiratory tract diseases (Atkinson et al., 1999b; Farhat et al., 2005; Hajat et al., 1999; Lin et al., 1999; Martins et al., 2002). All of the studies that characterized this relationship found a positive and statistically significant excess risk associated with increases in SO_2. Excess risks ranging from 3% to 33% per 10 ppb increase in 24-h avg SO_2 were reported by these studies.

In summary, few studies provide results with mixed respiratory health outcomes other than asthma and COPD. This makes it difficult to draw conclusions about the effects of SO_2 on these diseases. Limited evidence does exist to support a suggestive association between ambient SO_2 levels and ED visits for lower respiratory tract diseases.

3.1.4.6.5. Summary of Evidence on Emergency Department Visits and Hospitalizations for Respiratory Diseases

Small, positive associations exist between ambient SO_2 concentrations and ED visits and hospitalizations for all respiratory causes, particularly among children and older adults (65+ years), and for asthma, though not always statistically significant. The SO_2-related changes in ED visits or hospital admissions for respiratory causes ranged from -5% to 20% excess risk, with the large majority of studies suggesting an increase in risk. No association was observed between SO_2 levels and ED visits and hospitalizations for COPD. Given the limited number of studies with mixed results, it is difficult to draw conclusions about the effect of SO_2 on other respiratory diseases, though studies of lower respiratory tract diseases are somewhat suggestive of an association.

Multipollutant regression analyses indicate that SO_2 risk estimates, in general, are not sensitive to the inclusion of copollutants, including O_3 (Anderson et al., 1998; Hajat et al., 1999; Yang et al., 2003; 2005), PM (Hagen et al., 2000; Lin et al., 2003; 2005; Schwartz, 1995) CO (Farhat et al., 2005) and NO_2 (Anderson et al., 1998; Lin et al., 2004; Sunyer et al., 1997). Figure 3-8 presents SO_2 excess risk estimates with and without adjustment for various copollutants. PM and NO_2 are the main foci, since these pollutants have been found to be highly-correlated with SO_2 in epidemiological studies and have known respiratory health effects. Although the studies showed that copollutant adjustment had varying degrees of influence on the SO_2 effect estimates, the effect of SO_2 on respiratory health outcomes appears to be generally robust and independent of the effects of ambient particles or other gaseous copollutants.

The results of several studies (Anderson et al., 1998; Hajat et al., 1999; Schouten et al., 1996; Spix et al., 1998; Wong et al., 1999) have demonstrated a greater increase in ED visits and hospitalizations for respiratory illnesses during the summer months, despite the fact that the average concentrations for SO_2 in some of areas studied were greatest in winter. In contrast, some studies found the associations between ED visits and hospital admissions and respiratory disease with similar increases in SO_2 to be greater in winter than summer (Vigotti et al., 1996; Walters et al., 1994). Other studies were unable to discern a seasonal difference in ED visits and hospitalizations for respiratory causes (Castellsague et al., 1995; Tenias et al., 1998; Wong et al., 2002). These effects were not consistent across age groups. Warmer months were more likely to show evidence of an association with adverse respiratory outcomes in children, while older

adults appeared more likely to be affected during the cooler months. These seasonal associations remain somewhat uncertain and require additional investigation.

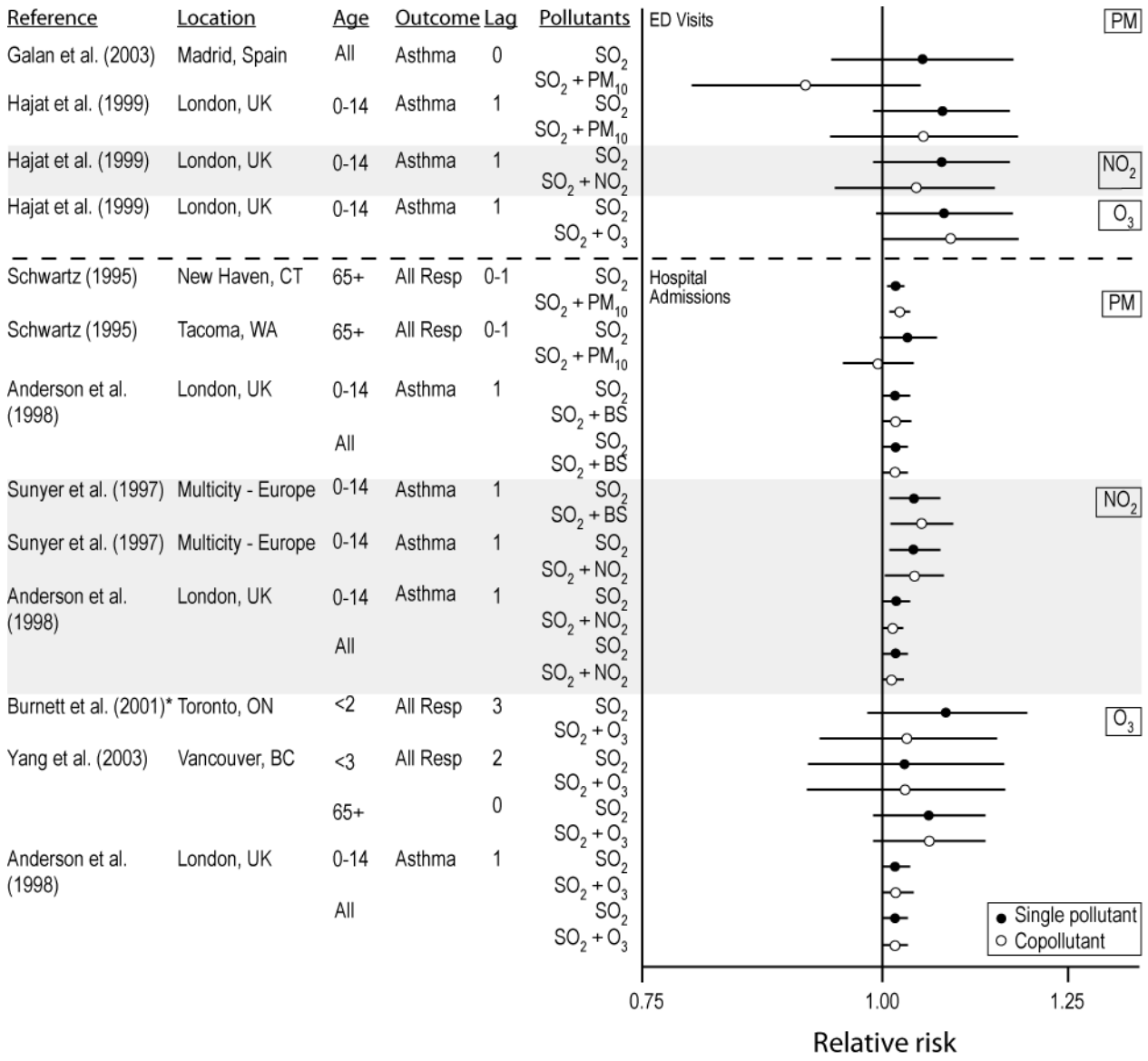

Figure 3-8. Relative risks (95% CI) of SO_2-associated emergency department visits and hospitalizations for all respiratory causes and asthma, with and without copollutant adjustment. Risk estimates are standardized per 10 ppb increase in 24-h avg SO_2 concentrations or 40 ppb increase in 1-h max SO_2. In Burnett et al. (2001), analyses were performed using default convergence criteria for Poisson GAM with a nonparametric LOESS prefilter applied to air pollution and hospitalization data.

In conclusion, a large number of epidemiologic studies provide evidence of an association between ambient SO_2 concentrations and ED visits and hospitalizations for all respiratory causes, in particular among children and older adults (65+ years), and for asthma. The findings are generally robust when additional copollutants are included in the model. These associations are supported by panel studies that observed SO_2-related increases in asthma and other respiratory symptoms in children, and human clinical and animal toxicological studies that found a positive relationship between SO_2 exposure and various respiratory outcomes.

3.1.4.7. Summary of Evidence on the Effect of Short-Term (≥ 1 h) Exposure on Respiratory Health

Numerous epidemiological studies have observed associations between short-term (≥ 1-h, generally 24-h avg) exposure to SO_2 and respiratory health effects, ranging from respiratory symptoms to ED visits and hospital admissions for respiratory causes. The associations between ambient SO_2 concentrations and several respiratory outcomes were generally consistent, with the large majority of studies showing positive associations, and multicity studies, as well as several single-city studies, indicating statistically significant findings. The respiratory effects related to short-term exposure to SO_2 found in animal toxicological studies, and to a more limited extent the human clinical studies, provide coherence and biological plausibility for the observed epidemiological associations. The causal effects of peak exposure to SO_2 on respiratory health found in the human clinical studies (see Section 3.1.3.5) provide further evidence of biological plausibility for the effects associated with short-term exposure to SO_2.

Two recent multicity studies (Mortimer et al., 2002; Schildcrout et al., 2006) and several other studies (Delfino et al., 2003; Neas et al., 1995; van der Zee et al., 1999) have found an association between short-term ambient SO_2 concentrations and respiratory symptoms in children. In the limited number of studies that assessed potential confounding by copollutants using multipollutant models, the SO_2 effect on respiratory symptoms was generally found to be robust to adjustment for copollutants. These findings provide supportive evidence for an association between short-term exposure to ambient SO_2 exposure and respiratory symptoms in children, particularly those with asthma. Several recent studies (Desqueyroux et al., 2002a; 2002b; van der Zee et al., 2000) found no association between ambient SO_2 levels and respiratory symptoms in adults, though there was limited epidemiological evidence which

suggested that atopic adults as well as children may be at increased risk for SO_2-induced respiratory symptoms (Boezen et al., 1999; 2005).

Animal toxicological studies in guinea pigs showed changes in lung function immediately following 1 ppm SO_2 exposure (Amdur et al., 1983). Guinea pigs, as a species, are typically more sensitive to air pollution than other laboratory animals and, thus, may provide a better model for characterizing the effects of air pollutants on lung function. Epidemiological studies do not provide strong evidence of an association between short-term ambient SO_2 exposure and lung function in either children (Mortimer et al., 2002; Roemer et al., 1998) or adults (e.g., Peters et al., 1996; Taggart et al., 1996). Several other studies reported positive results; however, the generally mixed findings, as well as the relative lack of evidence available to evaluate potential confounding by copollutants, limits the causal interpretation of ambient SO_2 on lung function.

Only one epidemiological study (Adamkiewicz et al., 2004) evaluated inflammation, as indexed by eNO, and found no association with SO_2 exposure. Animal toxicological studies found that repeated exposure to near ambient levels of SO_2 leads to increased airway inflammation in two models involving animals which were sensitized to an antigen (Park et al., 2001; Li et al., 2007). Studies of other ambient pollutants indicate that influx of macrophages and other inflammatory cells, with the related release of inflammatory cytokines, is a common response to — and may further contribute to — injury.

Effects of short-term exposure to SO_2 on AHR have been observed. In two animal toxicological studies, repeated exposure to 0.1 ppm SO_2 led to AHR in guinea pigs sensitized to an antigen (Riedel et al., 1988; Park et al., 2001). Human clinical studies by Devalia et al. (1994) and Rusznak et al. (1996) demonstrated increased sensitivity to an inhaled allergen in asthmatic subjects following exposure to a combination of SO_2 (0.2 ppm) and NO_2 (0.4 ppm). This effect was not observed following exposure to either SO_2 or NO_2 alone. These findings of increased pulmonary resistance are in concordance with the limited epidemiological findings of SO_2-induced AHR (Taggart et al., 1996).

Epidemiological studies provide suggestive evidence for an association between ambient SO_2 levels and ED visits and hospitalizations for all respiratory diseases in two susceptible populations: children (Dab et al., 1996; Petroeschevsky et al., 2001; Walters et al., 1994) and older adults (65+ years) (Fung et al., 2006; Schwartz, 1995; Spix et al., 1998; Wong et al., 1999). Evidence for an association between ambient SO_2 levels and these outcomes in adults was less

consistent. A modest association between ambient SO_2 and ED visits and hospitalizations for asthma was also suggested. SO_2 effect estimates were generally robust to the inclusion of copollutants, including PM, O_3, CO and NO_2, indicating that the observed effects of SO_2 on respiratory endpoints is independent of the effects of other ambient air pollutants.

3.1.5. Mixtures and Interactive Effects

3.1.5.1. Evidence from Human Clinical Studies

The interaction of SO_2 with other common air pollutants or the sequential exposure of SO_2 after prior exposure to another pollutant can potentially modify SO_2-induced respiratory effects. However, only a few human clinical studies have looked at the interactive effects of coexisting ambient air pollutants. In a human clinical study designed to simulate an ambient "acid summer haze," Linn et al. (1997) exposed healthy and asthmatic children (9–12 years of age) for 4 h with intermittent exercise to a mixture of SO_2 (0.1 ppm), H_2SO_4 (100 μg/m^3), and O_3 (0.1 ppm). Compared with exposure to filtered air, exposure to the air pollution mixture did not result in significant changes in lung function or respiratory symptoms. These findings are in agreement with a series of similar studies conducted by Kleinman et al. (1981; 1984; 1985).

In a human clinical study of asthmatic adolescents (12- to 16-years-old), Koenig et al. (1983) evaluated changes in FEV_1 following a 10-min exposure during moderate exercise to 1-mg/m^3 NaCl alone and in combination with 0.5 and 1.0 ppm SO_2. Significant decreases of 15 and 23% were reported in FEV_1 following exposure to 1 mg/m^3 NaCl in combination with 0.5- and 1.0-ppm SO_2, respectively. No significant changes in FEV_1 were observed between pre- and post-exposure to 1-mg/m^3 NaCl without SO_2. The effect observed in this study may be the result of the presence of hygroscopic particles that can carry SO_2 deeper into the lung.

Koenig et al. (1990) also examined the effect of 15-min exposures to 0.1 ppm SO_2 in adolescent asthmatics engaged in moderate levels of exercise. Immediately preceding this exposure, subjects were exposed for 45 min to 0.12 ppm O_3 during intermittent moderate exercise. Subjects also underwent two additional exposure sequences with the same exercise regimen: 15-min exposure to 0.1 ppm SO_2 following a 45-min exposure to clean air, and 15-min exposure to 0.12 ppm O_3 following a 45-min exposure to 0.12 ppm O_3. The authors found that the change in FEV_1 compared to baseline was significantly different following the O_3-SO_2

exposure (8% decrease) when compared to the change following the air-SO_2 or O_3-O_3 exposures (decreases of 3 and 2%, respectively). In a more recent study, Trenga et al. (2001) reported that among adult asthmatics, exposure to O_3 (0.12 ppm for 45 min) resulted in a slight increase in bronchial responsiveness to SO_2 at a concentration of 0.25 ppm (6.5% decrease in FEV_1 with pre-exposure to O_3, compared with a 3.4% decrease in FEV_1 with pre-exposure to filtered air). Hazucha and Bates (1975) demonstrated a synergistic effect of concurrent exposure to SO_2 (0.37 ppm) and O_3 (0.37 ppm) on lung function in healthy asthmatics; however, no such effect was observed in a similar study conducted by Bedi et al. (1979).

Jörres and Magnussen (1990) and Rubinstein et al. (1990) investigated the effects of a prior NO_2 exposure on SO_2-induced bronchoconstriction in asthmatic adults. While Jörres and Magnussen suggested that prior exposure to NO_2 increased the responsiveness to SO_2, Rubinstein et al. did not find that NO_2 exacerbated the effects of SO_2. Linn et al. (1980) reported no difference in lung function or respiratory symptoms among a group of exercising asthmatics exposed to both clean air and a combination of NO_2 (0.5 ppm) and SO_2 (0.3 ppm).

In summary, although findings from some human clinical studies suggest that respiratory effects of exposure to SO_2 may be enhanced when preceded by, or occurring concomitant with exposure to other air pollutants, this evidence is quite limited and inconsistent.

3.1.5.2. Evidence from Animal Toxicological Studies

As discussed earlier, SO_2 is a component of complex air pollution mixtures that vary geographically and temporally (e.g., by hour, week, and season). Depending on atmospheric conditions, SO_2 can be transformed to secondary sulfate particles and acid aerosols (H_2SO_4) and can adsorb onto particulate matter. Since SO_2, H_2SO_4 and PM share a common source—fossil fuels—health effects of fossil-fuel derived air pollution mixtures may be determined by interactions among individual components. Although epidemiological studies provide information on real-world exposure, it is difficult to evaluate causative factors and quantitative relationships from such studies. Animal studies are therefore useful in evaluating health effects of mixtures. The studies discussed below demonstrate important interactions between SO_2 and other air pollution components.

An informative study of complex air pollutants was conducted in dogs and addressed in the 1982 AQCD (EPA, 1982). In dogs that were exposed to SO_2 and H_2SO_4, with or without

irradiated or non-irradiated auto exhaust concentrations relevant to urban exposures, functional lung changes were observed at 61 months of exposure and at 2 years after exposures ended. Morphological and biochemical changes were observed at 2.5–3 years after exposure.

Since then, studies have demonstrated respiratory responses following inhalation of SO_2 which had been layered onto metal or carbon particles. The resulting particles were submicron in size; they would be expected to deposit in the lower respiratory tract. As discussed in Section 3.2.2, chemosensitive receptors are present at all levels of the respiratory tract and are known to activate reflexes involving the respiratory and cardiovascular systems. It has been postulated that bronchial C-fiber receptors are more sensitive to chemical irritants than pulmonary C-fibers receptors, but that more intense cardiovascular responses are triggered by the pulmonary receptors (Coleridge and Coleridge, 1994; Widdicombe and Lee, 2001). Some of the work involving SO_2 layered onto particles has been reviewed in the PM AQCD (EPA, 1996; 2004). Important studies are described briefly to show biological plausibility for the health effects of SO_2 which rarely, if at all, exists in nature in the absence of PM. This work is summarized in Annex Tables F-15 through 5-1.

3.1.5.2.1. Effects of SO_2 Layered on Metallic Particles

Studies examining interactions between SO_2 and metallic or carbonaceous particles are summarized in Annex Table E-14. Metal oxides may be released into the atmosphere with SO_2 during combustion of fossil fuels or by smelting operations (Lam et al., 1982). The 1982 AQCD noted that sorption of SO_2 onto liquid or solid particles, which may act as carriers, tended to increase its potency, but the mechanism for the effect was not known. The studies discussed below strongly suggest that SO_2 adsorbed to particles penetrates to more distal regions of the lung, compared with gaseous SO_2. In addition, SO_2 which is adsorbed to particles can transform to sulfite, sulfate, H_2SO_4 and sulfur trioxide.

In an early study, guinea pigs were exposed to submicron zinc oxide aerosols alone or to 0.8-6 mg/m^3 zinc oxide in combination with 1–2 ppm SO_2 for 3 h (Lam et al., 1982). The higher concentrations of zinc oxide served to carry more sulfur in the aerosol (Amdur et al., 1988). Animal exposure to zinc oxide alone resulted in a decrease in functional residual capacity; animal exposure to the combination of zinc oxide and SO_2 resulted in dose-dependent decreases in total lung capacity, vital capacity, functional residual capacity, residual volume, diffusion

capacity for carbon monoxide and alveolar volume (Amdur et al., 1988; Lam et al., 1982). Another study exposed guinea pigs to ~1 ppm SO_2 and 1–2 mg/m^3 zinc oxide for 1 h (Amdur et al., 1983). Results demonstrated the formation of sulfite, sulfate, and sulfur trioxide under conditions of high humidity and temperature, and greater than additive decrements in pulmonary function, compared with exposures to SO_2 or zinc oxide alone or with a mixture of SO_2 and zinc oxide where no transformation had taken place. Additional studies in guinea pigs involved 1 h exposures to ~1 ppm SO_2 and 1-3 mg/m^3 copper oxide (Chen et al., 1991) and ~1ppm SO_2 and 1-3 mg/m^3 zinc oxide (Chen et al., 1992). In the copper oxide-SO_2 study, components were mixed at either 37°C or 1,411°C prior to exposure (Chen et al., 1991). Results demonstrated increased pulmonary resistance when the compounds were mixed at low temperature, leading to the formation of sulfite; when components were mixed at high temperature, leading to the formation of sulfate, no increase was found. This suggested that sulfite has greater biological effect than sulfate. The zinc oxide-SO_2 study found a synergistic interaction between zinc oxide and SO_2. Co-exposure, but not exposure to either component alone, led to airway hyperresponsiveness following an acetylcholine challenge (Chen et al., 1991). A further study by these same investigators determined that H_2SO_4 was the predominant species of sulfur associated with the zinc oxide particles mixed with SO_2 under high temperature and humidity conditions (Amdur et al., 1988). H_2SO_4 has a valence of S(VI), unlike that of SO_2 and sulfite, which have a valence of S(IV). This study also correlated increased bronchial sensitivity to acetylcholine with the formation of H_2SO_4 at 21 and 30 µg/m^3 in animals exposed for 1 h to this mixture. The authors concluded that the response might have been enhanced by H_2SO_4 being carried on the metal particles. Furthermore, the H_2SO_4-coated zinc oxide particle was five- to tenfold more potent in eliciting a response than H_2SO_4 alone.

Several subacute studies were also conducted. One involved the exposure of guinea pigs for 3 h/day for 6 consecutive days to 6 mg/m^3 submicron zinc oxide particles generated in a humid furnace mixed with 1 ppm SO_2 or to SO_2 alone (Conner et al., 1985). Exposure to the zinc oxide/SO_2 particles resulted in significant decreases in total lung capacity, vital capacity and functional residual capacity compared with controls or exposure to SO_2 alone. These decreases were maintained for at least 72 h following the last exposure. Decreases in diffusing capacity for carbon monoxide and alveolar volume, as well as increased alveolar-duct inflammation, were observed in response to zinc oxide-SO_2 but not to SO_2 alone. Because the changes noted in

response to zinc oxide-SO_2 were identical to those seen in a previous study using zinc oxide, the authors concluded that SO_2 played a minor role in these responses. Subsequent studies employed a lower concentration of zinc oxide (1 and 2.5 mg/m^3) in order to unmask the effects of the SO_2-zinc oxide interaction (Amdur et al., 1988; Conner et al., 1989). In one of these, significant changes were observed in numbers of cells and other lavage fluid components in guinea pigs exposed for 3 h/day for 5 days to SO_2-zinc oxide compared with those exposed only to SO_2 or zinc oxide. As previously described, it was determined that the mixture of zinc oxide and SO_2 in a high temperature furnace with sufficient humidity resulted in the formation of a zinc oxide/ H_2SO_4 aerosol. Exposure of guinea pigs for 3 h/day for 5 days to this H_2SO_4-coated ultrafine aerosol at a concentration of 7-11 μg/m^3 S(VI) resulted in a significant decrease in diffusing capacity for carbon monoxide, an effect not seen with exposure to zinc oxide or SO_2 alone. The authors concluded that the response was due to the H_2SO_4 associated with the aerosol and delivered to the lower respiratory tract (Amdur et al., 1988).

3.1.5.2.2. Effects of SO_2 Layered on Carbon Particles

Effects of SO_2-containing mixtures on host defenses were examined in several studies. Host defense results will not be discussed since high concentrations (10 ppm) of SO_2 were used. However, these experiments were important since they demonstrated that mixing SO_2 and submicron particles of carbon black in the presence of 85% relative humidity led to significant adsorption of SO_2 onto the carbon black and oxidation of SO_2 to acid sulfate. No high temperature furnace was employed in these studies (Jakab et al., 1996; Clarke et al., 2000).

3.1.5.2.3. Effects of Sulfite Aerosols

Several studies used sulfite particles as a surrogate for SO_2 adsorbed onto carbonaceous or metallic particulates. These are discussed below and in Annex Table E-15. Sulfite and SO_2, both S(IV) species, were expected to have similar chemical reactivities. An acute 1-h exposure of guinea pigs to submicron aerosols of sodium sulfite (204-1,152 μg/m^3 of sulfite) resulted in significant effects on pulmonary function (Chen et al., 1987). A 50% increase in resistance and 19% decrease in compliance were observed using 972 μg/m^3 of sulfite, while dose-dependent decreases in total lung capacity, vital capacity, functional residual capacity, residual volume, diffusion capacity for carbon monoxide and increases in lung wet weight at concentrations of

204 μg/m^3 and above. The authors noted that aerosols of S(IV) were 6 times more potent than gaseous S(IV) in terms of bronchoconstriction and attributed these effects to greater pulmonary deposition of the S(IV) aerosol. An earlier study by the same group found that 1-h exposure of rabbits to greater than 1,200 μg/m^3 of sulfite led to accelerated clearance of a tracer aerosol from the bronchial tree (Chen and Schlesinger, 1983). Chronic studies involving sulfite aerosols are discussed in Section 3.4.2.5.

3.1.5.2.4. Other Mixtures

In addition to examining the interaction of SO_2 and particles, animal studies performed since the publication of the 1982 AQCD evaluated the effects of binary mixtures, laboratory-generated complex mixtures (e.g., simulation of regional air pollution), or actual ambient air mixtures. Annex Tables E-17 through E-20 summarize results from short-term studies on possible toxicity relationships between SO_2 and O_3, and between SO_2 and sulfates as well as the effects of complex air pollution mixtures in healthy animals and disease models. Possible interactions between SO_2 and cold air were also examined (Annex Table E-20). Generally, most studies with ambient or laboratory-generated complex mixtures did not include a SO_2-only exposure group, making it difficult to determine the contribution of SO_x. No definitive conclusions can be made from these studies.

3.1.5.2.5. Summary of Evidence on SO_2 Interactions with PM and Other Mixtures

The key findings by Amdur and others discussed above demonstrate that the effects of SO_2 may be enhanced when aerosol particles act as carriers and deliver SO_2 to the lower respiratory tract. Interaction of SO_2 and PM may also lead to transformation of SO_2 to other forms of SO_x which may have more potent biological effects than SO_2. Studies discussed above reported transformation of SO_2 adsorbed onto metal oxide or carbon particles to sulfite, sulfate, sulfur trioxide, and H_2SO_4 depending on conditions of temperature and relative humidity.

3.1.6. Evidence of the Effect of SO_2 on Respiratory Morbidity from Intervention Studies

Many epidemiological studies have examined the association of short-term SO_2 concentrations and various respiratory morbidity outcomes. These studies collectively suggest

that increased ambient SO_2 concentrations are associated with increased risk of respiratory outcomes, ranging from respiratory symptoms to ED visits and hospitalizations. Further contributing to the evidence base are intervention studies that reported decreases in respiratory morbidity following improvements in air quality, particularly reductions in SO_2 concentrations.

In Hong Kong, a sudden change in regulation in July 1990 required all power plants and road vehicles to use fuel oil with a sulfur content of ≤ 0.5% by weight. These regulations were enforced quickly, and provided opportunities to observe changes in morbidity before and after the intervention. Peters et al. (1996) followed 3,521 children (mean age 9.5 years) residing in two districts with good and poor air quality before the intervention from 1989 to 1991. The intervention resulted in large reductions in SO_2 (up to 80% in polluted district), along with a modest reduction in sulfate (38% in polluted district). Only a small change in TSP levels was observed after the intervention (15% decline in polluted district). In 1989 and 1990, an excess risk of respiratory symptoms was observed in the polluted district. After the intervention, there was a greater decline in reported symptoms of cough, sore throat, phlegm, and wheezing in the polluted compared with the unpolluted district. For example, the OR for cough, comparing the polluted to the unpolluted district, was 1.22 (95% CI: 1.05, 1.42) in 1989 and 1990, and decreased to 0.92 (95% CI: 0.73, 1.15) in 1991.

A study by Keles et al. (1999) evaluated the prevalence of chronic rhinitis among high school students before and after installation of a natural gas network for domestic heating and industrial works, in a polluted area of Istanbul, Turkey. Concentrations of CO, NO_2, and hydrocarbons were relatively low compared to SO_2 and TSP in this area. After the intervention, the annual mean TSP concentration declined by 23% from 89.7 $\mu g/m^3$ to 68.8 $\mu g/m^3$. An even greater decline (46%) was observed for SO_2, from an annual mean of 70.8 ppb to 38.2 ppb. The prevalence of rhinitis decreased significantly from 62.5% to 51% of the student population ($p < 0.05$) following the installation of the natural gas network. Symptoms of rhinitis were associated with air pollution levels, but not with any of the other factors considered, including sex, household crowding, heating source, and smoking status. Although the effects from TSP could not be separated from SO_2 effects, this study demonstrated that reductions in both pollutants (with greater declines in SO_2) resulted in significant reductions in the prevalence of chronic rhinitis in a highly polluted area.

Another study in Germany observed that reductions in air pollutant levels were associated with improvement in reported respiratory symptoms. Heinrich et al. (2002) examined the influence of reduced air pollution levels on respiratory symptoms in children aged 5 to 14 years (n = 7,632). Questionnaires were collected from the children during 1992–1993, 1995–1996, and 1998–1999 in three study areas. During the study period, SO_2 concentrations decreased by more than 90% and TSP concentrations decreased by approximately 60%. Concentrations of nucleation-mode particles (10-30 nm) increased during this time period. For most respiratory outcomes, the prevalence continued to decline in each of the three surveys. The temporal changes followed similar trends in all three study areas. Stronger effects between SO_2 and prevalence of respiratory symptoms were observed among children without indoor exposures. For those without indoor exposures, ORs of 1.21 (95% CI: 1.11, 1.32) were observed for prevalence of bronchitis and 1.11 (95% CI: 1.02, 1.22) for frequent colds per 5-ppb increase in the annual mean of SO_2. Frye et al. (2003) reported changes in lung function parameters associated with declines in SO_2 concentrations in 2,493 children during this period as well. The researchers observed a 0.6% (95% CI: 0.1, 1.2) increase in FVC and a 0.4% (95% CI: -0.1, 0.9) increase in FEV_1 per 5-ppb decrease in the annual mean of SO_2. They concluded that the decreasing prevalence of respiratory symptoms and the increase in lung function following decreases in air pollution levels might indicate the reversibility of adverse health effects in children.

In summary, these studies observed that improvements in air quality, in particular large decreases in SO_2 concentrations, were associated with improvements in respiratory symptoms and lung function. However, the decreased respiratory morbidity following large reductions in ambient SO_2 concentrations does not preclude the possibility that other constituents of the pollution mixture that share the same source as SO_2 are also responsible for adverse effects. In the German and Turkey studies, both SO_2 and TSP concentrations decreased dramatically. Although PM_{10} levels before and after the intervention were stable in Hong Kong, large reductions in ambient nickel and vanadium were observed concomitantly with reductions of sulfur after the intervention (Hedley et al., 2006). As discussed in Section 3.1.5, interactions of SO_2 and PM may lead to transformation of SO_2 to other forms of SO_x which have more potent biological effects; thus the improvements in respiratory health may also be attributable to both declines in SO_2 and PM. Nonetheless, considered collectively with the larger body of evidence

from epidemiological, human clinical, and animal toxicological studies, these studies are supportive of SO_2-related effects on respiratory morbidity.

3.1.7. Summary of Evidence of the Effect of Short-Term SO_2 Exposure on Respiratory Health

Evaluation of the health evidence led to the conclusion that it is *sufficient to infer a causal relationship between respiratory morbidity and short-term exposure to* SO_2. This conclusion is supported by the consistency, coherence, and plausibility of findings observed in human clinical studies with 5-10 min exposures, epidemiological studies using largely 24-h avg exposures and animal toxicological studies using exposures of minutes to hours.

The strongest evidence for this causal relationship comes from human clinical studies reporting respiratory symptoms and decreased lung function following peak exposures of 5-10 min duration to SO_2. These effects have been observed consistently across studies involving exercising mild to moderate asthmatics. Statistically significant decrements in lung function accompanied by respiratory symptoms including wheeze and chest tightness have been clearly demonstrated following exposure to 0.4-0.6 ppm SO_2. Although studies have not reported statistically significant respiratory effects following exposure to 0.2-0.3 ppm SO_2, some asthmatic subjects (5-20%) have been shown to experience moderate to large decrements in lung function at these exposure concentrations. A larger body of evidence supporting this determination of causality comes from numerous epidemiological studies reporting associations with respiratory symptoms, ED visits, and hospital admissions with short-term SO_2 exposures, generally of 24-h avg. Important new multicity studies and several other studies have found an association between 24-h avg ambient SO_2 concentrations and respiratory symptoms in children, particularly those with asthma. Furthermore, limited epidemiological evidence indicates that atopic children and adults may be at increased risk for SO_2-induced respiratory symptoms. Generally consistent and robust associations also were observed between ambient SO_2 concentrations and ED visits and hospitalizations for all respiratory causes, particularly among children and older adults (65+ years), and for asthma. Results of experiments in laboratory animals support these observations; studies in animals sensitized with antigen demonstrate that repeated exposure to near ambient SO_2 levels (as low as 0.1 ppm in guinea pigs) can exacerbate

allergic responses including mucin production, airway inflammation and airway hyperresponsiveness.

3.2. Other Morbidity Associated with Short-Term SO_2 Exposure

3.2.1. Summary of Findings from the Previous Review

The studies reviewed in the 1982 AQCD primarily investigated respiratory health outcomes. There were no key animal toxicological or human clinical studies available at the last review to address effects of SO_2 exposure on the cardiovascular system. The only report was a study in dogs exposed to air pollutant mixtures (SO_2 + H_2SO_4 with or without nonirradiated or irradiated auto exhaust). No changes were observed in cardiovascular function at the end of 3 years of exposure and 3 years after exposure. No epidemiological studies linking exposure to SO_2 with cardiovascular physiological endpoints or ED visits or hospital admissions for cardiovascular causes were examined in the last review. Other organ systems in addition to cardiovascular were not addressed in the 1982 AQCD.

3.2.2. Cardiovascular Effects Associated with Short-Term Exposure

The biological basis for SO_2-related cardiovascular health effects may lie in the stimulation of chemosensitive receptors found in the respiratory tract which respond to irritants like SO_2. Vagally-mediated responses may affect the cardiovascular system by inducing bradycardia and either hypotension or hypertension, as discussed in Section 3.1.2. Alternatively oxidation reactions mediated by the SO_2 metabolites sulfite and bisulfite which have been absorbed into the systemic circulation may potentially alter cardiovascular function. In general, vagally-mediated responses have been observed at lower concentrations of SO_2 than oxidative injury.

Since 1982, several animal toxicological studies have addressed the effects of SO_2 on cardiovascular endpoints. These are summarized below and in Annex Table E-5. In addition, there is one noteworthy study examining the hematological effects of short-term SO_2 exposure (Annex Table E-8). Acute exposure of rats to 0.87 ppm SO_2 for 24 h resulted in increased hematocrit, sulfhemoglobin and osmotic fragility as well as decreased whole blood and packed cell viscosities (Baskurt, 1988). These results indicate a systemic effect of inhaled SO_2 at

concentrations near ambient levels and are consistent with an oxidative injury to red blood cells. Only one study since 1982 measured systemic levels of sulfite or bisulfite following SO_2 inhalation (Gunnison et al., 1987; Annex Table E-22). Further studies are required to confirm that inhalation exposures of SO_2 at or near ambient levels increase blood sulfite and bisulfite levels sufficient for oxidative injury to blood cells or other tissues.

Recent epidemiological studies have examined the association between air pollution and cardiovascular effects, including increased heart rate (HR), reduced heart rate variability (HRV), incidence of ventricular arrhythmias, changes in blood pressure, incidence of myocardial infarctions (MI), and ED visits and hospitalizations due to cardiovascular causes. The results of these cardiovascular studies are summarized in Annex Tables F-3 and F-4.

3.2.2.1. Heart Rate and Heart Rate Variability

Heart rate variability (HRV) is generally determined by analyses of time (e.g., standard deviation of normal R-R intervals [SDNN]) and frequency domains (e.g., low frequency [LF] / high frequency [HF] ratio by power spectral analysis, reflecting autonomic balance) measured during 24 h of electrocardiography (ECG). Brook et al. (2004) stated that HRV, resting heart rate, and blood pressure are modulated by a balance between the two determinants of autonomic tone (the sympathetic and parasympathetic nervous systems). An imbalance of cardiac autonomic control may predispose susceptible people to greater risk of ventricular arrhythmias and consequent cardiac deaths (Brook et al., 2004; Liao et al., 2004).

A limited number of human clinical studies examined the effect of SO_2 on HRV. During a controlled exposure of 12 healthy subjects and 12 subjects with asthma to 0.2 ppm SO_2 for 1 h under resting conditions, Tunnicliffe et al. (2001) reported that HF power, LF power, and total power were higher with SO_2 exposures compared to air exposure in the healthy subjects, but that these indices were reduced during SO_2 exposure in the subjects with asthma. The LF/HF ratios were unchanged in both groups. The authors postulated two autonomic pathways for SO_2-mediated bronchoconstriction. In healthy subjects, the dominant pathway was proposed to be the rapidly adapting receptor/C-fiber route, which results in a central nervous system reflex with an increase in vagal tone. In the asthmatic subjects, proximal airway narrowing was proposed as the dominant response, possibly through neurogenic inflammation. This likely causes a compensatory central nervous system-mediated reduction in vagal tone, resulting in

bronchodilation of the distal airway. While there were no detectable changes in symptoms or lung function in either of the groups, this study provides some evidence that exposure to SO_2 may elicit systemic responses at these low levels (0.2 ppm).

In a similar study, Routledge et al. (2006) exposed patients with stable angina as well as healthy subjects to 50 $\mu g/m^3$ carbon particles, 0.2 ppm SO_2, alone and in combination, for 1 h under resting conditions. HRV, C-reactive protein, and coagulation markers were measured. The authors reported that for the healthy subjects, SO_2 exposure was associated with a decrease in HRV markers of cardiac vagal control 4 h after exposure. However, it should be noted that there was no apparent difference in the absolute value of the root mean square of successive RR interval differences (r-MSSD) at 4 h postexposure between the control, SO_2, carbon, and carbon/SO_2 groups. The significant difference reported in the change in r-MSSD from baseline to 4 h postexposure with SO_2 appears to be due to a higher baseline value of r-MSSD preceding the SO_2 exposure compared to the baseline value of r-MSSD preceding the air exposure. There were no changes in HRV among the patients with stable angina. The authors noted that this lack of response in the heart patients may be due to a drug treatment effect rather than decreased susceptibility; a large portion of the angina patients were taking beta blockers, which are known to increase indices of cardiac vagal control.

In an epidemiological study, Liao et al. (2004) investigated short-term associations between ambient pollutants and cardiac autonomic control from the fourth cohort examination (1996 through 1998) of the population-based Atherosclerosis Risk in Communities (ARIC) study using a cross-sectional study design. Men and women aged 45 to 64 years (n = 6,784) from three U.S. study centers in North Carolina, Minnesota, and Mississippi were examined. Resting, supine, and 5-min beat-to-beat R-R interval data were collected. The mean 24-h avg SO_2 level measured 1 day prior to the HRV measurement was 4 ppb (SD 4). In addition to SO_2, the potential effects of PM_{10}, O_3, CO, and NO_2 were evaluated. Previous-day SO_2 concentrations were positively associated with HR and inversely associated with SDNN and LF power. Consistently more pronounced associations were suggested between SO_2 and HRV among persons with a history of coronary heart disease. Significant associations with HRV indices also were observed for PM_{10} and the other gaseous pollutants. When the regression coefficients for each individual pollutant model were compared, the effects of PM_{10} on HRV were considerably

larger than the effects for the gaseous pollutants, including SO_2. No multipollutant analyses were conducted.

Gold et al. (2000; reanalysis 2003) examined the effect of short-term changes in air pollution on HRV in a panel study of 21 older adults (aged 53 to 87 years) in Boston, MA. The study participants were observed up to 12 times from June to September 1997. The mean 24-h avg SO_2 concentration was 3.2 ppb (range: 0, 12.6). The 24-h avg SO_2 concentration was associated with decreased HR in the first 5-min rest period, but not in the overall 25-min study protocol. The effect estimate for SO_2 slightly diminished but remained marginally significant in a two-pollutant model with $PM_{2.5}$. The inverse association between SO_2 and HR observed in this study are in contrast to the SO_2-related increases in HR observed by Liao et al. (2004) and Peters et al. (1999). No associations were observed between HRV and SO_2. The strongest associations with HRV were observed for $PM_{2.5}$ and O_3.

Another study of air pollutants and HRV was conducted in Boston, MA on 497 men from the Normative Aging Study (Park et al., 2005). The best 4-consecutive-min interval from a 7-min sample was used for the HRV calculations. For the exposure variable, 4-, 24-, and 48 h moving averages matched on the time of the ECG measurement for each subject were considered. The mean 24-h avg SO_2 concentration was 4.9 ppb (range: 0.95, 24.7). Associations with measures of HRV were reported for $PM_{2.5}$ and O_3, but not with SO_2 for any of the averaging periods. In another study conducted in Boston, MA, Schwartz et al. (2005) found significant effects of increases in $PM_{2.5}$ on measures of HRV, while no associations with SO_2 were observed. Other studies examined the relationship of SO_2 with HRV (Chan et al., 2005; de Paula Santos et al., 2005; Holguin et al., 2003; Luttmann-Gibson et al., 2006). Most of these studies, with the exception of de Paula Santos et al., did not observe associations with SO_2.

In the limited number of epidemiological studies that examined a possible effect of SO_2 on HRV, there were some suggestive findings; however, results reported from the human clinical studies were inconsistent. The overall evidence does not support the conclusion that SO_2 affects cardiac autonomic control.

3.2.2.2. Repolarization Changes

In addition to the role played by the autonomic nervous system in arrhythmogenic conditions, myocardial vulnerability and repolarization abnormalities are believed to be key factors contributing to the mechanism of such diseases.

Two in vitro studies (Nie and Meng, 2005) conducted with a 1:3 molar:molar mixture of the SO_2 derivatives bisulfite and sulfite demonstrated effects of a 10-µm bisulfite:sulfite mixture on sodium and L-type calcium currents (which included changes in inactivation and/or activation, recovery from inactivation, and inactivation/activation time constants) in ventricular myocytes. These in vitro observations suggested a potential role for L-type calcium current in cardiac injury following SO_2 exposure. However, in vivo cardiovascular effects were observed only at high SO_2 concentrations (10 ppm and higher). Additional toxicological studies are necessary to evaluate repolarization changes at ambient levels of SO_2.

In an epidemiological study, Henneberger et al. (2005) examined the association of repolarization parameters (QT duration, T-wave complexity, variability of T-wave complexity, and T-wave amplitude) with air pollutants in patients with preexisting coronary heart disease (n = 56, all males) in East Germany. The patients were examined repeatedly once every 2 weeks for 6 months, for a total of 12 ECG recordings. The mean 24-h avg SO_2 concentration was 2 ppb (range: 1, 4). Ambient SO_2 concentrations during the 24-h preceding the ECG were associated with the QT interval duration, but not with any other repolarization parameters. Stronger associations were observed between PM indices and QT interval duration, T-wave amplitude, and T-wave complexity.

To summarize, the evidence, while suggestive, is too limited to draw conclusions on the association of SO_2 exposure and repolarization changes at this time.

3.2.2.3. Cardiac Arrhythmias

One toxicological study examined the effects of PM, ultrafine carbon, and SO_2 on spontaneous arrhythmia frequency in 18-month-old rats (Nadziejko et al., 2004). The rats were exposed to 1 ppm SO_2 for 4 h. No significant change in the frequency of spontaneous arrhythmias was found with SO_2 and ultrafine carbon exposure. However, rats exposed to

concentrated ambient PM had a significantly greater increase in the frequency of delayed beats than rats exposed to air.

In a panel study of 100 patients with implanted cardioverter defibrillators (ICDs) in Eastern Massachusetts, Peters et al (2000) tested the hypothesis that patients with ICDs would experience life-threatening arrhythmias after an air pollution episode. The mean 24-h avg SO_2 concentration measured at two sites in Boston during the study period was 7 ppb (5th–95th percentile: 1, 19). ICDs monitor ECG abnormalities, and treat ventricular fibrillation or ventricular tachycardias by administering shock therapy to restore the normal cardiac rhythm. The ICD device also stores information on each tachyarrhythmia and shock. There was no association between SO_2 and defibrillator discharges in the 33 subjects who had any defibrillator discharges during the follow-up period or in the 6 subjects who had at least 10 discharges. There was some evidence that NO_2 was associated with increased defibrillatory interventions in the subjects with any defibrillator discharges. Among the patients with at least 10 events, NO_2, CO, and $PM_{2.5}$ were found to be associated with defibrillator discharges.

In a follow-up study designed to confirm the findings of Peters et al. (2000), Dockery et al. (2005) used a larger sample of ICD patients in Boston (n = 203) with a longer follow-up period. The median concentration of 48-h avg SO_2 averaged across multiple sites in Boston was 4.9 ppb (IQR 4.1). No significant associations were found between ventricular arrhythmic episode days and any of the air pollutants. However, when the analysis was stratified by recent arrhythmias (i.e., within 3 days), there was evidence of an excess risk of ventricular arrhythmia with SO_2, $PM_{2.5}$, black carbon, NO_2, and CO. Since $PM_{2.5}$, black carbon, NO_2, and CO were correlated with each other and with SO_2, the authors noted that differentiating the independent effects of the pollutants would be difficult. A case-crossover analysis of the same data by Rich et al. (2005) also observed associations with 48-h avg SO_2, but the SO_2 effect was not found to be robust to adjustment by $PM_{2.5}$. In a similar study conducted in St. Louis, MO, an excess risk was associated with SO_2 concentrations in the 24 h prior to an arrhythmia, but not with $PM_{2.5}$ and O_3 (Rich et al., 2006). In this study, none of the other measured pollutants (PM, elemental carbon, O_3, CO, NO_2) were correlated with SO_2. The authors suggested that the different effects observed in St. Louis and Boston may be due to differences in the source or mix of air pollutants in these cities. Finally, findings from a time series study of tachyarrythmic events among 518 patients

over a 10 year period in Atlanta do not indicate an association with SO_2, nor with the other pollutants studied including $PM_{2.5}$ and its components (Metzger et al., 2007).

Additional studies have examined the relationship of SO_2 with arrhythmias in Vancouver, and observed associations at very low ambient SO_2 concentrations (mean 24-h avg SO_2 of ~2.5 ppb with a max of 8.1 ppb). Vedal et al. (2004) stated that of all pollutants examined, the only one with somewhat consistent positive associations with arrhythmia events was SO_2. In season-stratified analyses, SO_2 was positively associated with arrhythmias in the winter, while in the summer the association was negative. On the other hand, in the Rich et al. (2004) study, positive associations were observed in the summer but not in the winter. The authors stated that it was difficult to interpret these findings.

Collectively, the epidemiological evidence for an association between short-term exposure to SO_2 and arrhythmias is inconsistent. The limited toxicological evidence does not provide biological plausiblity for an effect.

3.2.2.4. Blood Pressure

Two animal toxicological studies examined the effect of SO_2 on blood pressure (Annex Table E-5). Hälinen et al. (2000) examined blood pressure changes in guinea pigs. The animals were hyperventilated to simulate exercise, and exposed to 1-, 2.5-, and 5 ppm SO_2 in cold, dry air. After 10-min exposures to each SO_2 concentration, separated by 15-min exposures to clean, warm, humid air, a transient increase in blood pressure was observed during 5 ppm SO_2 exposure in cold, dry air. In a second study (Halinen et al., 2000b), hyperventilated guinea pigs were exposed to cold, dry air alone or to 1 ppm SO_2 in cold, dry air for 60 min. The study reported similar increases in blood pressure and HR with exposure to cold, dry air or to SO_2 in cold, dry air. The increase in HR was gradual, while increases in blood pressure generally occurred during the first 10 to 20 min of exposure. Similar effects were observed with exposure to cold, dry air or to SO_2 in cold, dry air, suggesting that effects were associated with cold, dry air rather than with SO_2.

Ibald-Mulli et al. (2001) examined the association between blood pressure and SO_2 using survey data from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Project. Blood pressure measurements were taken from 2,607 men and women. The mean 24-h avg SO_2 concentration was 23 ppb (range: 5, 91). An increase in systolic blood pressure was

associated with 24-h avg SO_2 and TSP. However, in a two-pollutant model with TSP, the effect of SO_2 on blood pressure was substantially reduced and became nonsignificant while the effect of TSP was robust.

In a study by de Paula Santos et al. (2005), changes in blood pressure in association with SO_2 were investigated in vehicular traffic controllers (n = 48) aged 31 to 55 years living in São Paulo, Brazil, where vehicles are the primary source of air pollution. The mean 24-h avg SO_2 level, measured at six different stations around the city, was 7 ppb (SD 3). Blood pressure was measured every 10 min when subjects were awake (6 a.m. to 11 p.m.) and every 20 min during sleep (11 p.m. to 6 a.m.). Results indicated that SO_2, as well as CO, were associated with increases in systolic and diastolic blood pressure. However, when a two-pollutant model was used to test the robustness of the associations, only the CO effect remained statistically significant.

Very few studies have examined the effects of short-term SO_2 exposure on blood pressure. Collectively, the limited toxicological and epidemiological evidence does not suggest that exposure to SO_2 has effects on blood pressure.

3.2.2.5. Blood Markers of Cardiovascular Risk

Folsom et al. (1997) demonstrated that elevated levels of fibrinogen, white blood cell count, factor VIII coagulant activity (factor VIII-C), and von Willebrand factor were associated with risk of cardiovascular disease. Schwartz (2001)investigated the association between various blood markers of cardiovascular risk and air pollution among subjects in the Third National Health and Nutrition Examination Survey (NHANES III) in the United States conducted between 1989 and 1994 across 44 counties. The NHANES III is a random sample of the U.S. population with oversampling for minorities (30% of NHANES sample) and the elderly (20% of the sample). The mean SO_2 concentration was 17.2 ppb (IQR 17) across the 25 counties where data were available. This study looked at fibrinogen levels, platelet counts, and white blood cell counts. After controlling for age, ethnicity, gender, body mass index, and smoking status and number of cigarettes per day, SO_2 was found to be positively associated with white blood cell counts. PM_{10} was associated with all blood markers. In two-pollutant models, PM_{10} remained a significant predictor of white blood cell counts after controlling for SO_2, but not vice versa.

A recent cross-sectional study by (Liao et al., 2005) investigated the effects of air pollution on plasma hemostatic and inflammatory markers in the ARIC study (n = 10,208). The authors hypothesized that short-term exposure to air pollutants was associated with increased levels of inflammatory markers and lower levels of albumin, as serum albumin is inversely associated with inflammation. The mean 24-h avg SO_2 concentration was 5 ppb (SD 4). Significant curvilinear relationships were observed between SO_2 and factor VIII-C, white blood cell counts, and serum albumin. The authors noted that since no biological explanation could be offered for the "U"-shaped curve between SO_2 and factor VIII-C and the "inverse U"-shape between SO_2 and albumin, generalization of the association should be exercised with caution. No associations were observed between SO_2 and fibrinogen or von Willebrand factor.

In another large cross-sectional study of 7,205 office workers in London, Pekkanen et al (2000) examined the association between plasma fibrinogen and ambient air pollutants. The mean 24-h avg SO_2 was 9 ppb (10th–90th percentile: 5, 19). Associations with fibrinogen were observed for all pollutants examined, either in all-year or summer-only analyses, except for SO_2 and O_3.

Taken together, results from the limited number of studies do not suggest that SO_2 is associated with various blood markers of cardiovascular risk.

3.2.2.6. Acute Myocardial Infarction

The association between air pollution and the incidence of MI was examined in a small number of studies. As part of the Determinants of Myocardial Infarction Onset Study, Peters et al. (2001) examined 772 patients with MI living in greater Boston, MA. A case-crossover design was used to assess changes in the risk of acute MI after exposure to potential triggers. The mean 24-h avg SO_2 was 7 ppb (range: 1, 20) during the study period. Similarly, the mean 1-h avg SO_2 was 7 ppb (range: 0, 23). In an analysis that considered both the 2-h avg (between 60 and 180 min before the onset of symptoms) and 24-h avg (between 24 and 48 h before the onset) concentrations jointly, the study found no significant association between risk of MI and SO_2. Of all the pollutants considered, only $PM_{2.5}$ and PM_{10} were found to be associated with an excess risk of MI. In a study of 5793 confirmed cases of acute MI in King County Washington, Sullivan et al. (2005) also used a case-crossover design to investigate the association of ambient levels of

several air pollutants 1, 2, 4 and 24 h before the MI onset. No association with SO_2 (or with $PM_{2.5}$) was observed. The mean SO_2 level was 9 ppb (range: 0-39 ppb) at the time of the study.

In the MONICA Project, the effect of air pollution on acute MI was studied in Toulouse, France, using a case-crossover study design (Ruidavets et al., 2005). The mean 24-h avg SO_2 level was 3 ppb (5th–95th percentile: 1, 5). A total of 399 cases of acute MI were recorded during the study period. O_3, but not SO_2 or NO_2, was found to be associated with the incidence of acute MI. Exposure to PM was not considered in this study.

Only a limited number of studies examined the association between ambient SO_2 concentrations and incidence of acute MI. These studies provide no evidence that exposure to SO_2 increases the risk of MI.

3.2.2.7. Emergency Department Visits and Hospitalizations for Cardiovascular Diseases

The current review includes more than 30 peer-reviewed studies that address the effect of SO_2 exposure on ED visits or hospitalizations for cardiovascular diseases. These studies are discussed briefly in this section and further summarized in Annex Table F-4.

3.2.2.7.1. All Cardiovascular Diseases

The disease grouping of all cardiovascular diseases typically includes all diseases of the circulatory system (e.g., heart diseases and cerebrovascular diseases, ICD9 Codes 390-459). A summary of the associations reported for ambient SO_2 concentrations with all cardiovascular diseases are presented in Figure 3-9.

In a study of 11 cities in Spain, an excess risk of 3.6% (95% CI: 0.6, 6.7) per 10 ppb increase in 24-h avg SO_2 at a 0-1 day lag was observed for all cardiovascular disease admissions (Ballester et al., 2006). The mean 24-h avg SO_2 level in the cities studied was 6.6 ppb. In addition, time-series data linking SO_2 with hospital admissions for cardiovascular diseases in three metropolitan areas in the United States (i.e., Cook, Maricopa, Los Angeles Counties) was conducted (Moolgavkar, 2000; reanalysis, 2003). Among older adults (65+ years) in Los Angeles County, a 13.7% (95% CI: 11.3, 16.1) excess risk in admissions was observed per 10 ppb increase in 24-h avg SO_2 at lag 0 day, using a Generalized Linear Model (GLM) and natural splines to adjust for temporal trends rather than GAM. The median 24-h avg SO_2 level for Los

Angeles County was 2 ppb during the study period. Results for Maricopa and Cook counties were not presented in the reanalysis.

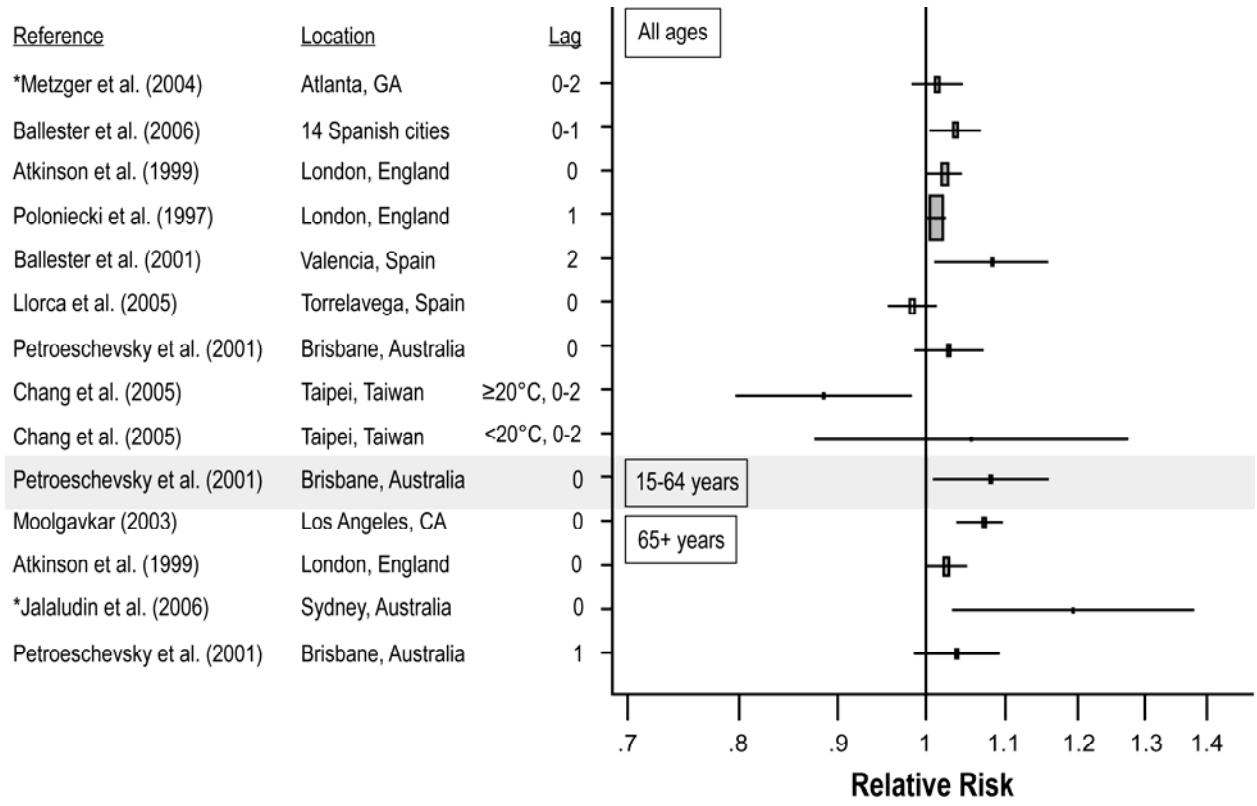

Figure 3-9. Relative risks (95% CI) of SO_2-associated emergency department visits (*) and hospitalizations for all cardiovascular causes, arranged by age group. Risk estimates are standardized per 10 ppb increase in 24-h avg SO_2 concentrations or 40 ppb increase in 1-h max SO_2. The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.

In a large single city study Metzger et al. (2004) examined approximately 4.4 million hospital visits to 31 hospitals from 1993 to 2000 in Atlanta, GA and reported a 1.4% (95% CI: 1.5, 4.4) excess risk in ED visits for cardiovascular causes per 40-ppb increase in 1-h max SO_2. Peel et al. (2006) conducted analyses using the same dataset to compare results obtained with a case-crossover design to the Metzger et al. (2007) results, which were obtained using a time series approach. Peel et al. and Metzger et al. report similar findings. The median 1-h max SO_2 level in Atlanta during the study period was 11 ppb (10th–90th percentile: 2–39). Results from several single-city studies in Europe, Australia, and Taiwan indicated positive associations with

SO_2 (Atkinson et al., 1999a; Ballester et al., 2001; Jalaludin et al., 2006; Petroeschevsky et al., 2001; Poloniecki et al., 1997), though others observed negative associations (Chang et al., 2005; Llorca et al., 2005) (see Figure 3-9).

3.2.2.7.2. Specific Cardiovascular Diseases

Several studies examined the effect of ambient SO_2 on hospital admissions for cardiac disease (ICD9 Codes 390-429), ischemic heart disease (IHD, ICD9 Codes 410-414), dysrhythmia (ICD9 Code 427), congestive heart failure (CHF, ICD9 Code 428), MI (410) or cerebrovascular diseases (ICD9 Codes 430-438). A European multicity study reported statistically significant positive associations with cardiac disease admissions (Ballester et al., 2006). However, adjustment for PM_{10} and CO in two-pollutant models diminished the association reported by Ballester et al. by approximately 50%. Findings for cardiac disease admissions reported in several additional single city studies conducted in the United States, Canada, Australia and Europe were inconsistent (Fung et al., 2005; Jalaludin et al., 2006; Llorca et al., 2005; Michaud et al., 2004).

Analyses restricted to diagnoses of IHD (Jalaludin et al., 2006; Lee et al., 2003; Lin et al., 2003a; Metzger et al., 2004; Peel et al., 2007), CHF (Koken et al., 2003; Metzger et al., 2004; Morris et al., 1995; Peel et al., 2007; Wellenius et al., 2005b), dysrhythmia (Koken et al., 2003; Metzger et al., 2004; Peel et al., 2007), MI (Koken et al., 2003; Lin et al., 2003a), and angina pectoris (Hosseinpoor et al., 2005) were also conducted. Metzger et al. (2004) observed weak nonsignificant or negative associations of 1-h max SO_2 with IHD, CHF, and dysrhythmia. Using the same dataset, Peel et al. (2007) investigated effect modification of cardiovascular disease outcomes across comorbid disease status categories, including hypertension, diabetes, COPD, dysrhythmia, and CHF. Authors observed only weak nonsignificant or negative associations for IHD, CHF, and dysrhythmia with ambient 1-h max SO_2 level in any comorbid disease category. Both increases in admissions or ED visits (Jalaludin et al., 2006; Koken et al., 2003; Wellenius et al., 2005a) and weak or negative associations (Hosseinpoor et al., 2005; Lee et al., 2003b; Lin et al., 2003a) were reported in other studies.

Studies of the effect of SO_2 on cerebrovascular admissions were also considered. Positive associations were reported for ischemic stroke (Villeneuve et al., 2006; Wellenius et al., 2005b; Wellenius et al., 2005a). However Wellenius et al. (2005b) reported stronger associations for

NO_2 and CO than SO_2, and the association reported by Villenueve et al. (2006) was diminished in two-pollutant models. No meaningful positive associations of ambient SO_2 with cerebrovascular diseases were observed in several other studies (Henrotin et al., 2007; Jalaludin et al., 2006; Metzger et al., 2004; Peel et al., 2007; Tsai et al., 2003).

3.2.2.7.3. Summary of Evidence on Emergency Department Visits and Hospitalizations from Cardiovascular Diseases

Several studies have observed positive associations between ambient SO_2 concentrations and ED visits or hospital admissions for cardiovascular diseases (e.g., all cardiovascular diseases, cardiac diseases, cerebrovascular diseases) particularly among individuals 65+ years of age, but results are not consistent across studies. The strongest evidence comes from a large multicity study conducted in Spain (Ballester et al., 2006) that observed statistically significant positive associations between ambient SO_2 and cardiovascular disease admissions; however, the SO_2 effect was found to diminish by half with PM_{10} and CO adjustment. Only a limited number of studies assessed potential confounding by copollutants despite the moderate to strong correlation between SO_2 and various copollutants in most studies. While some studies suggest that the association of SO_2 with cardiovascular hospitalizations were generally robust to adjustment for BS and PM_{10} (Ballester et al., 2001; Fung et al., 2005), several other studies, including that by Balleseter et al. (2006), observed that the effect of SO_2 on cardiovascular ED visits and hospitalizations may be confounded by copollutant exposures. Jalaludin et al. (2006) reported a 3% excess risk in cardiovascular disease hospital admissions per 0.75 ppb incremental change in 24-h avg SO_2 in single-pollutant models, which was reduced to null when CO was included. Chang et al. (2005) noted that the observed negative association of SO_2 with all cardiovascular disease hospitalizations they observed was strengthened after adjusting for NO_2, PM_{10}, and CO in two-pollutant models. The authors attributed this finding to possible collinearity problems between SO_2 and copollutants. None of the epidemiological studies examined effects of possible interactions among copollutants.

3.2.2.8. Summary of Evidence on the Effect of Short-Term SO_2 Exposure on Cardiovascular Health

The overall evidence on the effect of short-term exposure to SO_2 on cardiovascular health effects is *inadequate to infer the presence or absence of a causal relationship*. Epidemiological

studies of HRV, cardiac repolarization changes, and cardiac rhythm disorders provide limited evidence of associations with short-term exposure to SO_2. There was some suggestive evidence of an association between SO_2 exposure and HRV in the epidemiological studies, but the evidence from two human clinical studies were weak and inconsistent. Similarly, several studies observed positive associations between ambient SO_2 concentrations and ED visits or hospital admissions for cardiovascular diseases, but results were not consistent across studies and specific cardiovascular disease outcomes. In general, most epidemiological studies observed that these cardiac outcomes were associated more strongly with PM compared to SO_2. In the limited studies that examined potential confounding by copollutants using multipollutant models, the SO_2 effect was generally found to diminish with adjustment for PM indices or CO.

Given the lack of coherence among the cardiovascular outcomes examined and the limited evidence available to evaluate potential confounding and interaction by copollutants, the overall evidence for cardiovascular health effects following exposure to ambient SO_2 is weak and insufficient to make a causal determination.

3.2.3. Other Effects Associated with Short-Term SO_2 Exposure

The short-term effects of SO_2 on other organ systems were not examined in the previous review. A review of animal toxicological studies published since the 1982 AQCD indicates a limited number of research inquiries addressing the systemic effects of short-term SO_2 exposure in various other organs. The most recent studies on these are summarized in Annex Tables E-6 through E-9 and E-22 through E-24.

Of note are three ex vivo acute exposure studies using SO_2 derivatives (sulfite and bisulfite) on hippocampal or dorsal root ganglion neurons isolated from Wistar rats (Du and Meng, 2004a; b; 2006). Perturbations were observed in potassium-, sodium-, and calcium-gated channels at concentrations of 0.01-100 μM. These authors speculated that such effects might correlate with the neurotoxicity that has been associated with SO_2 inhalation. However effects on the nervous system have generally been studied using chronic exposures ≥ 5 ppm SO_2. Effects observed at these levels are of questionable significance in evaluating the health effects at ambient levels. These studies are summarized in Annex Table E-6.

3.3. Mortality Associated with Short-Term SO_2 Exposure

3.3.1. Summary of Findings from the Previous Review

The studies available to review in the 1982 AQCD were mostly from historical data including London, England, and New York City air pollution episodes. Effects of SO_x (mainly SO_2) were investigated along with PM indices because they shared a common source, coal burning, and separating their associations with mortality was a challenge that many of the earlier episodic studies could not resolve. The SO_2 levels observed in these air pollution episodes were several orders of magnitude higher than the current average levels observed in U.S. cities (e.g., in the 1962 New York City episode, SO_2 in Manhattan peaked at 400 to 500 ppb). Some of these London and New York City studies suggested that PM, not SO_2, was associated with observed mortality, but the 1982 AQCD could not resolve the relative roles of these two pollutants and suggested that the clearest mortality associations were seen when both pollutants were at high levels (24-h avg values of both BS and SO_2 exceeding 1000 $\mu g/m^3$ [~400 ppb for SO_2]) and less so at lower ranges although the review of the studies and reanalyses found no clear evidence of a threshold for SO_2.

The 1986 Second Addendum to the 1982 AQCD reviewed more reanalyses of the London data and analyses of New York City, Pittsburgh, and Athens data. While these reanalyses and some new analyses confirmed earlier findings (and suggested stronger evidence of BS effects than of the SO_2 effects), given the remaining uncertainties with exposure error and statistical modeling, there was not sufficient information to quantitatively determine concentration-response relationships at lower concentrations of either PM or SO_2.

A series of short-term mortality effects studies in the late 1980s and early 1990s (Pope, 1989; Fairley, 1990; Dockery et al., 1992; Pope et al., 1992; Schwartz and Dockery, 1992) showed associations between mortality and PM indices at relatively low levels. Since then, a large number of epidemiological studies have investigated the adverse health effects of air pollution with hypotheses mainly focused on PM, and SO_2 was often analyzed as one of the potential confounders in these studies.

3.3.2. Associations of Mortality and Short-Term SO_2 Exposure in Multicity Studies and Meta-Analyses

In reviewing the range of SO_2 mortality effect estimates, multicity studies provide especially useful information because they analyze data from multiple cities using a consistent method, avoiding potential publication bias. There have been several multicity studies from the United States, Canada, and Europe, some of which will be discussed in the sections below. Meta-analysis studies also provide useful information on describing heterogeneity of effect estimates across studies; however, in contrast to multicity studies, the observed heterogeneity may reflect the variation in analytical approaches across studies. In addition, the effect estimate from a meta-analysis may be subject to publication bias, unless the analysis specifically examines such bias and adjusts for it. These studies, as well as many other single-city studies, are summarized in Annex Table F-5.

3.3.2.1.1. Multicity Studies

3.3.2.1.2. National Morbidity, Mortality, and Air Pollution Study

The time-series analysis of the largest 90 U.S. cities (Samet et al., 2000; reanalysis Dominici et al., 2003) in the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) is by far the largest multicity study conducted to date to investigate the mortality effects of air pollution, but its primary focus was PM_{10}. It should also be noted that, according to the table of mean pollution levels in the original report (Samet et al., 2000), SO_2 data were missing in 28 of 90 cities. Annual 24-h avg mean SO_2 levels ranged from 0.4 ppb (Riverside, CA) to 14.2 ppb (Pittsburgh, PA), with a mean of 5.9 ppb during the study period of 1987 to 1994. The analysis in the original report used GAM models with default convergence criteria. Dominici et al. (2003) reanalyzed the data using GAM with stringent convergence criteria as well as using GLM. It should be noted that this model's adjustment for weather effects employs more terms than other time-series studies in the literature, suggesting that the model adjusts for potential confounders more aggressively than the models in other studies.

Figure 3-10 shows the all-cause mortality excess risk estimates for SO_2 from Dominici et al. (2003). The mortality excess risk estimate with a 1-day lag was 0.60% (95% CI: 0.26, 0.95) per 10 ppb increase in 24-h avg SO_2. PM_{10} and O_3 (in summer) appeared to be more strongly associated with mortality compared to the other gaseous pollutants. The model with PM_{10} and

NO_2 resulted in an appreciably reduced SO_2 excess risk estimate, 0.38% (95% CI: -0.62, 1.38) per 10 ppb increase in 24-h avg SO_2. These results suggest that the observed SO_2-mortality association could be confounded by PM_{10} and NO_2. The authors stated that the results did not indicate associations of SO_2, NO_2, and CO with all-cause mortality.

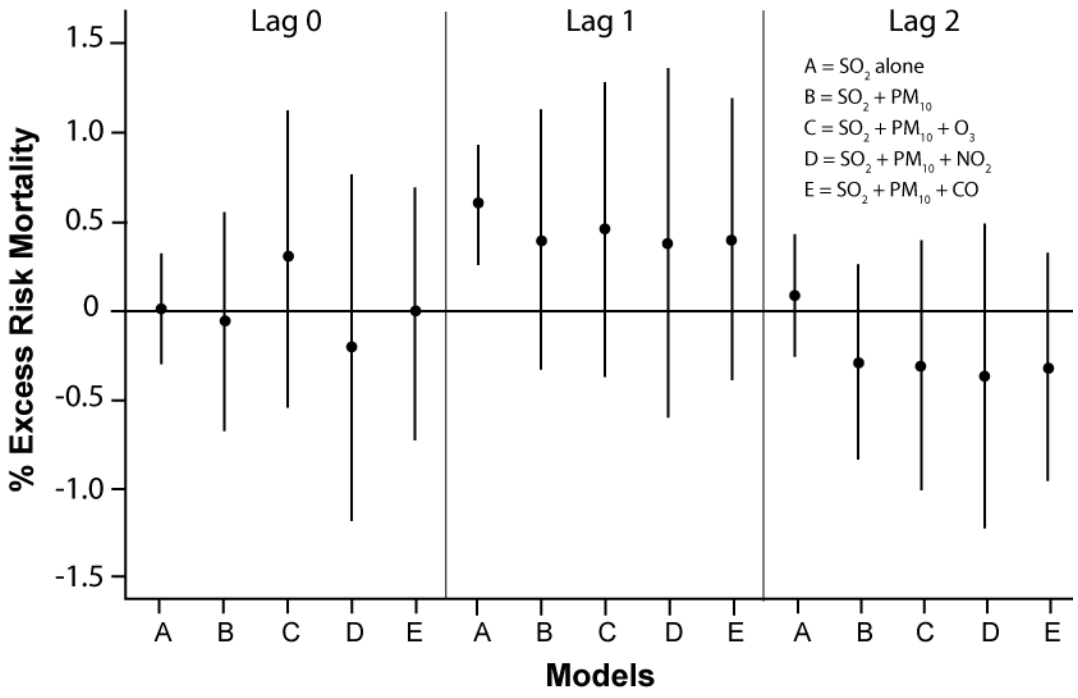

Figure 3-10. All cause mortality excess risk estimates for SO_2 from the National Morbidity, Mortality, and Air Pollution Study. Posterior means and 95% posterior intervals of national average estimates of SO_2 effects on all-cause mortality from non-external causes per 10 ppb increase in 24-h avg SO_2 at 0, 1, and 2-day lags within sets of the 62 cities with pollutant data available.

Source: Dominici et al. (2003).

3.3.2.1.3. Canadian Multicity Studies

There have been three Canadian multicity studies conducted by the same group of investigators examining the association between mortality and short-term exposure to air pollutants (Burnett et al., 1998; 2000b; 2004). This section focuses on Burnett et al. (2004) as this study is the most extensive Canadian multicity study, both in terms of the length and coverage of cities. The discussion in this study focused on NO_2, because NO_2 was the best

predictor of short-term mortality fluctuations among the pollutants. This was also the case in the Burnett et al. (1998) study of the gaseous pollutants in 11 Canadian cities. The mean 24-h avg SO_2 levels across the 12 cities was 5.8 ppb, with city means ranging from 1 ppb in Winnipeg to 10 ppb in Halifax. The population-weighted average was 5 ppb. The mean SO_2 levels in this study were similar to those in the NMMAPS (mean 24-h avg SO_2 levels across the 62 NMMAPS cities was 5.9 ppb).

All-cause (nonaccidental), cardiovascular, and respiratory mortality were analyzed in Burnett et al. (2004). For SO_2, $PM_{2.5}$, $PM_{10-2.5}$, PM_{10} (arithmetic addition of $PM_{2.5}$ and $PM_{10-2.5}$), CoH, and CO, the strongest mortality association was found at a 1-day lag, whereas for NO_2, it was the 3-day moving average (i.e., average of 0, 1, and 2-day lags), and for O_3, it was the 2-day moving average. The daily 24-h avg values showed stronger associations than the daily 1-h max values for all the gaseous pollutants and CoH except for O_3. The SO_2 all-cause mortality excess risk estimate was 0.74% (95% CI: 0.29, 1.19) per 10 ppb increase in the 24-h avg SO_2 with a 1-day lag. After adjusting for NO_2, the SO_2 effect estimate was reduced to 0.42% (95% CI: 0.01, 0.84), while the NO_2 effect estimate was only slightly affected. In this analysis, no regression analysis using both SO_2 and PM was conducted. The Burnett et al. (2000) analysis observed that the simultaneous inclusion of SO_2 and $PM_{2.5}$ in the model reduced the SO_2 effect estimate by half, whereas the $PM_{2.5}$ estimate was only slightly reduced. Overall, these results suggest that SO_2 was not an important predictor of daily mortality in the Canadian cities and that its mortality associations could be confounded with NO_2 or PM.

3.3.2.1.4. Air Pollution and Health: A European Approach

Several Air Pollution and Health: a European Approach (APHEA) analyses have reported SO_2 mortality excess risk estimates. Katsouyanni et al. (1997) examined the association of PM_{10}, BS, and SO_2 with all-cause mortality in 12 European cities using the standard APHEA (GLM) approach. The same data set was reanalyzed to adjust for the seasonal cycles (Samoli et al., 2001; 2003). The reanalysis by Samoli et al. (2003) produced results that were similar to those in the original analysis by Katsouyanni et al. (1997). Since the original analysis presented more results, including multipollutant model results, discussion will focus on this analysis.

The study by Katsouyanni et al. includes seven western European cities (Athens, Barcelona, Cologne, London, Lyon, Milan, and Paris) and five central eastern European cities

(Bratislava, Kracow, Lodz, Poznan, and Wroclaw). The data covered at least 5 consecutive years for each city within the years 1980 through 1992. The SO_2 levels in these cities were generally higher than in the United States or Canada, with the median 24-h avg SO_2 ranging from 5 ppb in Bratislava to 28 ppb in Kracow. Analysis was restricted to days when PM and SO_2 concentrations did not exceed 200 $\mu g/m^3$ (76 ppb for SO_2) to evaluate the effects of moderate to low exposures. The data were analyzed by each center separately following a standardized method, but the lag for the "best" model was allowed to vary in these cities from 0 to 3 days. The city-specific effect estimates were then examined in the second stage for source of heterogeneity using city-specific variables such as mean pollution and weather variables, accuracy of the air pollution measurements, health of the population, smoking prevalence, and geographical differences.

The city-specific estimates were found to be heterogeneous and, among the explanatory variables, only the separation between western and central eastern European cities resulted in more homogeneous groups. The all-cause mortality excess risk estimates were 1.14% (95% CI: 0.88, 1.39), 1.99% (95% CI: 1.15, 2.83), and 0.46% (95% CI: -0.23, 1.15) for all the 12 cities combined, western cities, and central eastern cities, respectively, per 10 ppb increase in the 24-h avg SO_2 at variable single-day lags. Zmirou et al. (1998) analyzed cardiovascular and respiratory mortality in 10 of the 12 APHEA cities and observed that the cause-specific mortality excess risk estimates were higher than those for all-cause mortality. As in the analyses of all-cause mortality, SO_2 effect estimates for these cause specific deaths were higher in western European cities than in central eastern European cities.

Seasonal analyses indicated that the summer estimate was slightly higher than the winter estimate in the western cities, but the difference was not statistically significant. The results for the two-pollutant model with SO_2 and BS were presented for the western cities, with a similar extent (~30%) of reductions in the estimates of both pollutants (1.31% [95% CI: 0.40, 2.23] for SO_2). Furthermore, for western cities, they estimated effects for SO_2 for days with high or low BS levels and the corresponding BS effects for days with high or low SO_2 levels and found that the effects were similar in the stratified data. From these results, Katsuoyanni et al. (1997) suggested that the effects of the two pollutants were independent.

Overall, the APHEA studies provide some suggestive evidence that the effect of short-term exposure to SO_2 on mortality is independent of PM. This is somewhat in contrast to the U.S. and

Canadian studies. The SO_2 levels were much higher in the European cities, but the type of PM constituents also might be different.

3.3.2.1.5. The Netherlands Study

In the Netherlands studies by Hoek et al. (Hoek et al., 2000; 2001; reanalysis, Hoek, 2003), the association between air pollutants and mortality were examined in a large population (14.8 million for the entire country) over the period of 1986 through 1994. The Netherlands were not part of the APHEA analysis. The median 24-h avg SO_2 level in the Netherlands was 4 ppb (6 ppb for the four major cities). All the pollutants examined, including PM_{10}, BS, O_3, NO_2, SO_2, CO, sulfate, and nitrate, were associated with all-cause mortality, and for single-day models, a 1-day lag showed the strongest associations for all the pollutants. The following effect estimates are all from the GLM models with natural splines for smoothing functions. The SO_2 excess risk estimate in a single-pollutant model was 1.31% (95% CI: 0.69, 1.93) per 10 ppb increase in 24-h avg SO_2 at a 1-day lag and 1.78% (95% CI: 0.86, 2.70) at an average of 0- to 6-day lag. Seasonal analyses showed slightly greater effect estimates during the summer compared to the winter. SO_2 was most highly correlated with BS ($r = 0.70$). The simultaneous inclusion of SO_2 and BS reduced the effect estimates for both pollutants (SO_2 effect estimate was 1.07% [95% CI: -0.27, 2.42] per 10 ppb increase with an average of 0- to 6-day lag of 24-h avg SO_2). PM_{10} was less correlated with SO_2 ($r = 0.65$), and the simultaneous inclusion of these pollutants resulted in an increase in the SO_2 effect estimate. These results from the analysis of the Netherlands data suggested some indication of confounding between SO_2 and BS.

Cause specific analysis showed larger excess risk estimates for COPD (3.61% [95% CI: -0.29, 7.67] per 10 ppb increase in the average of 0- through 6-day lags of 24-h avg SO_2) and pneumonia (6.56% [95% CI: 1.16, 12.24]) deaths compared to that from all causes, but because essentially all of the pollutants showed larger effect estimates for these sub-categories, it is difficult to interpret these estimates as effects of SO_2 alone. Similarly, the effect estimates for heart failure (7.1% [95% CI: 2.6, 11.7]) and thrombosis-related deaths (9.6% [95% CI: 3.1, 16.6]) were larger than that for total cardiovascular (2.7% [95% CI: 1.3, 4.1]) causes. Since the same pattern was seen for other pollutants as well, it is difficult to interpret these cause-specific effect estimates due to SO_2 alone or any one of the pollutants analyzed.

3.3.2.1.6. Other European Multicity Studies

Other European multicity studies were conducted in 8 Italian cities (Biggeri et al., 2005), 9 French cities (Le Tertre et al., 2002), and 13 Spanish cities (Ballester et al., 2002). The studies by Le Tertre et al. and Ballester et al. were conducted using GAM methods with the default convergence setting.

Biggeri et al. analyzed eight Italian cities (Turin, Milan, Verona, Ravenna, Bologna, Florence, Rome, and Palermo) for mortality and hospital admissions (mortality data were not available for Ravenna and Verona). The study period varied from city to city between 1990 and 1999. Only single-pollutant models were examined in this study. The SO_2 excess risk estimates were 4.14% (95% CI: 1.05, 7.33), 4.94% (95% CI: 0.41, 9.67), and 7.37% (95% CI: -3.58, 19.57) per 10 ppb increase with an average of 0- and 1-day lag of 24-h avg SO_2 for all-cause, cardiovascular, and respiratory deaths, respectively. Since all the pollutants showed positive associations with these mortality categories and the correlations among the pollutants were not presented, it is not clear how much of the observed associations are shared or confounded. The mortality excess risk estimates were not heterogeneous across cities for all the gaseous pollutants. It should be noted that in Turin, Milan, and Rome, the mean SO_2 values declined by 50% from the first half to the second half of the study period, while the levels of other pollutants declined by smaller fractions. This also complicates the interpretation of SO_2 effect estimates in this study, which are much higher than those from the APHEA studies.

The Le Tertre et al. study of nine French cities examined BS, SO_2, NO_2, and O_3 by generally following the APHEA protocol, but using GAM with default convergence criteria and using the average of lags 0 and 1 day for combined estimates. SO_2 data were not available in one of the nine cities (Toulouse). All four pollutants were positively associated with mortality outcomes. The study did not report descriptions of correlation among the pollutants or conduct multipollutant models, and therefore, it is difficult to assess the potential extent of confounding among these pollutants. The SO_2 effect estimates were homogeneous across cities, with the exception of Bordeaux, which was the only city that used strong acidity as a proxy for SO_2.

The Spanish Multicentre Study on Air Pollution and Mortality (EMECAM) examined the association of PM indices (i.e., PM_{10}, TSP, BS) and SO_2 with mortality in 13 cities (Ballester et al., 2002). These studies followed the APHEA protocol, but using the GAM approach. The daily mean 24-h avg SO_2 concentrations ranged from 3 to 17 ppb. In the seven cities where 1-h max

SO_2 data were also available, mean concentrations ranged from 21 to 43 ppb. The combined effect estimates for all-cause and respiratory mortality were statistically significant for both 24-h avg SO_2 and 1-h max SO_2. Controlling for PM indices substantially diminished the effect estimates for 24-h avg SO_2, but not for 1-h max SO_2. The authors reported that these results could indicate an independent impact of peak values of SO_2 more than an effect due to a longer exposure.

3.3.2.2. Meta-Analyses of Air Pollution-Related Mortality Studies

3.3.2.2.1. Meta-Analysis of All Criteria Pollutants

Stieb et al. (2002) reviewed time-series mortality studies published between 1985 and 2000, and conducted a meta-analysis to estimate combined effects for PM_{10}, CO, NO_2, O_3, and SO_2. Since many of the studies reviewed in that analysis used GAM with default convergence parameters, Stieb et al. (2003) updated the estimates by separating the GAM versus non-GAM studies. In addition, separate combined estimates were presented for single- and multipollutant models. There were more GAM estimates than non-GAM estimates for all the pollutants except for SO_2. For SO_2, there were 29 non-GAM estimates from single-pollutant models and 10 estimates from multipollutant models. The lags and multiday averaging used in these estimates varied. The combined estimate for all-cause mortality was 0.95% (95% CI: 0.64, 1.27) per 10 ppb increase in 24-h avg SO_2 from the single-pollutant models and 0.85% (95% CI: 0.32, 1.39) from the multipollutant models. Because these estimates are not from an identical set of studies, the difference (or lack of a difference, as in this case) between the two estimates may not necessarily be due to the effect of adding a copollutant in the model. Note that the data extraction procedure of this meta-analysis for the multipollutant models was to include from each study the multipollutant model that resulted in the greatest reduction in effect estimates compared with that observed in single-pollutant models. It should also be noted that all the multicity studies whose combined estimates have been discussed in the previous section were published after this meta-analysis.

3.3.2.2.2. Health Effects Institute Review of Air Pollution Studies in Asia

The Health Effects Institute (HEI) conducted a comprehensive review of air pollution health effects studies (HEI, 2004). They summarized the results from mortality and hospital

admission studies of the health effects of ambient air pollution in Asia (East, South, and Southeast) published in peer-reviewed scientific literature from 1980 through 2003. Of the 138 papers the report identified, most were studies conducted in East Asia (mainland China, Taipei, Hong Kong, South Korea, and Japan). The levels of SO_2 in these Asian cities were generally higher than in U.S. or Canadian cities, with more than half of these studies reporting mean 24-h avg SO_2 levels of > 10 ppb. Based on a comparison of the reported mean SO_2 levels from the same cities in different time periods, it is clear that the SO_2 levels declined significantly in the 1990s. The meta-analysis used the most recent estimate for each city to reflect recent pollution levels. Based on the criteria of having at least one year of data, model adjustment for major time-varying confounders, and reporting effect estimates per unit increase in air pollution, the meta-analysis included 28 time-series studies (11 from South Korea, 6 from mainland China, 6 from Hong Kong, and 1 each from Taipei, India, Singapore, Thailand, and Japan). The lags selected to compute combined estimates were inevitably variable; a systematic approach was used to favor the a priori lag stated in the study, followed by the most significant lag, and then the largest effect estimate.

Among the health outcomes examined in the meta-analysis, all-cause mortality was addressed in the largest number of studies (13 studies) and SO_2 was the most frequently studied pollutant (11 studies). The report generally focused on the results of single-pollutant models, as there were too few studies with results of comparable multipollutant models to allow meaningful analysis. The SO_2 mortality effect estimates showed evidence of heterogeneity. The combined estimate for all-cause mortality was 1.49% (95% CI: 0.86, 2.13) per 10 ppb increase in 24-h avg SO_2. One of the limitations noted in the report was that some degree of publication bias was present in these studies.

3.3.3. Evidence of the Effect of SO_2 on Mortality from an Intervention Study

Many time-series studies provide estimates of excess risk of mortality, but a question remains as to the likelihood of a reduction in deaths when SO_2 levels are actually reduced. A sudden change in regulation in Hong Kong in July 1990 required the conversion to fuel oil with low sulfur content. The reduction in respiratory symptoms among children living in the polluted district in Hong Kong after the intervention were previously discussed in Section 3.1.6. Hedley

et al. (2002) examined changes in mortality rates following the intervention. The SO_2 levels after the intervention declined about 50% (from about 17 ppb to 8 ppb), but the levels for PM_{10}, NO_2, and sulfate did not change and O_3 levels slightly increased. The seasonal mortality analysis results showed that the apparent reduction in seasonal death rate occurred only during the first winter, and this was followed by a rebound (i.e., higher than expected death rate) in the following winter, then returned to the expected pattern three to five years after the intervention. Using Poisson regression of the monthly deaths, the average annual trend in death rate significantly declined after the intervention for all causes (2.1%), respiratory causes (3.9%), and cardiovascular causes (2.0%), but not from other causes. These results seem to suggest that a reduction in SO_2 leads to an immediate reduction in deaths and a continuing decline in the annual trend in death rates. Hedley et al. estimated that the expected average gain in life expectancy per year due to the lower SO_2 levels was 20 days for females and 41 days for males.

Interpreting these results is somewhat complicated by an upward trend in mortality across the intervention point, which the authors noted was due to increased population size and aging. The results suggest that such an upward trend is less steep after the introduction of low sulfur fuel. While the Poisson regression model of monthly deaths does adjust for trend and seasonal cycles, the regression model does not specifically address the influence of influenza epidemics, which can vary from year to year. This issue also applies to the analysis of warm to cool season change in death rates. The most prominent feature of the time-series plot (or the fitted annual cycle of monthly deaths) presented in this study is the lack of a winter peak for respiratory and all-cause mortality during the year immediately following the intervention. Much could be made of this lack of a winter peak, but no discussion of the potential impact of (or a lack of) influenza epidemics is provided. These issues complicate the interpretation of the estimated decline in upward trend of mortality rate or the apparent lack of winter peak.

The decline in mortality following the intervention does not preclude the possibility that other constituents of the pollution mixture that share the same source as SO_2 are responsible for the adverse effects. Even though PM_{10} levels before and after the intervention were stable in Hong Kong, it is possible that constituents that do not explain a major fraction of PM may have declined. As also noted previously in Section 3.1.6, Hedley et al. (2006) noted large reductions in ambient nickel and vanadium concomitantly with reductions of sulfur after the intervention. SO_2 also may be serving as a modifier of the effect of respirable particles. Thus, while the Hong

Kong data are supportive of SO_2-mortality effects, the possibility remains that mortality effects may be caused by constituents of SO_2-associated sources.

3.3.4. Summary of Evidence on the Effect of Short-Term SO_2 Exposure on Mortality

The epidemiological evidence on the effect of short-term exposure to SO_2 on all-cause (nonaccidental) and cardiopulmonary mortality is *suggestive but not sufficient to infer a causal relationship* at ambient concentrations. The epidemiological studies are generally consistent in reporting positive associations between SO_2 and mortality; however, there was a lack of robustness of the observed associations to adjustment for copollutants.

Figure 3-11 presents all-cause SO_2 mortality excess risk estimates from the multicity studies and meta-analyses. The mortality effect estimates from single-pollutant models range from 0.6% (NMMAPS) to 4.1% (Italian 8-cities study) per 10 ppb increase in 24-h avg SO_2 concentrations, but given the large confidence band in the Italian study, a more stable range may be 0.6 to 2%. It is noteworthy that the SO_2 effect estimates for the NMMAPS and Canadian 12-city studies are quite comparable (0.6 and 0.7%, respectively), considering the differences in the modeling approach. The heterogeneity of estimates in the multicity studies and meta-analyses may be due to several factors, including the differences in model specifications, averaging/lag time, SO_2 levels, and effect-modifying factors. Only the APHEA study examined possible sources of heterogeneity for SO_2-related mortality. They examined several potential effect modifiers such as the mean levels of pollution and weather variables, accuracy of the air pollution measurements, health of the population, smoking prevalence, and geographical differences. The only variable that could explain the heterogeneity of city-specific effect estimates was the geographic separation (western versus central eastern European cities) for both SO_2 and BS, but heterogeneity in the SO_2 effect estimates remained within the western cities.

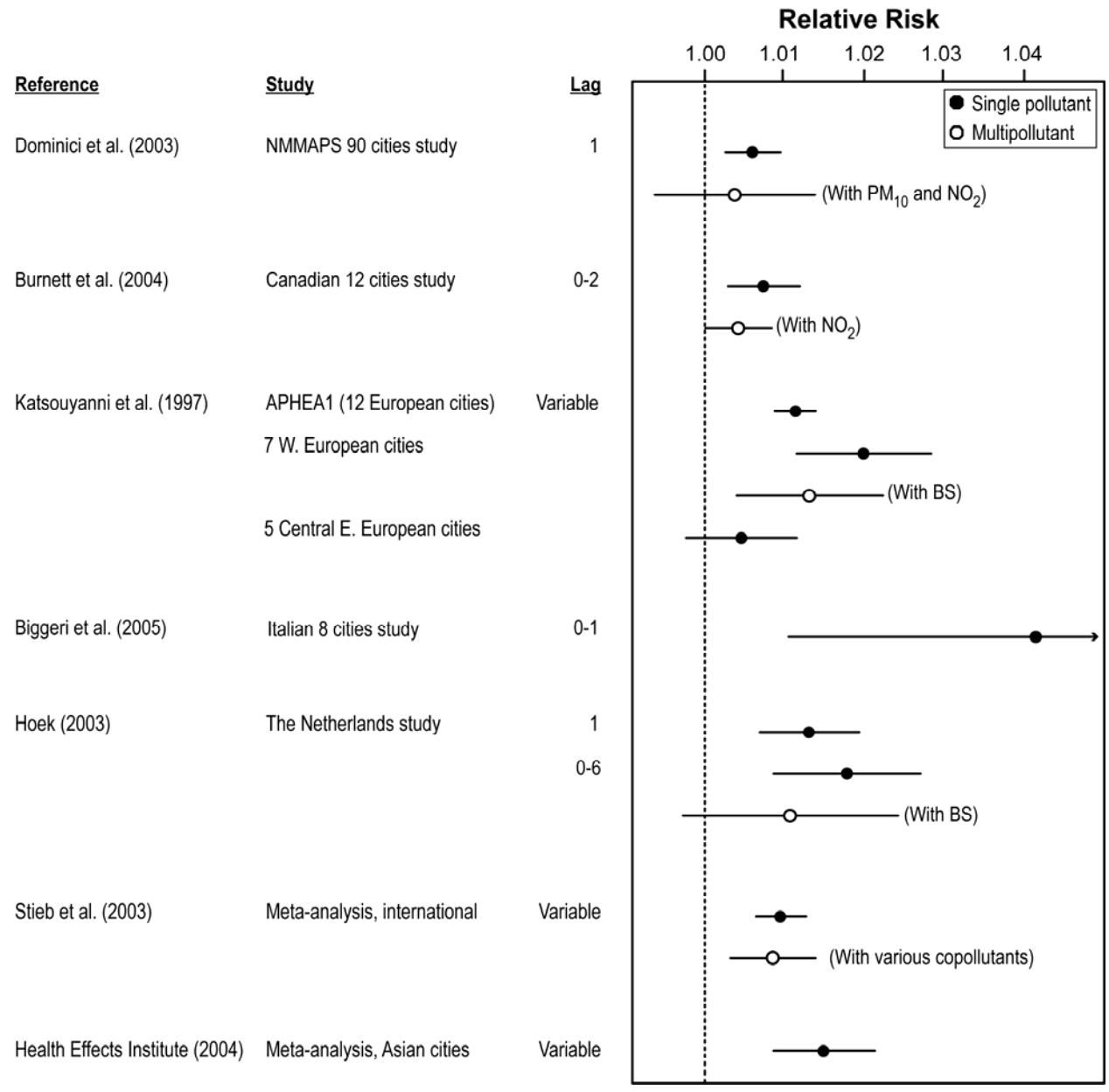

Figure 3-11. Relative risks (95% CI) of SO_2-associated all-cause (nonaccidental) mortality, with and without copollutant adjustment, from multicity and meta-analysis studies. Effect estimates are standardized per 10 ppb increase in 24-h avg SO_2 concentrations. For multipollutant models, results from the models that resulted in the greatest reduction in the SO_2 effects are shown. (NMMAPS = National Morbidity, Mortality, and Air Pollution Study; APHEA = Air Pollution and Health: a European Approach)

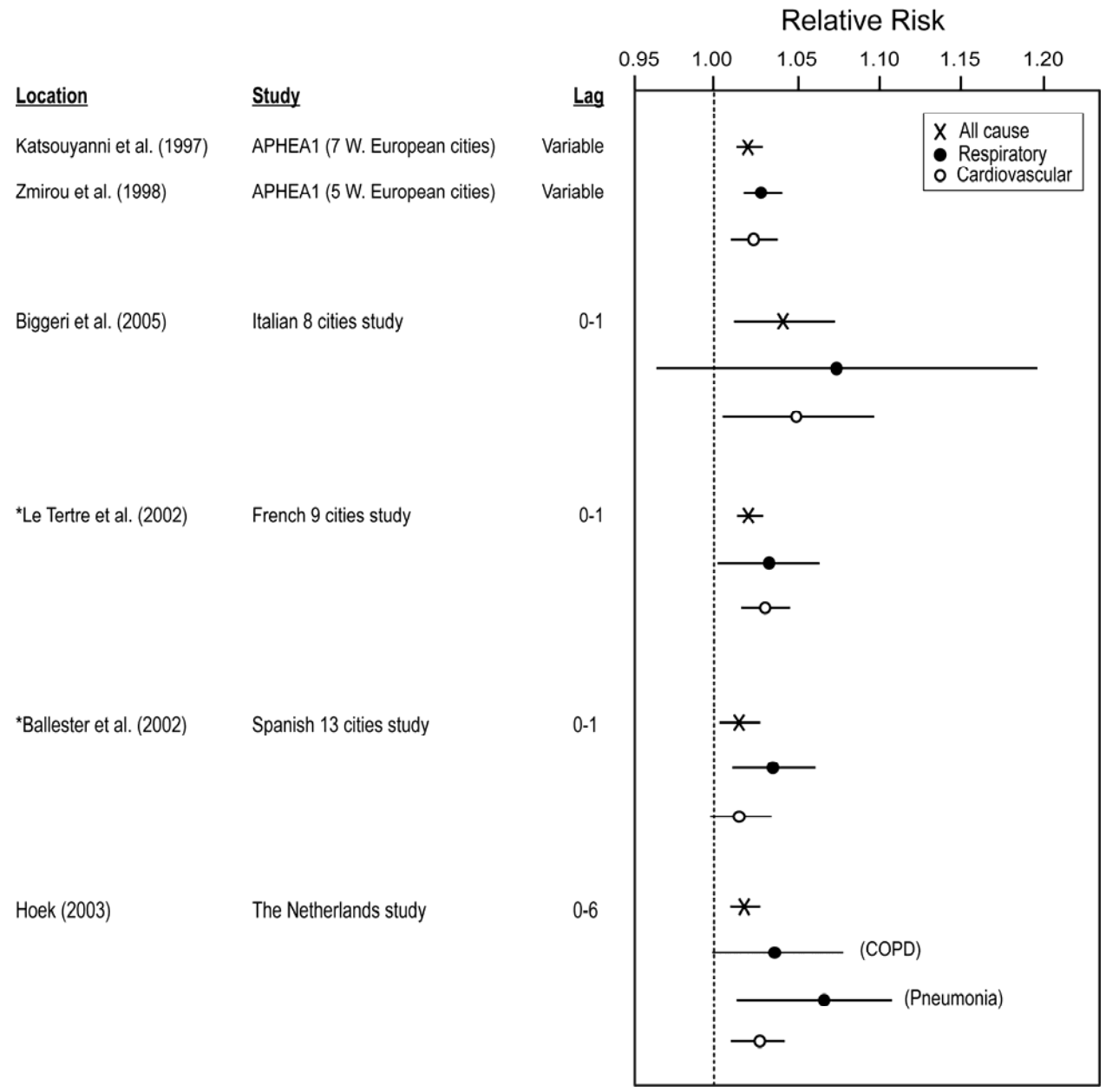

Figure 3-12. Relative risks (95% CI) of SO_2-associated mortality for all (nonaccidental), respiratory, and cardiovascular causes from multicity studies. Effect estimates are standardized per 10 ppb increase in 24-h avg SO_2 concentrations. (APHEA = Air Pollution and Health: a European Approach)

*Note: Le Tertre et alF. (2002) and Ballester et al. (2002) performed analyses using Poisson GAM with default convergence criteria.

Several multicity studies provided effect estimates for broad cause-specific categories, typically respiratory and cardiovascular mortality. A summary of these effect estimates, along with the all-cause mortality estimates for comparison, are presented in Figure 3-12. These results from multicity studies suggest that the mortality effect estimates for cardiovascular and respiratory causes were generally larger than that for all-cause mortality, though in some cases the effects were not statistically significant, possibly because of reduced statistical power by which to examine cause-specific associations. In these studies, the effect estimates for respiratory mortality were also found to be larger than the cardiovascular mortality effect estimates, suggesting a stronger association of SO_2 with respiratory mortality compared to cardiovascular mortality. This suggestive finding is consistent with the observed greater effects of SO_2 on respiratory morbidity compared to cardiovascular morbidity.

As shown previously in Figure 3-11, the mortality effect estimates from the multipollutant models in the multicity studies suggest some extent of confounding between SO_2 and PM and/or results from multicity studies generally suggest some evidence of confounding, in the sense of instability of effect estimates in multipollutant models. It should be noted, however, that interpretation of the single- versus multipollutant model results are complicated by potential interaction among copollutants and differing degrees of measurement error for correlated pollutants.

Very few studies specifically examined possible interactions among the copollutants. Katsouyanni et al. (1997) examined the effect estimates for SO_2 and BS in seven western European cities for subsets stratified by high and low levels of the other pollutant and found that the estimates were similar for days with low or high levels of the other pollutant. From these results, Katsuoyanni et al. suggested that the effects of SO_2 and BS were independent.

Other multi- or single-city studies did not consider examination of possible interaction effects between SO_2 and copollutants.

In summary, recent epidemiological studies have reported associations between mortality and SO_2, often at mean 24-h avg levels of < 10 ppb. The range of the excess risk estimates for SO_2 on all-cause mortality is 0.4 to 2% per 10 ppb increase in 24-h avg SO_2 in several multicity studies and meta-analyses. The effect estimates for more specific categories may be larger. The larger European study suggests that the observed heterogeneity in SO_2 effect estimates is at least in part regional. The intervention study from Hong Kong supports the idea that a reduction in

SO_2 levels results in a reduction in deaths, but this does not preclude the possibility that the causal agent is not SO_2 but rather something else that is associated with SO_2 sources. Results from the multicity studies suggest that SO_2-mortality excess risk estimates may be confounded to some extent by copollutants, making a definitive distribution of effects among the pollutants difficult. However, the interpretation of multipollutant model results also requires caution because of possible interaction among the copollutants and influence of varying measurement error. Very limited information was available to determine possible interaction effects between SO_2 and PM or other copollutants. Overall, the evidence that SO_2 is causally related to mortality at current ambient levels is suggestive, but limited by potential confounding and lack of understanding regarding the interaction of SO_2 with copollutants in the epidemiological data.

3.4. Morbidity Associated with Long-Term SO_2 Exposure

3.4.1. Summary of Findings from the Previous Review

The 1982 AQCD addressed some effects of long-term SO_2 exposure. It was reported that bronchoconstriction resulted from chronic exposure to 5.1 ppm SO_2 in dogs but not in monkeys. This increased pulmonary resistance was thought to occur as a result of morphological changes in the airway or hypersecretion of mucus leading to airway narrowing. However, there were no remarkable pulmonary pathological findings in monkeys and dogs in these studies. This could have been due to the conventional light microscopic examination applied, which could not detect alterations in surface membranes or subtle changes in cilia.

It was also noted that repeated exposures of rats ≥ 50 ppm SO_2 produced a chronic bronchitis similar to that seen in humans although there was no evidence to suggest that bronchitis developed in humans at ambient levels of SO_2. Furthermore, nasal mucosal alterations were observed in mice exposed to 10 ppm SO_2 for 72 h by inhalation. Lack of data on morphological effects of SO_2 at near ambient concentrations was noted. In addition, some alterations in lung host defenses were discussed with chronic exposure to SO_2 at doses exceeding ambient concentrations.

In the 1982 AQCD, only a few epidemiological studies provided sufficient quantitative evidence relating respiratory symptoms or pulmonary functions changes to long-term exposure

to SO_2. Briefly, a study by Lunn et al. (1967) in Sheffield, England, provided the strongest evidence of an association between pulmonary function decrements and increased frequency of lower respiratory tract symptoms in 5- to 6-year-old children chronically exposed to ambient BS (annual level of 230 to 301 $\mu g/m^3$) and SO_2 levels (69 to 105 ppb). A follow-up study in 1968 by Lunn (1970) found no effect with much lower levels of BS (range: 48, 169 $\mu g/m^3$) and SO_2 (range: 36, 97 ppb); it was suggested that this might be due to insufficient power to detect small health effect changes.

The 1986 Second Addendum presented three additional studies that examined the effects of long-term exposure on respiratory health. A study by Ware et al. (1986) reported that respiratory symptoms were associated with annual average TSP in the range of ~30 to 150 $\mu g/m^3$ in children (n = 8,380) from six U.S. studies. Only cough was found to be significantly associated with SO_2. Although the increase in symptoms did not appear concomitantly with any decrements in lung function, this may indicate different mechanisms of effect. Other studies by Chapman et al. (1985) and Dodge et al. (1985) also observed increased prevalence of cough among children and young adults living in areas of higher SO_2 concentrations; however, it was noted that the observed effects might have been due to intermittent high SO_2 peak concentrations.

In addition to respiratory effects from long-term exposure to SO_2, the potential carcinogenicity of SO_2 or other SO_x was also examined in the previous review. The 1982 AQCD concluded that little or no clear epidemiological evidence substantiated the hypothesized links between SO_2 or other SO_x and cancer, though there was some animal toxicological evidence that led to the conclusion that SO_2 may be considered a suspect carcinogen/cocarcinogen. There was very limited consideration of the effects of long-term exposure to SO_2 on other organ systems.

Since the 1982 AQCD and the 1986 Second Addendum, a number of animal toxicological and epidemiological studies have investigated the effect of long-term exposure to SO_2 on respiratory morbidity, including asthma, bronchitis and respiratory symptoms, lung function, morphological effects, and lung host defense. Additional studies have examined the effect of long-term SO_2 exposure on genotoxic and carcinogenic effects, cardiovascular effects, and prenatal and neonatal outcomes, which are also briefly discussed in this section.

3.4.2. Respiratory Effects Associated with Long-Term Exposure to SO_2

3.4.2.1. Asthma, Bronchitis, and Respiratory Symptoms

Several epidemiological studies have examined the association between long-term exposure to SO_2 and other air pollutants on asthma, bronchitis, and a variety of respiratory symptoms. These studies are summarized in Annex Table F-1. In the Six Cities Study of Air Pollution and Health, cross-sectional associations between air pollutants and respiratory symptoms were examined in 5,422 white children aged 10 to 12 years old from Watertown, MA, St. Louis, MO, Portage, WI, Kingston-Harriman, TN, Steubenville, OH, and Topeka, KS (Dockery et al., 1989). Annual means of 24 h avg SO_2 concentrations ranged from 3.5 ppb in Topeka to 27.8 ppb in Steubenville. Except for O_3, the correlations among pairs of pollution measures varied between 0.53 and 0.98. No associations were observed between SO_2 and a variety of respiratory symptoms, including bronchitis, chronic cough, chest illness, persistent wheeze, and asthma. Stronger associations were observed for PM indices.

Dockery et al. (1996) examined the respiratory health effects of acid aerosols in 13,369 white children aged 8 to 12 years old from 24 communities in the United States and Canada between 1988 and 1991. The city-specific annual mean SO_2 concentration was 4.8 ppb, with a range of 0.2 to 12.9 ppb. With the exception of the gaseous acids, nitrous and nitric acid, none of the particulate or gaseous pollutants, including SO_2, were associated with increased asthma or any asthmatic symptoms. Stronger associations with particulate pollutants were observed for bronchitis and bronchitic symptoms. For SO_2, the only significant association found was with chronic phlegm, with an OR of 1.19 (95% CI: 1.00, 1.40) per 5 ppb increase in SO_2.

Herbarth et al. (2001) performed a meta-analysis of three cross-sectional surveys conducted in East Germany investigating the relationship between lifetime exposure (from birth to completion of questionnaire survey) to SO_2 and TSP in children and the prevalence of chronic bronchitis. Using a logistic model that included variables on parental predisposition (mother or father with bronchitis) and environmental tobacco smoke exposure, the authors reported that the OR for bronchitis due to a lifetime exposure to SO_2 was 3.51 (95% CI: 2.56, 4.82) (the concentration change for which the OR was based was not presented). No associations were found between TSP and the prevalence of bronchitis in children.

As part of the international SAVIAH (Small-Area Variation in Air Pollution and Health) study, Pikhart et al. (2001) examined the respiratory health effects from long-term exposure to SO_2 in children (n = 6,959) from two central European cities with high pollution levels (Prague, Czech Republic, and Poznan, Poland). A novel technique was used to estimate the outdoor concentrations of SO_2 at a small-area level. Outdoor SO_2 was measured by passive samplers at 130 sites in the two cities during 2-week periods. Concentrations of SO_2 at each location in the study areas were estimated from these data by modeling using a geographic information system (GIS). The estimated mean exposure to outdoor SO_2 was 32 ppb, (range: 25, 37) in Prague and 31 ppb, (range: 17, 53) in Poznan. The prevalence of wheezing or whistling in the past 12 months was associated with SO_2 (OR of 1.08 [95% CI: 1.03, 1.13] per 5 ppb increase in SO_2). Moreover, the lifetime prevalence of wheezing or whistling (OR 1.03 [95% CI: 1.00, 1.07]) and lifetime prevalence of physician-diagnosed asthma (OR 1.09 [95% CI: 1.00, 1.19]) also were associated with SO_2 levels. In the SAVIAH study, the only other pollutant considered in relation to health outcomes was NO_2. An earlier publication by Pikhart et al. (2000) presented preliminary results of the Prague data and indicated that the observed associations between NO_2 and respiratory symptoms were generally similar to that of SO_2.

The International Study of Asthma and Allergies in Children (ISAAC) included thousands of children in several European countries and Taiwan (Hirsch et al., 1999; Hwang et al., 2005; Penard-Morand et al., 2005; Ramadour et al., 2000; Studnicka et al., 1997). Pénard-Morand et al. examined the effect of long-term exposures to air pollution and prevalence of exercise-induced bronchial reactivity (EIB), flexural dermatitis, asthma, allergic rhinitis, and atopic dermatitis in 9,615 children aged 9 to 11 years in six French communities. Using 3-year averaged concentrations of SO_2, the investigators reported that the prevalence of exercise-induced bronchial reactivity, lifetime asthma, and allergic rhinitis were significantly associated with increases in SO_2 exposure. The estimated 3-year averaged concentration of SO_2 was 2 ppb in the low-exposure schools and 4 ppb in the high-exposure schools. In a single-pollutant model, the ORs were 2.37 (95% CI: 1.44, 3.77) for EIB and 1.58 (95% CI: 1.00, 2.46) for lifetime asthma per 5 ppb increase in SO_2. In this study, SO_2 was correlated with PM_{10} (r = 0.76) but not with O_3 (r = -0.02). Using a two-pollutant model that included PM_{10}, the associations of SO_2 with EIB and lifetime asthma were fairly robust (< 5% change).

In a German study of 5,421 children, the annual mean SO_2 concentration was associated with morning cough reported in the last 12 months, but not bronchitis (Hirsch et al., 1999). This study further observed that the association of SO_2 and other air pollutants with respiratory symptoms were stronger in nonatopic than in atopic children. The authors noted that these findings were in line with the hypothesis that these air pollutants induce nonspecific irritative rather than allergic inflammatory changes in the airway mucosa, as irritative effects would affect the clinical course in nonatopic children more strongly than in atopics whose symptoms are also determined by allergen exposure.

In contrast to the studies noted above, other studies using the ISAAC protocol did not observe an association between long-term exposure to SO_2 and respiratory symptoms. In France, (Ramadour et al., 2000) performed an epidemiological survey of 2,445 children aged 13 to 14 years living in communities with contrasting levels of air pollution to determine the relationship between long-term exposure to gaseous air pollutants and prevalence rate of rhinitis, asthma, and asthma symptoms. The average SO_2 concentrations during the 2-month survey period ranged from 7 ppb to 22 ppb across the seven communities. This study found no relationship between the mean levels of SO_2, NO_2, or O_3 and the above-mentioned symptoms. Another study of 843 children from eight nonurban communities in Austria did not observe consistent associations between SO_2 and prevalence of asthma and symptoms (Studnicka et al., 1997). Compared to the lowest SO_2 concentration category, the ORs in the higher SO_2 concentration categories (third and fourth quartiles) did not exceed one for any of the symptoms examined (wheeze, cough, bronchitis, and asthma).

A cohort study was conducted by (Goss et al., 2004) to examine the effect of air pollutants on a potentially susceptible population, patients with cystic fibrosis. Study participants included 11,484 patients (mean age 18.4 years) enrolled in the Cystic Fibrosis Foundation National Patient Registry in 1999–2000. Exposure was assessed by linking air pollution values from ambient monitors with the patient's home ZIP code. During the study period, the mean SO_2 concentration was 4.9 ppb (SD 2.6, IQR: 2.7, 5.9). This study found no association between SO_2 and the odds of having two or more pulmonary exacerbations. One of the limitations addressed by the authors was the lack of information regarding tobacco use or environmental tobacco smoke, an important risk factor for pulmonary exacerbations.

Several studies examined the effects of long-term exposure to SO_2 on asthma, bronchitis, and respiratory symptoms. The studies reported positive associations in children; the notable exception was the Harvard Six Cities Study. However, there were inconsistencies in the results observed: some found effects on bronchitic but not asthmatic symptoms; others found the converse. A major limitation was that some subjects were asked to recall prevalence of symptoms in the last 12 months or in a lifetime; such long recall periods may have caused significant recall bias. Another concern is the high correlation of long-term average SO_2 and copollutant concentrations, particularly PM, and the very limited evaluation of potential confounding in these studies. Overall, while the evidence is suggestive, the variety of outcomes examined and the inconsistencies in the observed results make it difficult to assess the direct impact of long-term exposure of SO_2 on asthma, bronchitis, or respiratory symptoms.

3.4.2.2. Lung Function

Only a few new animal toxicological studies involving longer-term inhalation exposures to SO_2 were conducted since the last review. These studies are summarized here and in Annex Table E-1. Rabbits that were neonatally immunized to Alternaria tenuis and exposed to 5 ppm SO_2 for 13 weeks beginning in the neonatal period (Douglas et al., 1994) did not demonstrate alterations in lung resistance, dynamic compliance, trans-pulmonary pressure, tidal volume, respiration rate or minute volume. Similarly, no changes in physiological function were noted in dogs exposed to 15 ppm SO_2 for 2 h/day and 4-5 days/week for 5 months (Scanlon et al., 1987), although changes were noted at 50 ppm. However, Smith et al. (1989) found decreased residual volume and quasistatic compliance in rats at 4 months of exposure to 1 ppm SO_2 for 5 h/day and 5 days/week.

Only a limited number of epidemiological studies examined the association between long-term exposure to SO_2 and changes in lung function. The Harvard Six Cities Study by Dockery et al. (1989) reported that no associations were observed between lung function and long-term exposure to air pollution, including SO_2, in a cohort of more than 5,000 children. An analysis of NHANES II data by Schwartz (1989), which included information on children and youths from 44 cities but was limited by a cross-sectional study design, also did not observe an association with SO_2, though inverse associations of FVC and FEV_1 with annual concentrations of TSP, NO_2 and O_3 were found. Additional studies conducted in Europe observed mixed results.

In a longitudinal cohort study of 1,150 children in nine communities in Austria, Frischer et al. (1999) examined the effect of long-term exposure to air pollutants on lung function. Lung function was measured in the spring and fall over a 3-year period from 1994 through 1996. Annual mean SO_2 concentrations ranged from 2 to 6 ppb across the nine communities. The authors reported no consistent associations between SO_2, PM_{10}, or NO_2 and lung function. For SO_2, a negative parameter estimate was observed during the summer, but a positive estimate was found during the winter period. Horak et al. (2002a; b) extended the study of Frischer et al. (1999) with an additional year of data. The mean SO_2 concentration was 6 ppb in the winter and 3 ppb in the summer. This study found a positive association between wintertime SO_2 concentrations and changes in FVC, which became null with PM_{10} in a two-pollutant model.

Jedrychowski et al. (1999) conducted a prospective cohort study of 1,001 preadolescent children from two areas of Krakow, Poland, that differed in ambient air pollutants. In the city center, which had higher pollution area, the mean annual level of SO_2 was 16.7 ppb (SD 12.5). In comparison, the mean annual SO_2 level in the control area was 12.1 ppb (SD 8.4). A similar difference in TSP levels was observed between the city center and control area. The adjusted ORs comparing the city center to the control area for the occurrence of slower lung function growth over a two-year period were 2.10 (95% CI: 1.27, 3.46) for FVC and 2.10 (95% CI: 1.27, 3.48) for FEV_1 in boys. The adjusted ORs for girls were 1.54 (95% CI: 0.89, 2.64) for FVC and 1.51 (95% CI: 0.90, 2.53) for FEV_1. However, as both TSP and SO_2 levels were higher in the city center, the observed effects on lung function growth cannot be specifically attributable to SO_2.

One notable study examined the potential effect of long-term exposure to air pollution on lung function in adults. The study by Ackermann-Liebrich et al. (1997) included 9,651 adults aged 18 to 60 years old residing in eight different areas in Switzerland (Study on Air Pollution and Lung Diseases in Adults [SAPALDIA]). They observed a 0.1% decrease in FEV_1 per 5 ppb increase in SO_2 for adults. Significant associations also were observed for PM_{10} and NO_2. The limited number of study areas and high intercorrelation between the pollutants made it difficult to assess the effect of an individual pollutant. The authors concluded that air pollution from fossil fuel combustion, which was the main source of air pollution for SO_2, NO_2, and PM_{10} in Switzerland, was associated with decrements in lung function parameters in this study.

Collectively, the results from the limited number of animal toxicological and epidemiological studies do not give support to long-term exposure to ambient SO_2 having a detrimental effect on lung function.

3.4.2.3. Morphological Effects

Three animal toxicological studies of morphological effects resulting from subacute to chronic SO_2 exposures have been published since the 1982 AQCD. These studies are summarized in Annex Table E-11. No alveolar lesions (including electron microscopic evaluation) or changes in numbers of tracheal secretory cells were observed in guinea pigs exposed to 1 ppm SO_2 for 3 h/day for 6 days (Conner et al., 1985). No pulmonary or nasal lesions were observed in rats exposed to 5 ppm SO_2 for 5 days/week for 4 weeks (Wolff et al., 1989). A weakness of the latter study is that histopathological methods were not reported. However, a third study reported histopathological changes in the respiratory system involving lesions in the bronchioles. Smith et al. (1989) exposed rats for 4 to 8 months to 1 ppm SO_2 for 5 h/day and 5 days/week and observed increased incidence of bronchiolar epithelial hyperplasia and a small increase (12%) in numbers of nonciliated epithelial cells in terminal respiratory bronchioles at 4 but not 8 months of exposure. A limitation of the study was the examination of a single concentration, which does not allow for concentration-response assessment or identification of a no-effect-level.

In summary, results from these animal toxicological studies do not support an association between long-term exposure to ambient SO_2 and prolonged effects on lung morphology.

3.4.2.4. Lung Host Defense

The 1982 AQCD reported some detrimental effects of SO_2 on lung host defenses that generally occurred at concentrations exceeding ambient exposure concentrations. In rats exposed to 0.1 ppm SO_2 for ~2 to 3 weeks, clearance of labeled particles from the lung was accelerated at 10 and 23 days following exposure. In rats exposed to 1 ppm for ~2 to 3 weeks, clearance was accelerated at 10 days and slowed down at 25 days. Tracheal mucus flow was decreased with a 1-year exposure of dogs to 1 ppm SO_2, but was unaffected by a 30-minute exposure of donkeys to 25 ppm SO_2. Studies in mice suggested no effect on susceptibility to bacterial infection with

exposure to SO_2 concentrations of ≤ 5 ppm for 3 months. Antiviral defenses were impaired in mice exposed to 7-10 ppm SO_2 for 7 days. No alterations in pulmonary immune system were reported with chronic exposure of mice to 2 ppm SO_2.

Several studies on lung host defense have been conducted since the last review and are summarized in Annex Table E-4. Only one study published after the last review evaluated mucociliary clearance in rats after exposure to SO_2. In this subchronic study, no effect on clearance of radiolabeled particles from the lung was observed in rats exposed to 5 ppm SO_2 for 2 h/day for 4 weeks (Wolff et al., 1989). These findings are in contrast to the altered clearance reported in the 1982 AQCD. Three other recent studies were conducted evaluating the effects of 10 ppm SO_2 on immune responses.

In summary, animal toxicological studies do not provide much evidence for long-term exposure to ambient SO_2 having detrimental effects on lung host defense.

3.4.2.5. SO_2 Interactions with PM and Other Mixtures

An elegant series of experiments was conducted in dogs exposed to 0.31 mg/m^3 neutral sulfite aerosol for 22.5 h/day for 290 days (Heyder et al., 1992). The aerosol particles were submicron in size. These studies are summarized in Annex Table E-14. Although sulfite particles are not usually found in nature, they were engineered and used in these studies for the purpose of delivering SO_2-like reactivity to the lower respiratory tract. It should be noted that the reactivity of SO_2 is due to the IV-valent sulfur, a feature shared by sulfite but not sulfate which has VI-valent sulfur. The concentration of sulfite particles used in these studies was comparable to ambient levels of SO_2 on smog-alert days in Germany (i.e., 0.25 ppm). Important findings from these studies included a significant decrease in specific lung compliance and increase in alveolar-capillary permeability in sulfite-exposed dogs compared with controls (Maier et al., 1992; Schulz et al., 1992). In addition, macrophage respiratory burst activity and phagocytic capacity were significantly decreased while intrapulmonary particle transport to the larynx was increased (Maier et al., 1992; Kreyling et al., 1992). Morphological effects included hyperplastic changes in the respiratory mucosa of the nasal cavity and a moderate mononuclear cell infiltration. Loss of cilia in larynx and trachea was also noted. Some of the dogs also exhibited changes in the larynx and trachea (Takenaka et al., 1992). The authors concluded that chronic exposure to a low dose of sulfur (IV) aerosols can initiate a pathophysiological response.

A second set of studies was conducted by these same investigators in dogs exposed to sulfite and sulfate aerosols for 13 months (Heyder et al., 1999). These are summarized in Annex Table E-14. This protocol involved daily exposures of 16.5 h neutral sulfite aerosol at the same concentration used in the previous study followed by 6 hrs of an acidic sulfate aerosol at a concentration of 15.2 μmol/m^3 hydrogen ions. Both aerosols were about 1 μm MMAD in size. The authors stated that the dose received by each dog in 13 months was equivalent to what a person living for 70 years in an urban environment would receive. Results of these experiments demonstrated no change in lung compliance or other measure of lung function in dogs exposed consecutively to sulfite and sulfate each day (Schulz et al., 1999). Alveolar-capillary permeability was no different than in controls (Maier et al., 1999). Intrapulmonary particle transport to the larynx was decreased while transport to the tracheobronchial lymph nodes was increased in dogs exposed to both sulfite and sulfate (Kreyling et al., 1999). No alteration in the surfactant system was observed (Griese et al., 1999). Slight morphological effects were observed in the proximal alveolar region but not in the nasal cavity, larynx or trachea (Takenaka et al., 1999). The authors attributed this milder response to a modulating effect of the acidic sulfate aerosol. They concluded that inhalation of low levels of sulfite and hydrogen ion is not likely to constitute a health risk. These results are somewhat surprising given the pathophysiologic response to sulfite alone found by these same authors in a similar model. Possibly they indicate an antagonistic interaction between sulfate and sulfite.

In addition to studies examining the interaction of SO_2 and particles, other animal studies performed since the 1982 AQCD involved binary mixtures, laboratory-generated complex mixtures (e.g., simulation of regional air pollution), or actual ambient air mixtures (Annex Tables E-18 through E-20). Generally, most studies with ambient or laboratory-generated complex mixtures did not include an SO_2-only exposure group, making it difficult to determine the contribution of SO_x. No definitive conclusions can be made from these studies.

3.4.2.6. Summary of Evidence on the Effect of Long-Term Exposure on Respiratory Health

The overall epidemiological evidence on the respiratory effects of long-term exposure to SO_2 is *inadequate to infer the presence or absence of a causal relationship*. Studies that examined the effects of long-term exposure to SO_2 on asthma, bronchitis, and respiratory

symptoms observed positive associations in children. However, the variety of outcomes examined and the inconsistencies in the observed results make it difficult to assess the impact of long-term exposure of SO_2 on respiratory symptoms. In the limited number of studies examining the SO_2 associations with lung function, results were generally mixed. A major consideration in evaluating SO_2-related health effects in these epidemiological studies of long-term exposure is the high correlation among the pollutant levels observed, particularly between long-term average SO_2 and PM concentrations. The lack of evidence available to evaluate potential confounding by copollutants limits the ability to make a causal determination based on these studies.

A limited number of animal toxicological have examined the effect of long-term exposure to SO_2 on lung function. Results from these studies do not provide strong biological plausibility for effects of long-term exposure to SO_2 on respiratory morbidity. These studies observed no effects on physiological lung function at SO_2 concentrations ≤ 5 ppm in rabbits and dogs; however, one study found decreased residual volume and quasistatic compliance at 1 ppm SO_2 in rats. In addition, no morphological changes were found in guinea pigs exposed subacutely to 1 ppm SO_2, or in rats exposed subchronically to 5 ppm SO_2. While mild, bronchiolar epithelial hyperplasia was observed in rats exposed to 1 ppm for 4 months, this change was not apparent at 8 months. Furthermore, animal toxicological studies provide no evidence for decrements in lung host defense at or near ambient levels of SO_2.

Overall, results from the generally limited number of epidemiological and animal toxicological studies do not give support to respiratory effects from long-term exposure to SO_2 at ambient concentrations. However, chronic studies in dogs exposed to sulfite particles at concentrations equivalent to near ambient levels of SO_2 demonstrated a mild pathophysiologic response, suggesting that deposition of SO_x in the lower respiratory tract may lead to more profound effects on the respiratory system than those observed with gaseous SO_2 alone. These changes were modulated and in some cases reversed by sequential exposure to sulfate particles, suggesting an antagonistic interaction among the different PM in the mixture.

3.4.3. Carcinogenic Effects Associated with Long-Term Exposure

The 1982 AQCD concluded that little or no clear epidemiological evidence substantiated the hypothesized links between SO_2 or other SO_x and cancer. From the toxicological studies, it was noted that while there were some indications of carcinogenicity for both SO_2 and SO_2 +

benzo[*a*]pyrene (B[*a*]P), complex exposure regimens, problematic dose determinations, and/or inadequately reported experimental details led to the conclusion that SO_2 could only be considered a suspect carcinogen/cocarcinogen.

Since the last review, numerous studies have examined the genotoxic effects of SO_2. These are summarized in Annex Table E-22. SO_2 and its metabolite sulfite were found not to be mutagenic or to induce DNA damage in vitro (Pool et al., 1988; Pool-Zobel et al., 1990). However, inhalation studies demonstrated increased mouse bone marrow micronucleated polychromatic erythrocytes and DNA damage in cells isolated from various organs when mice were exposed for 4-6 h/day for 7 days to 5-30 ppm SO_2 (Meng et al., 2002; 2005; Ruan et al., 2003). These in vivo studies suggest that inhaled SO_2 may have systemic effects at high concentrations, but they are of questionable significance in evaluating the effects of SO_2 at ambient levels.

The carcinogenic potential of SO_2 was examined in animal toxicological studies which are summarized in Annex Table E-11. Gunnison et al. (1988) conducted a two-part study in which rats were exposed either for 21 weeks (6 h/day, 5 days/week) by inhalation to 0, 10, or 30 ppm SO_2, or for 21 weeks to two tungsten-supplemented, molybdenum-deficient diets. This latter regimen induced a condition of sulfite oxidase deficiency, resulting in elevated systemic levels of sulfite:bisulfite relative to control values (e.g., in plasma, from 0 to 44 μM; and in tracheal tissue, from 33 to 69 or 550 nmol/g wet weight). Beginning with week 4, some groups from each regimen received weekly tracheal installations of 1-mg B[*a*]P for 15 weeks. Overall results indicated that squamous cell carcinoma was not induced, or in the B[*a*]P groups coinduced or promoted, by SO_2 inhalation or elevated systemic sulfite:bisulfite. Researchers found a very high incidence of animals with tumors in the groups exposed to only B[*a*]P (128/144). As a result, carcinogenicity or cocarcinogenicity of SO_2 or sulfite:bisulfite could only have been detected as a shortening of tumor induction time or an increase in rate of tumor appearance, and neither was observed. As noted by the authors, these findings do not support the conclusion that SO_2 exposure enhances the carcinogenicity of B[*a*]P . It was proposed that SO_2 exposure, by elevating systemic sulfite:bisulfite, would generate glutathione-*S*-sulfonates, which in turn could inhibit glutathione *S*-transferase (GST) and reduce intracellular GSH and, thus, interfere with a major detoxication pathway for B[*a*]P. See Annex Table E-21 for further discussion from the work of Menzel et al., (1986).

Two similar studies were published that investigated the ability of 10 to 11 months of exposure (16 h/day) to 4 ppm SO_2, 6 ppm NO_2, or their combination to affect the carcinogenicity of either urban suspended PM (SPM) (Ito et al., 1997) or diesel exhaust particle (DEP) (Ohyama et al., 1999) extract-coated carbon particles. The former study found that, while exposure to SPM extract-coated carbon particles significantly increased pulmonary endocrine cell (PEC) hyperplasia, coexposure to SO_2, NO_2, or their combination was without additional affect. Also, irrespective of gas coexposure, SPM extract-coated carbon particles demonstrated a few PEC papillomas versus control frequencies of zero.

Using Syrian golden hamsters, Heinrich et al. (1989) investigated whether coexposure to 10 ppm SO_2 and 5 ppm NO_2 for 6 to 8 months (5 days/week, 19 hours/day) could enhance tumorigenesis induced by a single subcutaneous injection of diethylnitrosamine (DEN) during week 2. The combined gas exposure did not affect body weight gain and only minimally shortened survival times. Compared to the DEN groups, serial sacrifices of gas-exposed animals demonstrated progressively increasing numbers of tracheal mucosal cells and aberrant tracheal cell cilia. In the lung, effects related to gas mixtures were largely limited to a progressive type of alveolar lesion that involved the lining of bronchiolar epithelium and the appearance of pigment-containing AM and to a mild, diffuse thickening of the alveolar septa. Exposure to the combined gases by itself did not induce tumors of the upper respiratory tract, nor did it enhance the induction of such tumors by DEN.

In addition to the animal toxicological studies that examined the genotoxic and carcinogenic potential of SO_2, a limited number of recent epidemiologic studies have investigated the relationship between long-term exposure to SO_2 and lung cancer incidence and mortality. These studies are summarized in Annex Table F-7. Nyberg et al. (2000) conducted a case-control study of men aged 40 to 75 years with (n = 1,042) and without (n = 2,364) lung cancer in Stockholm County, Sweden. They mapped residence addresses to a GIS database to assign individual exposures to SO_2 from defined emission sources (mainly local oil-fueled residential heating). Available SO_2 measurement data were used to calibrate the model. In this study, SO_2 was considered an indicator of air pollution from residential heating. Exposure to NO_2, considered to be a marker of traffic pollution, also was evaluated in this study. The 90th percentile 30-year average SO_2 level was 30 ppb. After adjusting for potential confounders (e.g., smoking, occupational exposures), long-term average heating-related SO_2 exposure was not

associated with an increase in risk of lung cancer incidence. A weak association for the 30-year average traffic-related NO_2 exposure was observed.

Very similar results were reported in a Norwegian study by Nafstad et al. (2003). The study population is a cohort of 16,209 men who enrolled in a study of cardiovascular diseases in 1972. The Norwegian cancer registry identified 422 incident cases of lung cancer. SO_2 exposure data were modeled based on residence using data for observed concentrations and emission from point sources (e.g., industry and heating of buildings and private homes) and traffic. Once again, no association was observed between long-term exposure to SO_2 and lung cancer incidence.

Three additional European cohort studies examined the associations between long-term exposure to air pollution and lung cancer mortality (Beelen et al., 2008; Filleul et al., 2005; Nafstad et al., 2004) in cohorts ranging in size from 14,284 to 120,852 subjects, who were followed for 9 to > 20 years. Consistent with the results for lung cancer incidence, none of these studies observed an association between long-term SO_2 exposure and lung cancer mortality. These studies are discussed in further detail in Section 3.5.2.2.

Similar to the European cohort studies, studies conducted in the United States generally did not observe an association between long-term exposure to SO_2 and lung cancer mortality. In the reanalysis of the Harvard Six Cities study, Krewski et al. (2000) estimated a RR of 1.03 (95% CI: 0.91, 1.16) per 5 ppb increase in average SO_2 over the study period, while Pope et al. observed a positive but not statistically significant (RR ~1.04 per 5 ppb increase in average SO_2 from 1982 to 1998) association in the extended analysis of the American Cancer Society (ACS) cohort. The California Seventh-day Adventists study by Abbey et al. (1999) did observe a statistically significant association between lung cancer mortality and SO_2 (and most of the pollutants examined including PM_{10}, sulfate, O_3, and NO_2), but the number of lung cancer deaths in this cohort was very small (12 for female, 18 for male) and, therefore, it is difficult to interpret these estimates. More detailed discussions of these studies are provided in Section 3.5.2.2.

In conclusion, the toxicological studies indicate that SO_2 at high concentrations may cause DNA damage but fails to induce carcinogenesis, cocarcinogenesis, or tumor promotion. Furthermore, the epidemiological studies did not provide evidence that long-term exposure to SO_2 is associated with an excess risk of lung cancer.

3.4.4. Cardiovascular Effects Associated with Long-Term Exposure

The effects of SO_2 on the cardiovascular system were not addressed in the 1982 AQCD. Since then, animal toxicological studies have reported oxidation (Meng et al., 2003) and glutathione (GSH) depletion (Langley-Evans et al., 1996; Meng et al., 2003; Wu and Meng, 2003) in the hearts of rodents which were exposed by inhalation to SO_2. However, as concentrations of SO_2 used in these studies were 5 ppm and above, the oxidative injury observed is probably not relevant to cardiovascular effects seen at ambient levels of SO_2. These and other animal toxicology studies measuring cardiovascular endpoints are summarized in Annex Table E-5.

A recent epidemiological study examined the association between long-term exposure to air pollution, including SO_2, and one or more fatal or nonfatal cardiovascular events. In the Women's Health Initiative cohort study, Miller et al. (2007) studied 65,893 postmenopausal women between the ages of 50 and 79 years without previous cardiovascular disease in 36 U.S. metropolitan areas from 1994 to 1998. Subjects' exposures to air pollution were estimated using residents' five-digit ZIP code, assigning the annual mean levels of air pollutants measured at the nearest monitor. A total of 1,816 women had one or more fatal or nonfatal cardiovascular events, including 261 deaths from cardiovascular causes. Hazard ratios for the first cardiovascular event were estimated. The results for models that only included subjects with non-missing exposure data for all pollutants (n = 28,402 subjects, resulting in 879 cardiovascular events) are described here. In the single-pollutant models, $PM_{2.5}$ showed the strongest associations with cardiovascular events among the pollutants (Hazard Ratios = 1.24 [95% CI: 1.04, 1.48] per 10 $\mu g/m^3$ increase in annual average), followed by SO_2 (1.07 [95% CI: 0.95, 1.20] per 5 ppb increase in the annual average). In the multipollutant model where all the pollutants (i.e., $PM_{2.5}$, $PM_{10-2.5}$, CO, SO_2, NO_2, O_3) were included in the model, the $PM_{2.5}$ association with overall cardiovascular events was even stronger (1.53 [95% CI: 1.21, 1.94]). The association with SO_2 also became stronger (1.13 [95% CI: 0.98, 1.30]). Correlations among these pollutants were not described and, therefore, the extent of confounding among these pollutants in these associations could not be examined, but among all the air pollutants considered, $PM_{2.5}$ was clearly the best predictor of cardiovascular events.

The available toxicological and epidemiological evidence to assess the effect of long-term exposure to SO_2 on cardiovascular health is too limited to make any conclusions at this time.

3.4.5. Prenatal and Neonatal Outcomes Associated with Long-Term Exposure

Several animal toxicological studies examined developmental effects of SO_2 and are summarized in Anne Table E-7. No changes in birth weight or neurobehavioral development were noted in mouse pups prenatally exposed to 5-30 ppm SO_2 (1996), while some behavioral modifications were seen in adults exposed prenatally to these same levels (Fiore et al.). However, effects observed at such high concentrations of SO_2 are of questionable relevance.

In recent years, the effects of prenatal and neonatal exposure to air pollution have been examined in epidemiologic studies by several investigators. These studies are summarized in Annex Table F-8. The most common endpoints studied are low birth weight, preterm delivery, and measures of intrauterine growth. Preterm birth and low birth weight may result in serious long-term health outcomes for the infant. Preterm birth is the leading cause of infant mortality and is a major determinant of a variety of adverse neurodevelopmental outcomes and chronic adverse respiratory effects (Berkowitz and Papiernik, 1993). Low birth weight has also been linked with increased risk of infant mortality and morbidity. Other studies have examined associations between maternal exposure to ambient air pollution and sudden infant death syndrome (SIDS) and neonatal hospitalizations.

These studies analyzed air pollution data and birth certificates from a given area. In evaluating the results of these studies, it is important to consider the limitations of these data. For example, the reliability and validity of birth certificate data have been reviewed (Buescher et al., 1993; Piper et al., 1993) and have been found to vary in degrees of reliability by specific variables. The variables considered the most reliable include birth weight, maternal age, race, and insurance status. Whereas gestational age, parity and delivery type (vaginal vs. cesarean) were reasonably reliable, obstetrical complications and maternal lifestyle factors such as smoking and alcohol consumption were not reliable. Another concern in these studies regards adequate control for potential confounders. While most of these studies adequately controlled for maternal education, parity, age, and sex of child, many did not adjust for socioeconomic status, occupational exposures, indoor pollution levels, maternal smoking, alcohol use, prenatal care, or concurrent temperature exposures as fetal growth is associated with all of these factors. This makes overall comparisons across studies a difficult task.

While most studies analyzed average SO_2 exposure for the whole pregnancy, many also considered exposure during specific trimesters, or other time periods (e.g., first and last months of gestation). Different exposure periods have been examined because the biological mechanisms and timing of critical exposures that link air pollution to adverse birth outcomes are yet to be determined. For example, fetal growth is much more variable during the third trimester; therefore, exposure during the third trimester would have the greatest likelihood of an association. However, insufficient placentation during the first trimester may be associated with early environmental insult, whereby subsequent fetal growth is hindered. Similarly, it is possible that preterm delivery is associated with insufficient placentation resulting from early exposure. Furthermore, preterm delivery may be the result of acute exposures just prior to delivery.

Epidemiological studies examining the effects of air pollutants on low birth weight are summarized in Figure 3-13. Maisonet et al. (2001) examined the association between air pollution and low birth weight in six northeastern cities: Boston, MA; Hartford, CT; Philadelphia, PA; Pittsburgh, PA; Springfield, MA; and Washington, DC. The study population consisted of 89,557 singleton, full-term, live births (37-44 weeks of gestation) born between January 1994 and December 1996. Low birth weight was classified as < 2,500 g (5.5 lbs.). This study observed an association between low birth weight and SO_2 concentrations during each trimester among Caucasians; however, the association was not consistent in other races and ethnicities.

An excess risk for low birth weight associated with ambient SO_2 concentrations was reported by Dugandzic et al. (2006) in a large cohort study of 74,284 women with full-term, singleton births from 1988–2000 in Nova Scotia, Canada. The mean 24-h avg SO_2 concentration over the study period was 10 ppb (IQR 7). These investigators found that exposure only during the first trimester was associated with increased risk of low birth weight. The RR was 1.14 (95% CI: 1.04, 1.26) per 5 ppb increase in SO_2 level.

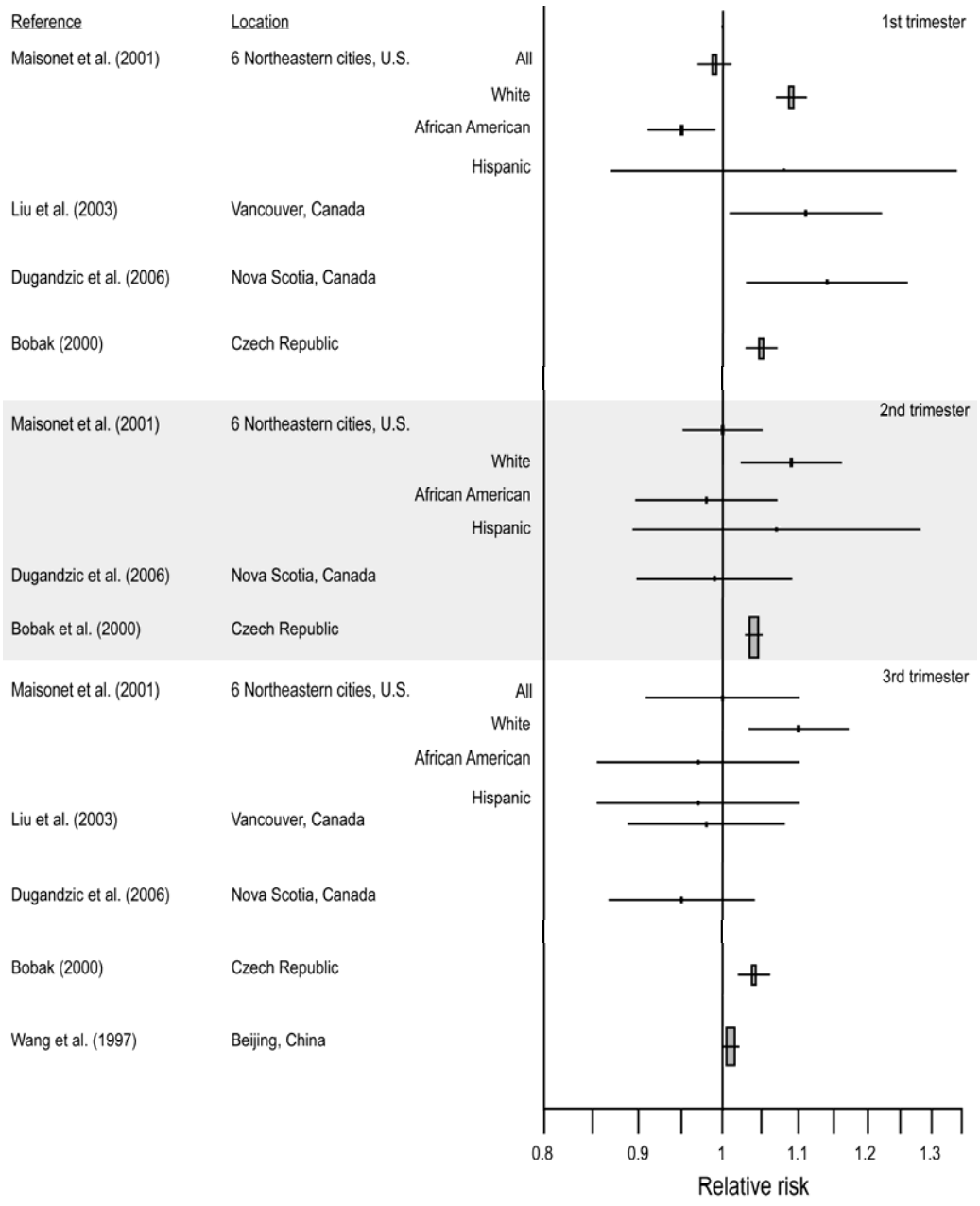

Figure 3-13. Relative risks (95% CI) for low birth weight, grouped by trimester of SO_2 exposure. Risk estimates are standardized per 5 ppb increase in SO_2 concentrations. The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.

Liu et al. (2003) found similar results in a study of pregnancy outcomes and air pollution in Vancouver, Canada. The mean 24-h avg SO_2 concentration was 4.9 ppb (IQR 7.7) from 1985 to 1998. Maternal exposure during the first month was associated with an increased risk of low

birth weight (OR 1.11 [95% CI: 1.01, 1.22]). Additional studies from the United States, Europe, Latin America and Asia have reported positive associations between low birth weight and maternal exposure to SO_2 during the first (Bell et al., 2007; Bobak, 2000; Ha et al., 2001; Mohorovic, 2004; Yang et al., 2003a), second (Bobak, 2000; Gouveia et al., 2003; Lee et al., 2003a) and third (Bobak, 2000; Lin et al., 2004; Wang et al., 1997) trimesters.

Preterm delivery, intrauterine growth retardation (IUGR), and birth defects are additional adverse birth outcomes that have been associated with ambient SO_2 levels. In a time-series analysis using data from four Pennsylvania counties, (Sagiv et al., 2005) reported that the mean 6-week SO_2 exposure prior to birth was associated with increased risk of preterm birth, with a RR of 1.05 (95% CI: 1.00, 1.10) per 5 ppb increase in SO_2. A 5 ppb increase in SO_2 concentrations three days before birth was associated with a RR of 1.02 (95% CI: 0.99, 1.05). The authors discussed two plausible mechanisms for the effects of air pollution on preterm birth: (1) changes in blood viscosity due to inflammation as a result of air pollution (citing Peters et al., 1997); and (2) maternal infection during pregnancy as a consequence of impaired immunity from air pollution exposure. Liu et al. (2003) reported that SO_2 exposure during the last month of pregnancy was associated with preterm birth, with an OR of 1.09 (95% CI: 1.01, 1.19) for a 5 ppb increase in SO_2, in Vancouver, Canada. Similar results were found for studies conducted in the Czech Republic (Bobak, 2000), Korea (Leem et al., 2006), and Beijing (Xu et al., 1995).

Liu et al. (2003) further reported that SO_2 exposure during the last month of pregnancy was associated with IUGR (OR 1.07 [95% CI: 1.01, 1.13]). However, in a later study in the Canadian cities of Calgary, Edmonton and Montreal, (Liu et al., 2007) did not observe associations between maternal exposure to SO_2 and increased risk of IUGR.

Two Brazilian studies examined exposure to SO_2 and neonatal deaths. Pereira et al. (1998) found a positive association between SO_2 and intrauterine mortality in São Paulo during a 2-year period, though the effect was sensitive to model specifications and did not support a concentration-response relationship. The most robust association was observed for an index of three gaseous pollutants (NO_2, SO_2, CO) with mortality. Lin et al. (2004) found that a 5 ppb increase in SO_2 was associated with an increase of 8.8% (95% CI: 5.8, 11.8). A similar relationship was found for PM_{10}. The creation of an index containing both PM_{10} and SO_2 allowed the observation of their cumulative effects on daily death counts. The result of this analysis was

similar in magnitude to the effect of SO_2 alone. An ecologic cohort study of infant mortality in the U.S. found no association with annual averages of SO_2 concentration (Lipfert et al., 2000a).

Gilboa et al. (2005) conducted a population-based case-control study to investigate the association between maternal exposure and air pollutant exposure during weeks 3-8 of pregnancy, the risk of selected cardiac birth defects and oral clefts in live births, and fetal deaths between 1997 and 2000 in seven Texas counties. When the highest quartile of exposure was compared to the lowest, the authors observed a positive association between SO_2 and isolated ventricular septal defects (OR 2.16 [95% CI: 1.51, 3.09]). Although this is the only study to have examined the effect of maternal exposure to SO_2 on birth defects, it supports the notion that the developing embryo and growing fetus is susceptible to maternal air pollution exposure.

Several studies examined adverse health outcomes in relation to SO_2 concentrations during the neonatal period. Dales et al. (2006) evaluated hospitalizations for respiratory disorders in neonates < 4 weeks of age from hospitals in 11 large Canadian cities during a 15-year study period (population-weighted average 24-h avg SO_2 of 4.3 ppb). The researchers observed a 5.5% (95% CI: 2.8, 8.3) excess risk in respiratory hospitalizations associated with a 10 ppb increase in 24-h avg SO_2 concentrations with a 2-d lag. This effect was slightly attenuated after adjusting for PM_{10} and gaseous copollutants. To investigate the influence of ambient SO_2 concentrations on SIDS, Dales et al. (2004) conducted a time-series analysis comparing daily rates of SIDS and daily SO_2 concentrations from 12 large, Canadian cities during a 16-year period. The mean 24-h avg SO_2 level across the 12 cities was 5.51 ppb (IQR 4.92). There was an 18.0% (95% CI: 4.4, 33.4) excess risk in SIDS incidence for a 10 ppb increase in 24-h avg SO_2 levels. The authors concluded that the effect of SO_2 was independent of sociodemographic factors, temporal trends, and weather.

In summary, epidemiological studies on birth outcomes have found suggestive positive associations between SO_2 exposure and low birth weight; however, toxicological studies provide very little biological plausibility for reproductive outcomes related to SO_2 exposure. The inconsistent results across trimesters of pregnancy and the lack of evidence regarding confounding by copollutants further limit the interpretation of these studies. The limited number of studies addressing preterm delivery, IUGR, birth defects, neonatal hospitalizations, and infant mortality make it difficult to draw conclusions regarding the effect of SO_2 on these outcomes.

3.4.6. Other Organ System Effects Associated with Long-Term Exposure

The 1982 AQCD presented only one chronic exposure study which was relevant to nervous system effects. Dogs were exposed for 68 months to a mixture of SO_2 and H_2SO_4. No effects on visual evoked brain potentials during or immediately after exposure to the SO_x mixture were observed. Since then, numerous studies have examined brain lipid content, lipid peroxidation and glutathione content and antioxidant enzymes following inhalation exposure of rodents to SO_2 at concentrations of 10 ppm or higher. Concentrations of 5 ppm or higher SO_2 were used in studies examining neurobehavior and neurodevelopment in mice. These studies are summarized in Annex Table E-6.

In the past 25 years, numerous animal toxicological studies have evaluated the effects of long-term SO_2 exposure on other organ systems such as reproductive, hematological, gastrointestinal, renal, lymphatic, and endocrine systems. Most of these studies used concentrations of SO_2 of 5 ppm or higher. Many of these studies examined alteration profiles of lipid peroxidation and antioxidant levels (Langley-Evans et al., 1996; Meng and Bai, 2004; Meng et al., 2003b) and are summarized in Annex Table E-7 through E-9 and E-22 through E-24.

3.5. Mortality Associated with Long-Term SO_2 Exposure

3.5.1. Summary of Findings from the Previous Review

At the time of the 1982 AQCD, the available studies on the effects of long-term exposure to SO_2 on mortality were all ecological cross-sectional studies. This study design could not take into consideration such confounders as cigarette smoking, occupational exposures, and social status. In addition, there were questions regarding how representative the aerometric data used were for community exposure. Therefore, it was concluded that the epidemiological studies did not provide valid quantitative data relating respiratory disease or other types of mortality to long-term (annual average) exposures to SO_2 or PM.

The 1986 Secondary Addendum reviewed more studies of this type, with information on more detailed components of PM (inhalable and fine particles, and particulate sulfate). While some studies suggested importance of the size of PM, the fundamental problem of the study

design made it difficult to interpret the effect estimates. The 1986 Secondary Addendum also reviewed a Japanese study in which the death rates from asthma and chronic bronchitis in a highly polluted section of Yokkaichi, an industrial city with large SO_2 emissions from the largest oil-fired power plant in Japan, were compared with those in a less polluted area of the same city. SO_x levels (measured using the lead peroxide method) averaged across several monitoring sites in the polluted harbor area ranged from around 1.0 to 2.0 mg/day (annual average) during 1964 through 1972 and then steadily declined to less than 0.5 mg/day in 1982. This is in contrast to levels consistently < 0.3 mg/day in the low pollution areas throughout 1967 through 1982. Annual average levels for other pollutants (i.e., NO_2, TSP, oxidants) monitored in the high pollution area were consistently low from 1974 through 1982. The results indicated elevated rates of chronic bronchitis mortality in the highly polluted area compared to the less polluted area, but the 1986 Secondary Addendum could not conclude that this was due to SO_2 alone, because sulfate or other particulate SO_x such as H_2SO_4 could have been responsible.

Several, more recent studies have examined long-term exposure effects of air pollution, including SO_2, on mortality. These studies are summarized in Annex Table F-9. As with short-term exposure studies, the focus of most of these studies was mainly on PM though some focused on traffic-related air pollution. They all used Cox proportional hazards regression models with adjustment for potential confounders. The designs of these studies were better than earlier cross-sectional studies as the outcome and most of the potential confounders (e.g., smoking history, occupational exposure) were measured on an individual basis. However, the geographic scale and method for exposure estimates varied across these studies.

3.5.2. Associations of Mortality and Long-Term Exposure in Key Studies

3.5.2.1. U.S. Cohort Studies

3.5.2.1.1. Harvard Six Cities Studies

Dockery et al. (1993) conducted a prospective cohort study to study the effects of air pollution with the main focus on PM components in six U.S. cities. These cities were chosen based on levels of air pollution, with Portage, WI and Topeka, KS representing the least polluted cities and Steubenville, OH representing the most polluted city. Mean SO_2 levels ranged from

1.6 ppb in Topeka to 24.0 ppb in Steubenville from 1977 to 1985. Cox proportional hazards regression was conducted with data from a 14- to 16-year follow-up study of 8,111 adults in the six cities. Dockery et al. reported that lung cancer and cardiopulmonary mortality were more strongly associated with the concentrations of inhalable and fine PM, and sulfate particles, than with the levels of TSP, SO_2, NO_2, or acidity of the aerosol.

Krewski et al. (2000) conducted a sensitivity analysis of the Harvard Six Cities study and examined associations between gaseous pollutants (i.e., O_3, NO_2, SO_2, and CO) and mortality. SO_2 showed positive associations with total mortality (RR = 1.05 [95% CI: 1.02, 1.09] per 5 ppb increase in average SO_2 over the study period) and cardiopulmonary deaths (1.05 [95% CI: 1.00, 1.10]), but in this dataset SO_2 was highly correlated with $PM_{2.5}$ (r = 0.85), sulfate (r = 0.85), and NO_2 (r = 0.84).

3.5.2.1.2. American Cancer Society Cohort Studies

Pope et al. (1995) investigated associations between long-term exposure to PM and the mortality outcomes in the ACS cohort. Ambient air pollution data from 151 U.S. metropolitan areas in 1981 were linked with individual risk factors in 552,138 adults who resided in these areas when enrolled in the prospective study in 1982. Death outcomes were ascertained through 1989. $PM_{2.5}$ and sulfate were associated with total, cardiopulmonary, and lung cancer mortality, but not with mortality for all other causes. Gaseous pollutants were not analyzed in this study.

Krewski and co-investigators (Jerrett et al., 2003; Krewski et al., 2000) conducted an extensive sensitivity analysis of the Pope et al. (1995) ACS data, augmented with additional gaseous pollutants data. The mean SO_2 concentrations were 7.18 ppb in the warm season (April to September) and 11.24 ppb in the cool season (October to March). Among the gaseous pollutants examined, only SO_2 showed positive associations with mortality. The RR for total mortality was 1.06 (95% CI: 1.05, 1.07) per 5 ppb increase in the annual average SO_2. Analysis using SO_2 measured in different seasons produced a somewhat higher estimate for the warm season than that for the cool season (7% compared to 5% excess risk per 5 ppb increase). Although the subjects in the ACS cohort came from all regions of the United States, the majority of the 151 cities were located in the eastern United States, where both SO_2 and sulfate tend to be higher. $PM_{2.5}$ levels are also higher in the east. To address the influence of these spatial patterns, which may confound associations between mortality and these pollutants, Krewski et al. (2000)

conducted extensive two-stage regression modeling. In these models, the association between SO_2 and mortality was diminished but persisted after adjusting for sulfate, $PM_{2.5}$, and other variables. For example, in the spatial filtering model (which resulted in the largest reduction of the SO_2 effect estimate when sulfate was included), the SO_2 total mortality RR estimate was 1.07 (95% CI: 1.03, 1.11) in the single-pollutant model and 1.04 (95% CI: 1.02, 1.06) with sulfate in the two-pollutant model. The effect estimates for $PM_{2.5}$ and sulfate also were diminished when SO_2 was included in the models. The result further showed that SO_2 effect estimates were generally insensitive to adjustment for spatial correlation. Thus, these results suggest that the association between SO_2 and mortality may be confounded with PM, but the association cannot be accounted for by $PM_{2.5}$ or sulfate alone. Krewski et al. (2000) noted that their reanalysis of the ACS and Harvard Six Cities studies suggested that mortality might be attributed to more than one component of the complex mixture of ambient air pollutants in urban areas in the United States.

The original Pope et al. (1995) study and the Krewski et al. (2000) reanalysis both used the air pollution exposure estimates that are based on the average over the Metropolitan Statistical Area (MSA), which consists of multiple counties. To investigate the effects of geographic scale over which the air pollution exposures are averaged, Willis et al. (2003) reanalyzed the ACS cohort data using the exposure estimates averaged over the county scale, and compared the results with those based on the MSA-scale average exposure. Less than half of the cohort used in the MSA-based study was used in the county-scale based analysis, because of the limited availability of sulfate monitors and the reduced sample size due to the loss of subjects when using the five-digit ZIP codes. The mean (9.3 ppb versus 10.7 ppb) and range (0.0 to 29.3 ppb versus 0.0 to 27.2 ppb) of the MSA- and county-level SO_2 data sets were similar. In the analysis comparing the two-pollutant model with sulfate and SO_2, they found that the inclusion of SO_2 reduced sulfate effect estimates substantially (> 25%) in the MSA-scale model but not substantially (< 25%) in the county-scale model. In the MSA-level analysis (with 113 MSAs), the SO_2 RR estimate was 1.04 (95% CI: 1.02, 1.06) per 5 ppb increase, with sulfate in the model. In the county-level analysis (91 counties) with sulfate in the model, the corresponding estimate was smaller (1.02 [95% CI: 1.00, 1.05]). It should also be noted that the correlation between covariates were different between the MSA-level data and county-level data. The correlation between SO_2 and sulfate was 0.48 in the MSA-level data, but it was 0.56 in the county-level

data. The correlation between poverty rate and SO_2 was -0.16 in the MSA-level data, but it was 0.15 in the county-level data. Thus, the extent of confounding between SO_2 and PM components as well as among other covariates in the model can be affected by the geographic scale of aggregation of exposure estimates. It is not clear, however, if the smaller geographic scale increases or decreases exposure characterization error for SO_2, because a certain extent of smoothing (averaging) over distance may reduce very local concentration peaks that are not relevant to the city-wide population.

Pope et al. (2002) extended analysis of the ACS cohort with double the follow-up time (to 1998) and triple the number of deaths compared to the original Pope et al. (1995) study. In addition to $PM_{2.5}$, all the gaseous pollutant data were retrieved for the extended period and analyzed for their associations with death outcomes. As in the 1995 analysis, the air pollution exposure estimates were based on the MSA-level averages. $PM_{2.5}$ was associated with total, cardiopulmonary, and lung cancer mortality but not with deaths for all other causes. SO_2 was associated with all the mortality outcomes, including all other causes of deaths. The SO_2 RR estimate for total mortality was 1.03 (95% CI: 1.02, 1.05) per 5 ppb increase (1982 to 1998 average). The association of SO_2 with mortality for all other causes (sulfate also showed this pattern) makes it difficult to interpret the effect estimates. This lack of specificity for SO_2 (in contrast to PM) is not consistent with causal inference.

3.5.2.1.3. The EPRI-Washington University Veterans' Cohort Mortality Studies

Lipfert et al. (2000b) conducted an analysis of a national cohort of ~70,000 male U.S. military veterans who were diagnosed as hypertensive in the mid 1970s and were followed up for about 21 years (up to 1996). This cohort was 35% black and 57% were current smokers (81% of the cohort had been smokers at one time). $PM_{2.5}$, PM_{10}, $PM_{10\text{-}2.5}$, TSP, sulfate, CO, O_3, NO_2, SO_2, and lead were examined in this analysis. No mean or median level of SO_2 was reported. The county of residence at the time of entry to the study was used to estimate exposures. Four exposure periods (from 1960 to 1996) were defined, and deaths during each of the three most recent exposure periods were considered. The results for SO_2 were presented only qualitatively as part of their preliminary screening regression results. Lipfert et al. (2000b) noted that lead and SO_2 were not found to be associated with mortality, thus were not considered further. They also noted that the pollution effect estimates were sensitive to the regression model specification,

exposure periods, and the inclusion of ecological and individual variables. The authors reported that indications of concurrent mortality risks were found for NO_2 and peak O_3.

Lipfert et al. (2006b) examined associations between traffic density and mortality in the same cohort, whose follow-up period was extended to 2001. As in their 2000 study, four exposure periods were considered but included more recent years. The 95th percentiles of daily average in each of the exposure periods were considered for SO_2. For the 1997–2001 data period, the estimated mortality RR for SO_2 was 0.99 (95% CI: 0.97, 1.01) per 5 ppb increase in a single-pollutant model. They reported that traffic density was a better predictor of mortality than ambient air pollution variables with the possible exception of O_3. The log-transformed traffic density variable was only weakly correlated with SO_2 ($r = 0.32$) and $PM_{2.5}$ ($r = 0.50$) in this data set.

Lipfert et al. (2006a) further extended analysis of the veterans' cohort data to include the EPA's Speciation Trends Network (STN) data, which collected chemical components of $PM_{2.5}$. They analyzed the STN data for year 2002, again using county-level averages. $PM_{2.5}$ and gaseous pollutants data for 1999 through 2001 were also analyzed. As in the previous Lipfert et al. (2006) study, traffic density was the most important predictor of mortality, but associations were also seen for elemental carbon, vanadium, nickel, and nitrate. O_3, NO_2, and PM_{10} also showed positive but weaker associations. Once again, no associations were observed between long-term exposure to SO_2 and mortality.

3.5.2.1.4. Seventh-day Adventist Study

Abbey et al. (1999) investigated associations between long-term ambient concentrations of PM_{10}, sulfate, SO_2, O_3, and NO_2 (1973 through 1992) and mortality (1977 through 1992) in a cohort of 6,338 nonsmoking California Seventh-day Adventists. Monthly indices of ambient air pollutant concentrations at 348 monitoring stations throughout California were interpolated to ZIP codes according to home or work location of study participants, cumulated, and then averaged over time. They reported associations between PM_{10} and total mortality for males and nonmalignant respiratory mortality for both sexes. SO_2 was not associated with total mortality (RR 1.07 [95% CI: 0.92, 1.24] for males and 1.00 [95% CI: 0.88, 1.14] for females per 5 ppb increase in multiyear average SO_2), cardiopulmonary deaths, or respiratory mortality for either gender.

3.5.2.2. European Cohort Studies

A study by Beelen et al. (2008) examined associations between traffic-related air pollution and mortality. They analyzed data from the Netherlands Cohort Study on Diet and Cancer with 120,852 subjects who were followed from 1987 to 1996. BS, NO_2, SO_2, $PM_{2.5}$, and four types of traffic-exposure estimates were analyzed. While the local traffic component was estimated for BS, NO_2, and $PM_{2.5}$, no such attempt was made for SO_2, because there was "virtually no traffic contributions to this pollutant." Thus, only "background" SO_2 levels were reflected in the exposure estimates. Traffic intensity on the nearest road was associated with all-cause mortality and a larger RR was observed for respiratory mortality. Results were similar for BS, NO_2 and $PM_{2.5}$, but no associations were found for SO_2 (RR = 0.98 [95% CI: 0.93, 1.03] per 5 ppb increase in multiyear average SO_2).

Nafstad et al. (2004) investigated the association between mortality and long-term exposure to air pollution exposure in a cohort of Norwegian men followed from 1972–1973 through 1998. Data from 16,209 males (aged 0 to 49 years) living in Oslo, Norway, in 1972–1973 were linked with data from the Norwegian Death Register and with estimates of the average annual air pollution levels at the participants' home addresses. PM was not considered in this study because measurement methods changed during the study period. Exposure estimates for nitrogen oxides (NO_x) and SO_2 were constructed using models based on subject addresses, emission data for industry, heating, and traffic, and measured concentrations. While NO_x was associated with total, respiratory, lung cancer, and ischemic heart disease deaths, SO_2 did not show any associations with mortality. The authors noted that the SO_2 levels were reduced by a factor of 7 during the study period (from 5.6 ppb in 1974 to 0.8 ppb in 1995), whereas NO_x did not show any clear downward trend.

Filleul et al. (2005) investigated long-term effects of air pollution on mortality in 14,284 adults who resided in 24 areas from seven French cities when enrolled in the Air Pollution and Chronic Respiratory Diseases (PAARC) survey in 1974. Daily measurements of SO_2, TSP, BS, NO_2, and NO were made in the 24 areas for 3 years (1974 through 1976). Models were run before and after exclusion of six area monitors influenced by local traffic as determined by a NO:NO_2 ratio of > 3. Before exclusion of the six areas, none of the air pollutants was associated with mortality outcomes. After exclusion of these areas, analyses showed associations between total mortality and TSP, BS, NO_2, and NO but not SO_2 (RR = 1.01 [95% CI: 0.97, 1.06] per

5 ppb multiyear average) or acidimetric measurements. It should be noted that SO_2 levels in these French cities declined markedly between the 1974 through 1976 period and the 1990 through 1997 period by a factor of 2 to 3, depending on the city. The changes in air pollution levels over the study period complicate interpretation of reported effect estimates.

3.5.2.3. Cross-Sectional Analysis Using Small Geographic Scale

Elliott et al. (2007) examined associations of BS and SO_2 with mortality in Great Britain using a cross-sectional analysis. However, unlike the earlier ecological cross-sectional mortality analyses in the United States in which mortality rates and air pollution levels were compared using large geographic boundaries (i.e., MSAs or counties), in the Elliot et al. analysis, the mortality rates and air pollution were compared using a much smaller geographic unit, the electoral ward, with a mean area of 7.4 km^2 and a mean population of 5,301 per electoral ward. Death rates were computed for four successive 4-year periods from 1982 to 1994 and associated with 4-year exposure periods from 1966 to 1994. The number of deaths from all causes in the 10,520 wards was 420,776. Of note, SO_2 levels declined from 41.4 ppb in the 1966 to 1970 period to 12.2 ppb in 1990 to 1994. This type of analysis does not allow adjustments for individual risk factors, but the study did adjust for socioeconomic status data available for each ward from the 1991 census. Social deprivation and air pollution were more highly correlated in the earlier exposure windows. They observed associations for both BS and SO_2 and mortality outcomes. The estimated effects were stronger for respiratory illness than other causes of mortality for the most recent exposure period and most recent mortality period (when pollution levels were lower). The adjustment for social deprivation reduced the effect estimates for both pollutants. The adjusted mortality RRs for SO_2 for the pooled mortality periods using the most recent exposure windows were 1.021 (95% CI: 1.018, 1.024) for all causes, 1.015 (95% CI: 1.011, 1.019) for cardiovascular, and 1.064 (95% CI: 1.056, 1.072) for respiratory causes per 5 ppb increase in SO_2. The effect estimates for the most recent mortality period using the most recent exposure windows were larger. Simultaneous inclusion of BS and SO_2 reduced effect estimates for BS but not SO_2. Elliott et al. (2007) noted that the results were consistent with those reported in the Krewski et al. (2000) reanalysis of the ACS study. This analysis was ecological, but the exposure estimates in the smaller area compared to that in the U.S. cohort studies may have resulted in less exposure misclassification error, and the large underlying

population appears to be reflected in the narrow confidence bands of effect estimates. The results from this study suggest an association between long-term exposures (especially in recent years) to SO_2 and mortality.

3.5.3. Summary of Evidence on the Effect of Long-Term Exposure on Mortality

The available epidemiological evidence on the effect of long-term exposure to SO_2 on mortality is *inadequate to infer the presence or absence of a causal relationship* at this time. The ecological cross-sectional studies examined in the 1982 AQCD and 1986 Secondary Addendum found suggestive relationships between long-term exposure to SO_2 and mortality. However, there were concerns as to whether the observed association was due to SO_2 alone, because sulfate or other particulate SO_x such as H_2SO_4 could have been responsible. In the more recent longitudinal cohort studies, once again, positive associations have been observed between long-term exposure to SO_2 and mortality; however, several issues affect the interpretation of these results.

Figure 3-14 presents all-cause mortality RR estimates associated with long-term exposure to SO_2 from the U.S. and European cohort studies. The overall range of RRs spans 0.97 to 1.07 per 5 ppb increase in the annual (or longer period) average SO_2. The analyses of the Harvard Six Cities and the ACS cohort data, which likely provide effect estimates that are most useful for evaluating possible health effects in the United States, observed RRs of 1.02 to 1.07. Note that each of the U.S. cohort data has its own advantages and limitations. The Harvard Six Cities data have a small number of exposure estimates, but the location of the monitors were chosen carefully for epidemiological purposes. The ACS cohort had far more subjects, but the population was more highly educated than the representative U.S. population. Since educational status appeared to be an important effect modifier of air pollution effects in both studies, the overall effect estimate for the ACS cohort may underestimate that for the more general population. However, it should also be noted that several other U.S. and European studies did not observe an association between long-term exposure to SO_2 and mortality.

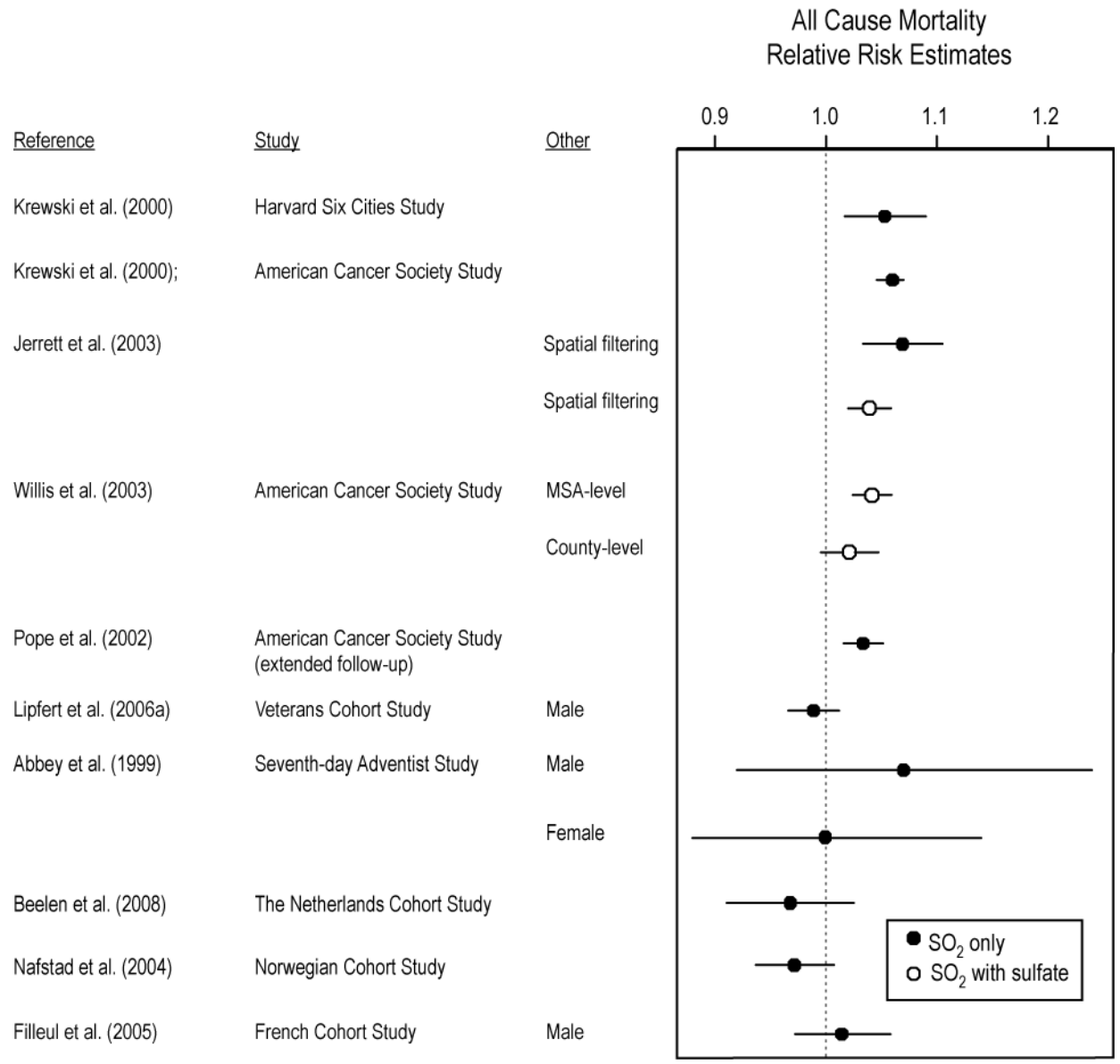

Figure 3-14. Relative risks (95% CI) of SO_2-associated all-cause (nonaccidental) mortality, with and without adjustment for sulfate, from longitudinal cohort studies. Effect estimates are standardized per 5 ppb increase in SO_2 concentrations. The exposure estimates for Krewski et al. (2000) and Pope et al. (2002) are based on MSA (Metropolitan Statistical Area)-level averaging; Lipfert et al. (2006a) used county-level averaging.

The geographic scale of analysis appears to influence SO_2 effect estimates and exposure error. In a reanalysis of the ACS data, the county-level analysis showed a smaller SO_2 effect estimate than MSA-level analysis. For sulfate, the opposite pattern was found. Thus, the impact of the geographic scale of analysis may also depend on the spatial distribution of air pollutants. The cross-sectional analysis in Great Britain using small-scale electoral wards observed an effect

estimate similar to the lower end of the range of effect estimates for all-cause mortality from U.S. cohort studies, though it is not clear if the effect estimates from this cross-sectional study are directly comparable to those from cohort studies.

Another important issue that these studies could not resolve was the possible confounding and/or interaction among PM indices and SO_2. The possibility that the observed effects may not be due to SO_2, but other constituents that come from the same source as SO_2, or that PM may be more toxic in the presence of SO_2 or other components associated with SO_2, cannot be ruled out. For example, the ACS cohort came from all regions of the United States, but a major fraction of the ACS cities were located in the eastern United States, where both SO_2 and sulfate levels tend to be higher. Therefore, even with sophisticated spatial modeling, separating possible confounding of SO_2 effects by PM is challenging. Future and on-going studies that take into consideration within- versus between-city variation of these pollutants may help elucidate this issue.

Overall, the results from two major U.S. epidemiological studies observe an association between long-term exposure to SO_2 or sulfur-containing particulate air pollution and mortality. However, several other U.S. and European cohort studies did not observe an association. The lack of consistency across studies, inability to distinguish potential confounding by copollutants, and uncertainties regarding the geographic scale of analysis limit the interpretation of a causal relationship.

Chapter 4. Public Health Impact

This chapter addresses several issues relating to the broader public health impact from exposure to ambient SO_2. First, the shape of the concentration-response relationship for SO_2 is discussed, with consideration of interindividual variability in responses and evaluation of the limited evidence available to assess a population threshold value for health effects. The next section identifies characteristics of subpopulations which may experience increased risks from SO_2 exposures, through either enhanced susceptibility (e.g., as a result of pre-existing disease, genetic factors, age) and/or differential vulnerability associated with increased exposure (e.g., close proximity to sources, activities). The final section discusses the potential public health impact from adverse health effects associated with SO_2 by examining the prevalence of susceptible individuals in the U.S. population.

4.1. Assessment of Concentration-Response Function and Potential Thresholds

An important consideration in characterizing the public health impacts associated with SO_2 exposure is whether the concentration-response relationship is linear across the full concentration range, or if there are concentration ranges where there are departures from linearity (i.e., nonlinearity). Of particular interest is the shape of the concentration-response curve at and below the level of the current SO_2 NAAQS level of a 24-h avg level of 0.14 ppm or the annual average of 0.03 ppm.

Some human clinical studies provide individual-level response data in relation to different levels of SO_2 exposure; this allows evaluation of both the percentage of individuals showing responses across the range of exposures as well as the concentration at which an individual begins to indicate a response. In epidemiological studies, rather than identifying interindividual differences in response, most studies evaluate whether there is a population-level threshold, which is the concentration of SO_2 that must be exceeded to elicit a health response in the study population. Low data density in the lower concentration range, measurement error in the response, and exposure measurement error are some of the factors that complicate the ability to determine the shape of the concentration-response curve, including the presence of any

threshold. Biological characteristics that tend to linearize concentration-response relationships include individual biological differences in susceptibility to air pollution health effects, additivity of SO_2-induced effects to a naturally occurring background level, and additivity of effects from other pollutant exposures. Epidemiological and human clinical studies that examined the shape of the concentration-response function for different averaging times or exposure durations are presented below. The discussion focuses on respiratory morbidity effects associated with short-term exposure to SO_2, for which the strongest causal evidence exists.

4.1.1. Evidence from Human Clinical Studies

In human clinical studies of exercising asthmatics, moderate SO_2-induced decrements in lung function have been observed at the lowest levels tested (i.e., 0.2 to 0.3 ppm, 5 to 10 min exposures) in the most sensitive individuals (approximately 5-20% of subjects). Statistically significant respiratory effects have been consistently observed at concentrations of 0.4-0.6 ppm, with 20-60% of asthmatics experiencing moderate to large decrements in lung function following 5-10 min exposures (see Table 3-1). Smaller, yet statistically significant decrements in lung function have also been demonstrated at SO_2 concentrations < 0.2 ppm when preceded by exposure to O_3 (see Section 3.1.5.1).

With increasing exposure concentration between 0.2 and 1.0 ppm, there is a clear increase both in magnitude of respiratory effect and percent of asthmatics affected (Table 3-1). A subset of the data presented in this table was taken from a series of studies conducted by Linn et al. (1987; 1988; 1990) and is presented graphically in Figure 4-1 through Figure 4-3. In these studies, mild and moderate asthmatics were exposed for 10 min to SO_2 concentrations between 0 and 0.6 ppm during moderate to heavy exercise. These particular studies were selected for inclusion in this meta-analysis owing to similarities between exposure protocols, with all subjects being exposed to multiple concentrations of SO_2. In the 1987 study, subjects were exposed to SO_2 concentrations of 0, 0.2, 0.4, and 0.6 ppm, while in the 1988 and 1990 studies, subjects were exposed to concentrations of 0, 0.3, and 0.6 ppm. The percent of asthmatics experiencing moderate or greater SO_2-induced decrements in lung function (increase in sRaw $\geq$ 100% or decrease in $FEV_1 \geq 15\%$) is shown in Figure 4-1. At 0.2 ppm, between 5 and 13% of subjects are affected, and this fraction increases with increasing concentration, with approximately 50% of subjects experiencing respiratory effects at a concentration of 0.6 ppm.

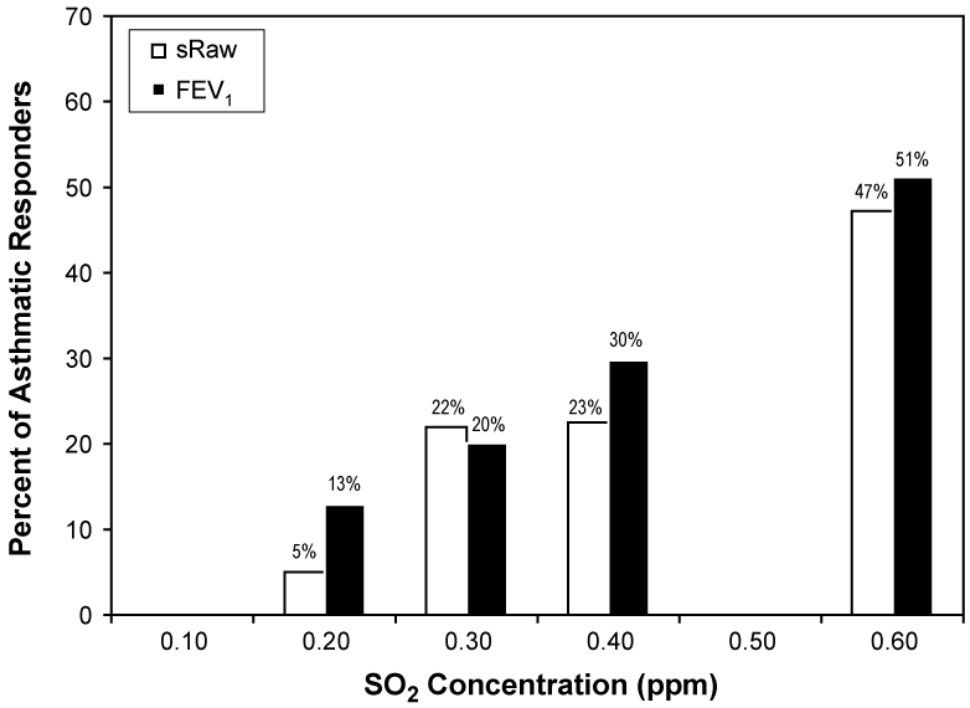

Figure 4-1. Percent of mild and moderate asthmatics ($\dot{V}_E$ = 40-50 L/min) experiencing an SO_2-induced increase in sRaw of ≥ 100% or a decrease in FEV_1 of ≥ 15%, adjusted for effects of moderate to heavy exercise in clean air. The data represents lung function measurements from 40, 41, 40, and 81 subjects at concentrations of 0.2, 0.3, 0.4, and 0.6 ppm, respectively.

Source: Data taken from Linn et al. (1987; 1988; 1990)

Figure 4-2 and Figure 4-3 present the concentration-response relationship between SO_2 and decrements in lung function in SO_2-sensitive asthmatics, i.e., those asthmatics experiencing significant decrements in lung function at the highest exposure concentration (0.6 ppm) used in the Linn et al. studies (1987; 1988; 1990). This analysis demonstrates a clear increase in the magnitude of respiratory effects with increasing exposure concentration, with more marked effects observed at SO_2 concentrations greater than 0.3 ppm. The results of a study by Gong et al. (1995) support this conclusion: the authors observed a linear relationship between SO_2 concentration (0, 0.5, and 1.0 ppm) and both lung function (decrease in FEV_1, and increase in sRaw) and respiratory symptoms.

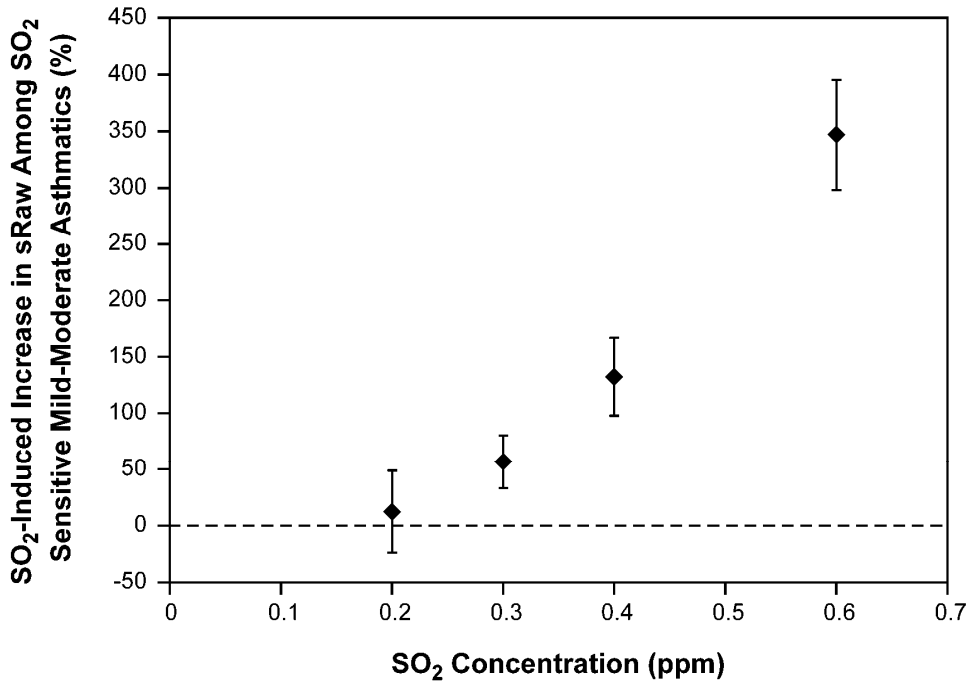

Figure 4-2. SO_2-induced increase in sRaw among SO_2-sensitive mild and moderate asthmatics (n=38) following 10-min exposures during moderate to heavy exercise (V_E = 40-50 L/min). Only SO_2-sensitive asthmatics, defined here as asthmatics experiencing ≥ 100% SO_2-induced increase in sRaw at 0.6 ppm, were included in this analysis. The analysis includes data from 14 SO_2-sensitive subjects from Linn et al. (1987) exposed to concentrations of 0.2, 0.4, and 0.6 ppm, as well as 24 SO_2-sensitive subjects from Linn et al. 1988 and 1990 exposed to 0.3 and 0.6 ppm. Error bars = ± 1 SE.

4.1.2. Evidence from Epidemiological Studies

Although there are numerous epidemiological studies that examined the association between SO_2 and various health effects, only a few of these studies attempted to evaluate the concentration-response function. Most studies assumed a linear or log-linear relationship between ambient SO_2 concentrations and the health outcome in their evaluations.

Epidemiological studies have examined the concentration-response relationship for SO_2 using various statistical methods, including the comparison of effect estimates in increasing quartiles or quintiles, plotting the risk observed against increasing SO_2 concentrations, and using nonparametric smoothed curves to assess the nonlinearity of the SO_2-effect relationship. Most of the epidemiological studies that examined the concentration-response function between SO_2 exposure and respiratory morbidity observed that the relationship was linear across the entire concentration range.

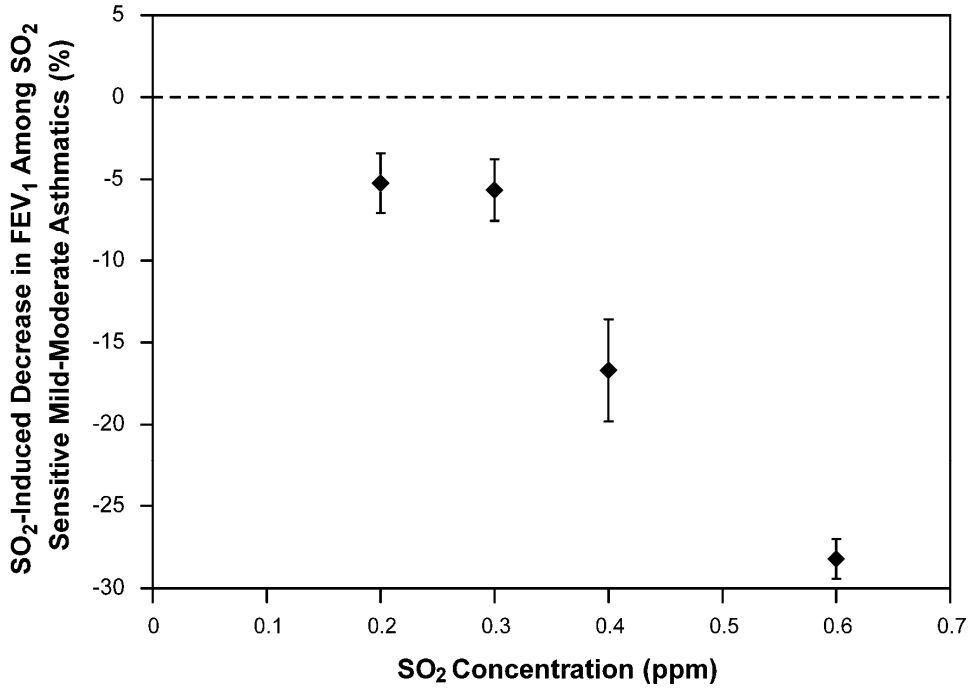

Figure 4-3. SO_2-induced decrease in FEV_1 among SO_2-sensitive mild and moderate asthmatics (n=41) following 10 min exposures during moderate to heavy exercise (V_E = 40-50 L/min). Only SO_2-sensitive asthmatics, defined here as asthmatics experiencing ≥ 15% SO_2-induced decrease in FEV_1 at 0.6 ppm, were included in this analysis. The analysis includes data from 21 SO_2-sensitive subjects from Linn et al. (1987) exposed to concentrations of 0.2, 0.4, and 0.6 ppm, as well as 20 SO_2-sensitive subjects from Linn et al. 1988 and 1990 exposed to 0.3 and 0.6 ppm. Error bars = ± 1 SE.

Only one epidemiological study investigated the concentration-response function of peak SO_2 exposures. The association between asthma hospitalizations and ambient 1-h max SO_2 concentrations was examined in a case-control study of children in Bronx County, NY (Lin et al., 2004). The 1-h max concentration ranged from 2.9 to 66.4 ppb. The authors categorized 1-h max SO_2 concentrations and estimated ORs for each category using the lowest exposure group as the reference (2.9 to 9.2 ppb). They observed an increasing linear trend across the range of concentrations, with more marked effects observed at 1-h max SO_2 concentrations greater than 40 ppb Figure 4-4. A 1-h max SO_2 concentration of 40 ppb falls between the 90th and 95th percentiles of the ambient regulatory data for the years 2003-2005; during these years 24-h avg SO_2 concentrations for the 90th and 95th percentiles were 10 and 13 ppb, respectively.

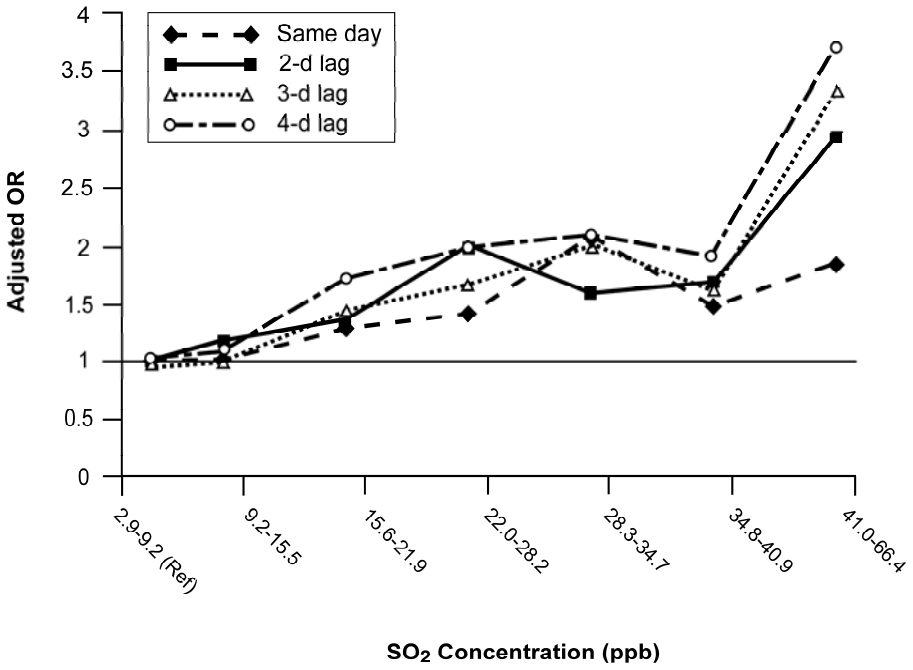

Figure 4-4. Adjusted odds ratios of asthma hospitalizations by groupings of 1-h max SO_2 concentrations in Bronx County, New York. All groups were compared with the lowest exposure group (2.9-9.2 ppb). ORs for 1-h max SO_2 concentrations on the same day, as well as from a 2-day, 3-day, and 4-day moving average lag are presented.

Source: Lin et al. (2004)

Most epidemiological studies investigating the concentration-response function examined the effects of short-term 24-h avg exposures to SO_2. The Harvard Six Cities study by Schwartz et al. (1994) investigated the concentration-response function and observed a nonlinear relationship between SO_2 concentrations and respiratory symptoms. A figure plotting the relative odds of incidence of lower respiratory tract symptoms against SO_2 concentrations lagged 1 day indicated that no statistically significant increase in the incidence of lower respiratory tract symptoms was seen until concentrations exceeded a 24-h avg SO_2 of 22 ppb though an increasing trend was observed at concentrations as low as 10 ppb (see Figure 4-5). In a study of respiratory hospitalizations, Ponce de Leon et al. (1996) found that a weak relationship with SO_2 was only observable at 24-h avg SO_2 concentrations above 23 ppb. In both this study and the study by Schwartz et al. (1994), a statistically significant increased risk was observable only at 24-h avg SO_2 concentrations that were above the 90th percentile. The nonlinearity observed in

these concentration-response functions is dependent on only a few influential observations; thus, the results should be viewed with caution.

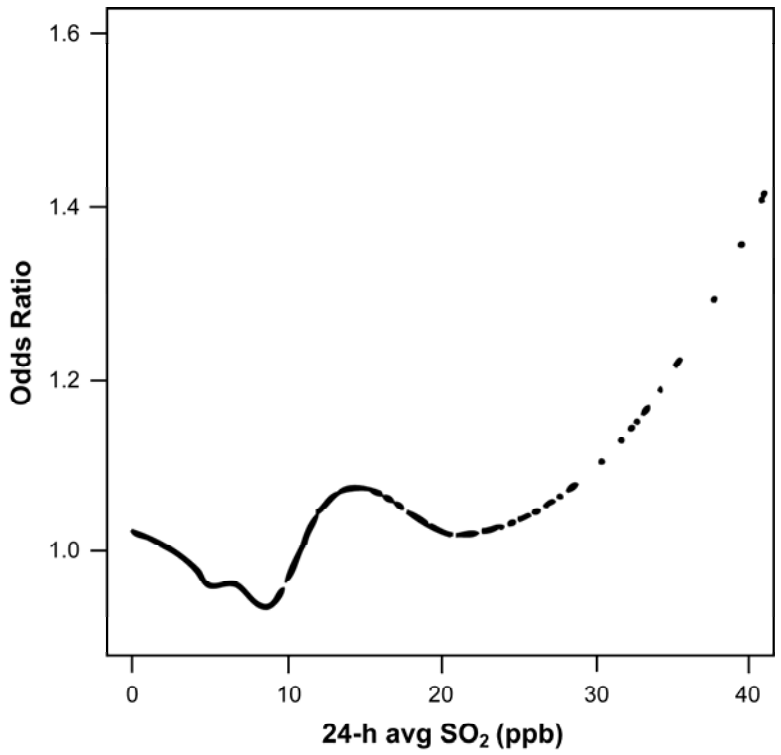

Figure 4-5. Relative odds ratio of incidence of lower respiratory tract symptoms smoothed against 24-h avg SO_2 concentrations on the previous day, controlling for temperature, city, and day of week.

Source: Schwartz et al. (1994).

A study by Jaffe et al. (2003) examined the association between SO_2 and emergency department (ED) visits for asthma in three cities in Ohio, and found significant associations only in Cincinnati using Poisson regression analysis. To examine the concentration-response function, they also conducted quintile analyses. In Cincinnati, an increasing linear trend in risk was observed across the range of concentrations. Wong et al. (2002; using GAM with default convergence criteria) constructed a plot of risk against 24-h avg SO_2 concentrations to examine the concentration-response relationship in Hong Kong and London. In general, a linear relationship between risk of respiratory hospitalizations and SO_2 was observed across the range

of SO_2 concentrations in Hong Kong, but not in London. Several other studies that examined the concentration-response relationship found that the association between respiratory hospitalizations and SO_2 did not deviate from linearity (Atkinson et al., 1999a; Burnett et al., 1997a; 1997b; 1999; Hajat et al., 2002).

4.1.3. Summary of Evidence on Concentration-Response Functions and Thresholds

In the previous two sections, evidence from human clinical and epidemiological studies on the concentration-response function that may inform identification of any potential population threshold was presented. Evidence from human clinical studies indicates a clear increase in the magnitude of respiratory effects with increasing exposure concentration between 0.2 and 1.0 ppm with 5-10 min SO_2 exposures. Epidemiological studies also have observed generally increasing trends across the entire range of SO_2 exposures; however, in a limited number of studies a marked increase in effect was observed only at the higher concentrations (above 90^{th} percentile values).

Discerning a possible population-level threshold for air pollution-related effects in epidemiological studies is quite challenging. Using $PM_{2.5}$ as an example, Brauer et al. (2002) examined the relationship between ambient concentrations and mortality risk in a simulated population with specified common individual threshold levels. They found that no population threshold was detectable when a low threshold level was specified. Even at high-specified individual threshold levels, the apparent threshold at the population level was much lower than specified. Brauer et al. (2002) concluded that the use of surrogate measures of exposure (i.e., those from centrally located ambient monitors) that were not highly correlated with personal exposures made it difficult to discern population-level thresholds in epidemiological studies even if a common threshold exists for individuals within the population.

The wide interindividual variability in sensitivity to SO_2 exposure further hinders the ability to discern a potential threshold level in population studies. Human clinical studies have shown that asthmatics experience greater increases in sRaw following peak SO_2 exposures compared to healthy individuals (Linn et al., 1987). Among asthmatics, interindividual differences in response also have been noted, with some asthmatics experiencing SO_2-related effects at much lower levels than others (Horstman et al., 1986).

Another factor that complicates the identification of a possible threshold of effects is that currently deployed ambient monitors may be inadequate for accurate and precise measurements at lower 24-h avg SO_2 levels. Ambient concentrations of SO_2 have been declining since the 1980s and are now at or very near the limit of detection of the ambient monitors in the regulatory network. The mean 24-h avg SO_2 concentration across the metropolitan statistical areas (MSAs) from 2003 through 2005 was 4 ppb (5th–95th percentile: 1, 13). Thus, there is greater uncertainty at the lower concentration range compared to the higher concentrations, which likely limits the ability to detect any clear-cut potential threshold.

In conclusion, evidence from human clinical studies indicates wide interindividual variability in response to SO_2 exposures, with peak (5 to 10 min) exposures at levels as low as 0.2-0.3 ppm eliciting respiratory responses in some asthmatic individuals. Several epidemiological studies that examined the concentration-response function between short-term (24-h avg or 1-h max) exposure to SO_2 and respiratory morbidity observed that the relationship was linear across the entire concentration range, suggesting a lack of a threshold in effect. However, given the various limitations in observing a possible threshold in population studies, the lack of evidence does not necessarily indicate that there is indeed no threshold in SO_2 health effects. Some epidemiological studies did report that though there was generally an increasing trend at the lower SO_2 concentrations, a marked increase in SO_2-related respiratory health effects was observed at higher concentrations. However, as these observations were based on a few potentially influential data points (24-h avg SO_2 concentrations above the 90th percentile), the results should be interpreted with caution. The overall limited evidence from epidemiological studies examining the concentration-response function of SO_2 health effects is inconclusive regarding the presence of an effect threshold at current ambient levels.

4.2. Susceptible and Vulnerable Populations

Interindividual variation in human responses to air pollutants indicates that not all individuals exposed to pollutants respond similarly. That is, some subpopulations are at increased risk to the detrimental effects of pollutant exposure. The NAAQS are intended to provide an adequate margin of safety for both general populations and sensitive subpopulations, or those subgroups potentially at increased risk for ambient air pollution health effects. For the purposes of this document, a susceptible population is defined as one that might exhibit an adverse health

effect to a pollutant at concentrations lower than those needed to elicit the same response in the general population, and a vulnerable population as one that might be differentially exposed to higher concentrations of a pollutant than the general population, regardless of health outcome. The previous review of the SO_2 NAAQS identified certain groups within the population that may be more susceptible to the effects of SO_2 exposure, including asthmatics, individuals not diagnosed as asthmatic but with atopic disorders (e.g., allergies), and individuals with COPD or cardiovascular disease. Other subgroups considered to be somewhat sensitive in this document include children and older adults; people with other respiratory disease; genetic factors; socioeconomic status (SES); and populations experiencing heightened exposure levels (e.g., those living near roadways or other "hot spots" or engaged in outdoor work or exercise). Also of concern are individuals who generally may not be susceptible to SO_2-related health effects but may experience transient airways reactivity to respiratory irritants such as SO_2 following a recent viral respiratory infection (Stempel and Boucher, 1981). These groups comprise a large fraction of the U.S. population. Given the likely heterogeneity of individual responses to air pollution, the severity of health effects experienced by a susceptible subgroup may be much greater than that experienced by the population at large (Zanobetti et al., 2000).

4.2.1. Preexisting Disease as a Potential Risk Factor

Several researchers have investigated the effect of air pollution among potentially susceptible groups with preexisting medical conditions. A recent report of the National Research Council emphasized the need to evaluate the effect of air pollution on susceptible groups, including those with respiratory illnesses and cardiovascular diseases (National Research Council., 2004). Generally, asthma, COPD, conduction disorders, congestive heart failure (CHF), diabetes, and myoardial infarction (MI) are conditions believed to put persons at greater risk of adverse events associated with air pollution. Asthmatics are known to be one of the most SO_2-responsive subgroups in the population; the evidence related to respiratory illness, including asthma and other factors, is discussed in further detail below.

4.2.1.1. Individuals with Respiratory Diseases

The 1982 AQCD concluded that asthmatics are more susceptible to respiratory effects from SO_2 exposures than the general public. This conclusion was primarily drawn from the strong

human clinical evidence. Recent epidemiological studies have strengthened this conclusion, reporting associations between a range of health outcomes with both short-term and long-term SO_2 exposures in subjects with respiratory disease.

In human clinical studies, asthmatics have been shown to be more responsive to respiratory effects of SO_2 exposures than healthy non-asthmatics. While SO_2-attributable decrements in lung function generally have not been demonstrated at concentrations < 1.0 ppm in non-asthmatics (Lawther et al., 1975; Linn et al., 1987; Schachter et al., 1984), statistically significant increases in respiratory symptoms and decreases in lung function have been observed in exercising asthmatics following peak (5 to 10 min) SO_2 exposures to concentrations as low as 0.4-0.6 ppm (Gong et al., 1995; Horstman et al., 1986; Linn et al., 1983). Respiratory effects have been observed in some sensitive asthmatics at concentrations as low as 0.2-0.3 ppm (Horstman et al., 1986; Linn et al., 1987). There is no evidence that individuals with COPD have increased susceptibility to SO_2-induced respiratory effects.

A number of epidemiological studies reported increased respiratory morbidity associated with SO_2 exposures in asthmatics and atopic individuals. Notably, two U.S. multicity studies observed associations between ambient SO_2 concentrations and respiratory symptoms in asthmatic children (Mortimer et al., 2002; Schildcrout et al., 2006). Additional studies also have generally indicated positive associations for asthma among children and included a U.S. study (Delfino et al., 2003) and several European studies (Higgins et al., 1995; Neukirch et al., 1998; Peters et al., 1996; Roemer et al., 1993; Segala et al., 1998; Taggart et al., 1996; Timonen and Pekkanen, 1997; van der Zee et al., 1999). Studies of adults found no consistent association between respiratory symptoms among asthmatics and SO_2 concentrations (Desqueyroux et al., 2002a; 2002b; Romieu et al., 1996; van der Zee et al., 2000).

A suggestive association between ambient SO_2 concentrations and ED visits and hospitalizations provides further evidence that asthmatics are susceptible to the effects of SO_2. The associations between ambient concentrations of 24-h avg SO_2 and ED visits and hospitalizations for asthma in the United States are generally positive (Jaffe et al., 2003; Lin et al., 2004; Michaud et al., 2004; Wilson et al., 2005), though a large time-series study conducted in Atlanta, GA did not find an association between ambient 1-h max SO_2 levels and ED visits (Peel et al., 2005). Studies conducted outside the United States (Atkinson et al., 1999a; Hajat et al., 1999; Sunyer et al., 1997; Thompson et al., 2001) also generally found positive results.

In summary, substantial evidence from epidemiological studies suggests that individuals with preexisting respiratory diseases, particularly asthma, are more susceptible to respiratory health effects, though not mortality, from SO_2 exposures than the general public. The observations from human clinical studies indicating increased sensitivity to SO_2 exposures in asthmatic subjects compared to healthy subjects provide coherence and biological plausibility for these observations in epidemiological studies.

4.2.1.2. Individuals with Cardiovascular Diseases

The evidence available to evaluate the susceptibility of individuals with cardiovascular disease for SO_2-related health effects is very limited. One human clinical study observed no evidence to suggest that patients with stable angina were more susceptible to SO_2-related health effects compared with healthy subjects (Routledge et al., 2006). The authors noted that this lack of response in the heart patients may be due to a drug treatment effect rather than decreased susceptibility, as a large portion of the angina patients were taking beta blockers, which are known to increase indices of cardiac vagal control.

Liao et al. (2004) investigated short-term associations between ambient pollutants and cardiac autonomic control and observed that consistently more pronounced associations were found between SO_2 and heart rate variability among persons with a history of coronary heart disease. In another epidemiological study, Henneberger et al. (2005) examined the association of repolarization parameters with air pollutants in East German men with preexisting coronary heart disease. Ambient SO_2 concentrations during the 24-h preceding the ECG were associated with the QT interval duration, but not with any other repolarization parameters.

Evidence is inconsistent in studies analyzing the associations between ambient levels of air pollutants and ED visits or hospitalizations for cardiovascular diseases. A recent epidemiological study investigated the association of SO_2 with cardiac-related hospital admissions among persons with preexisting cardiopulmonary conditions and observed no associations with ambient 1-h max SO_2 level for any cardiac disease investigated (i.e., ischemic heart disease [IHD], CHF, and dysrhythmia) across strata of comorbid disease status, including hypertension, diabetes, and COPD (Peel et al., 2007).

Goldberg et al. (2003) compared the risk estimates for death with the underlying cause of CHF and those deaths classified as having CHF 1 year before death and did not find associations

between air pollution and those with CHF as an underlying cause of death. The authors found associations between some of the air pollutants examined (coefficient of haze [CoH], SO_2, and NO_2) and the deaths that were classified as having CHF 1 year before death, but the association with the specific cause of death was not unique to SO_2. This pattern of association, including but not specific to SO_2, with specific causes of death also was observed in an additional cohort of patients with CHF (Kwon et al., 2001).

In conclusion, the very limited evidence examining the susceptibility of individuals with preexisting cardiovascular disease to adverse health effects from ambient SO_2 exposures is inconclusive.

4.2.2. Genetic Factors for Oxidant and Inflammatory Damage from Air Pollutants

A consensus now exists among scientists that genetic factors related to health outcomes and ambient pollutant exposures merit serious consideration (Gilliland et al., 1999; Kauffmann, 2004). Several criteria must be satisfied in selecting and establishing useful links between polymorphisms in candidate genes and adverse respiratory effects. First, the product of the candidate gene must be significantly involved in the pathogenesis of the effect of interest, which is often a complex trait with many determinants. Second, polymorphisms in the gene must produce a functional change in either the protein product or in the level of expression of the protein. Third, in epidemiological studies, the issue of confounding by other genes or environmental exposures must be carefully considered.

Several glutathione S-transferase (GST) families have common, functionally important polymorphic alleles (e.g., homozygosity for the null allele at the GSTM1 and GSTT1 loci, homozygosity for the A105G allele at the GSTP1 locus) that significantly reduce expression of enzyme function in the lung. Exposure to radicals and oxidants from air pollution induces decreases in GSH that increase GST transcription. Individuals with genotypes that result in enzymes with reduced or absent glutathione peroxidase activity are likely to have reduced oxidant defenses and increased susceptibility to inhaled oxidants and radicals.

Gilliland et al. (2002) examined effects of GSTM1, GSTT1, and GSTP1 genotypes and acute respiratory illness, specifically respiratory illness-related absences from school. The goal was to examine potential susceptibilities on this basis, but not specifically to air pollutants. They

concluded that fourth grade schoolchildren who inherited a GSTP1 Val-105 variant allele had a decreased risk of respiratory illness-related school absences, indicating that GSTP1 genotype influences the risk and/or severity of acute respiratory infections in school-aged children.

Lee et al. (2004) studied ninth grade schoolchildren with asthma in Taiwan for a gene-environmental interaction between GSTP1-105 genotypes and outdoor pollution. They examined general district air pollution levels of low (mean SO_2 level of 3.6 ppb from 1994 to 2001), moderate (mean SO_2 of 6.2 ppb), and high (mean SO_2 of 8.6 ppb) and found that compared with individuals with any Val-105 allele in the low air pollution district, Ile-105 homozygotes in the high air pollution district had a significantly increased risk of asthma.

Gauderman et al. (2007) describe a study method that uses principal components analysis computed on single nucleotide polymorphism (SNP) markers to test for an association between a disease and a candidate gene. For example, they evaluated the association between respiratory symptoms in children and four SNPs in the GSTP1 locus, using data from the Southern California Children's Health Study (CHS). The authors observed stronger evidence of an association using the principal components approach ($p = 0.044$) than using either a genotype-based ($p = 0.13$) or haplotype-based ($p = 0.052$) approach. This method may be applied to relationships in this and other databases to evaluate aspects of air pollutants such as SO_2.

Winterton et al. (2001) attempted to identify a genetic biomarker for susceptibility to SO_2. They screened 62 asthmatic subjects for SO_2 responsiveness using an inhalation challenge and collected genetic material via buccal swabs to test for associations between SO_2 sensitivity and specific gene polymorphisms. Subjects inhaled 0.5 ppm SO_2 by mouthpiece for 10 min while wearing noseclips during moderate exercise on a treadmill. Subjects were defined as SO_2-sensitive if FEV_1 was decreased 12%. Genetic polymorphisms as biomarkers of susceptibility were evaluated in five regions coding for the β2-adrenergic receptor, the α subunit of the interleukin-4 (IL-4) receptor, the Clara cell secretory protein (CC16), tumor necrosis factor-α (TNF-α), and lymphotoxin-α (also known as TNF-β). The authors found a significant association between response to SO_2 and the homozygous wild-type allele of TNF-α. All of the SO_2-sensitive subjects had the homozygous wild-type allele for TNF-α, while 61% of the nonresponders had this genotype. Homozygosity for the TNF-1 allele was associated with a 5-fold increased risk of physician-diagnosed asthma relative to other genotypes. None of the other polymorphisms showed significant trends.

In summary, the differential effects of air pollution among genetically diverse subpopulations have been examined for a number of GST genes and other genotypes. The limited number of studies may provide some insight into susceptible groups and a potential genetic role in such. Only one of these studies specifically examined SO_2 as the exposure of interest, and it found a significant association with the homozygous wild-type allele for TNF-α. Khoury et al. (2005) states that while genomics is still in its infancy, opportunities exist for developing, testing, and applying its tools to public health research of outcomes with possible environmental causes. At this time, there are insufficient data on which to base a conclusion regarding the effect of SO_2 exposure on genetically distinct subpopulations.

4.2.3. Age-Related Susceptibility

The American Academy of Pediatrics (2004) notes that children and infants are among the most susceptible to many air pollutants, including SO_2. Eighty percent of alveoli are formed postnatally and changes in the lung continue through adolescence; furthermore, the developing lung is highly susceptible to damage from exposure to environmental toxicants (Dietert et al., 2000). Children also have increased vulnerability as they spend more time outdoors, are highly active, and have high minute ventilation, which collectively increase the dose they receive (Plunkett et al., 1992; Wiley, 1991a; 1991b). In addition to children, the elderly are frequently classified as being particularly susceptible to air pollution. The basis of the increased sensitivity in the elderly is not known, but one possibility is that it may be related to changes in the respiratory tract lining fluid antioxidant defense network (Kelly and Mudway, 2003) or a general reduction in immune competence.

Adverse respiratory effects have been observed in adolescents following SO_2 exposure in a laboratory setting (Koenig et al., 1981; 1983; 1987; 1988; 1990). However, there is no evidence from human clinical studies to suggest that the respiratory effects in adolescents are more severe than those observed in adults. Similarly, a number of epidemiological studies have observed increased respiratory symptoms in children associated with increasing SO_2 exposures (Mortimer et al., 2002; Schildcrout et al., 2006; Schwartz et al., 1994), though there is no evidence from a limited number of studies suggesting this same effect in adults (Desqueyroux et al., 2002a; Romieu et al., 1996; van der Zee et al., 2000).

A number of studies, investigating the association between ambient SO_2 levels and ED visits or hospital admissions for all respiratory causes or asthma, stratified their analyses by age group. Figure 4-6 summarizes the evidence of age-specific associations between SO_2 and acute respiratory ED visits and hospitalizations. Several studies demonstrated that the excess risk of ED visits or hospitalizations for all respiratory causes or asthma was higher for children (Anderson et al., 2001; Atkinson et al., 1999a; Atkinson et al., 1999b; Petroeschevsky et al., 2001) and older adults (Anderson et al., 1998; Petroeschevsky et al., 2001; Ponce de Leon et al., 1996; Wilson et al., 2005) when compared to the risk for all ages together. Increased risks for children and older adults were more prevalent in the studies of all respiratory disease than those considering asthma as the outcome.

Cakmak et al. (2007) reported that among seven Chilean urban centers, the percent increase in nonaccidental mortality associated with a 10 ppb increase in 24-h avg SO_2 was 3.4% (95% CI: 0.7, 6.1) for those < 65 years of age and 5.6% (95% CI: 2.2, 9.1) for those > 85 years of age. The authors concluded that the elderly are particularly susceptible to dying from air pollution, and suggested that concentrations deemed acceptable for the general population may not adequately protect the very elderly.

There is limited epidemiologic evidence to suggest that children and older adults (65+ years) are more susceptible to the adverse respiratory effects associated with ambient SO_2 concentrations when compared to the general population.

4.2.4. Other Potentially Susceptible Populations

There are a number of other potentially susceptible groups that, while not included here due to a lack of data specific to SO_2 exposures, deserve mention in this document. These include obese individuals, individuals in a chronic pro-inflammatory state (e.g., diabetics), and children born prematurely or with low birth weight.

Enhanced susceptibility for air pollution-related cardiovascular events has been shown for older individuals and persons with conditions associated with chronic inflammation, such as

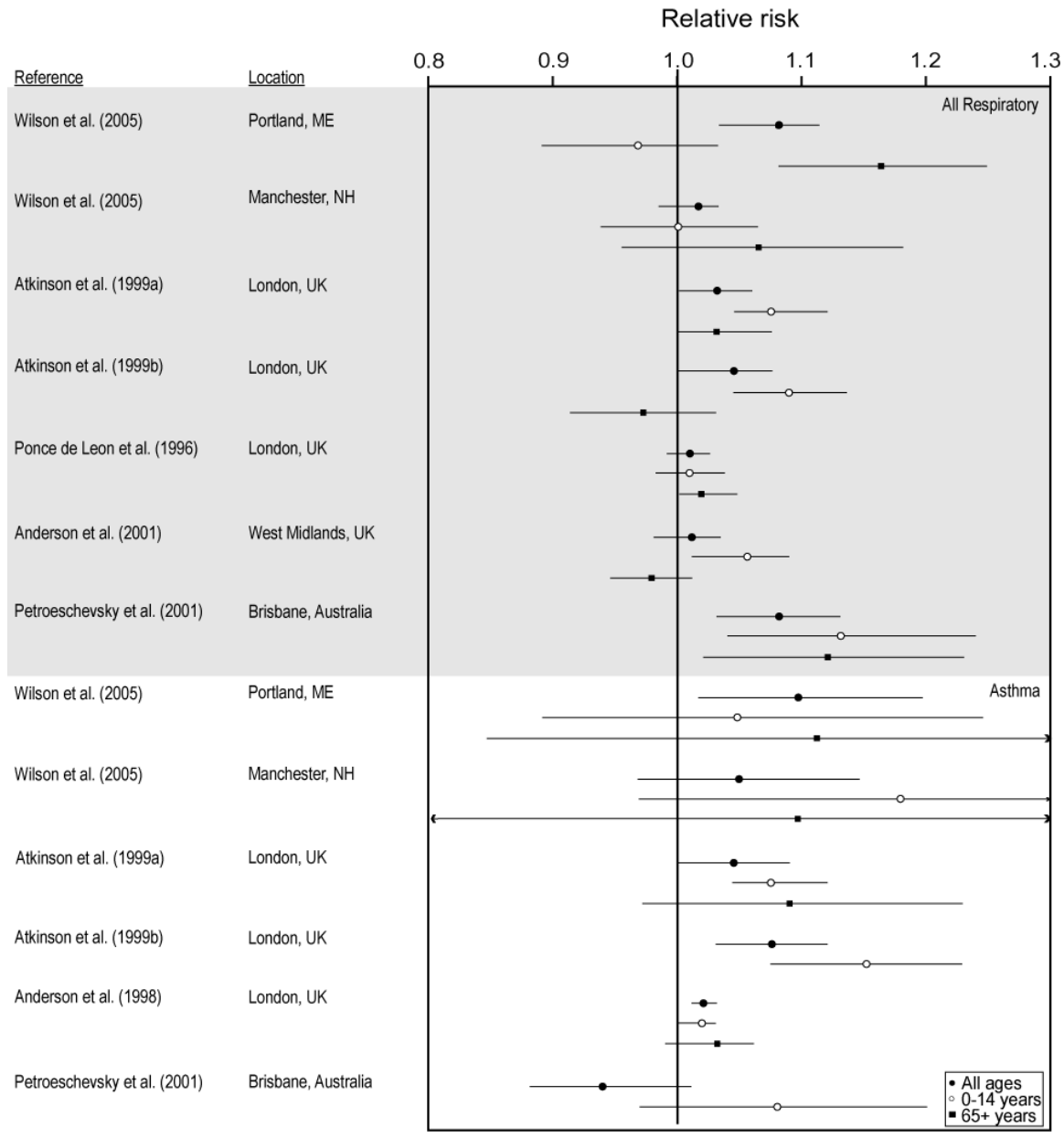

Figure 4-6. Relative risks (95% CI) of age-specific associations between short-term exposure to SO_2 and respiratory ED visits and hospitalizations. Risk estimates are standardized per 10 ppb increase in 24-h avg SO_2 concentrations or 40 ppb increase in 1-h max SO_2.

diabetes, coronary artery disease, and past myocardial infarctions (Bateson and Schwartz, 2004; Goldberg et al., 2001; Zanobetti and Schwartz, 2002). Dubowsky et al. (2006) observed that individuals with conditions associated with both chronic inflammation and increased cardiac risk were more vulnerable to the short-term pro-inflammatory effects of air pollution. This included

individuals with diabetes; obesity; and concurrent diabetes, obesity and hypertension. Zanobetti and Schwartz (2001) reported more than twice the risk for hospital admissions for heart disease in persons with diabetes than in persons without diabetes associated with exposure to ambient air pollution, indicating that persons with diabetes are an important at-risk group. Data from the Third National Health and Nutrition Examination Survey indicate that 5.1% of the U.S. population older than 20 years of age have diagnosed diabetes and an additional 2.7% have undiagnosed diabetes (Harris et al., 1998). Moreover, another study found that subjects with impaired glucose tolerance without type II diabetes also had reduced heart rate variability (Schwartz, 2001). This suggests the at-risk population may be even larger.

Mortimer et al. (2000) reported that among asthmatic children, birth characteristics continue to be associated with increased susceptibility to air pollution later in life, demonstrating that air pollution-induced asthma symptoms are more severe in children born prematurely or of low birth weight. Specifically, the authors revealed asthmatic children born more than three weeks prematurely or weighing less than 2,500 grams (5.5 pounds) had a six-fold decrease in breathing capacity associated with air pollution compared to full-weight, full-term children. The low birth weight and premature children also reported a five-fold greater incidence of symptoms like wheezing, coughing and tightness in the chest.

4.2.5. Factors that Potentially Increase Vulnerability to SO_2

A limited amount of information exists on exposures to SO_2 among vulnerable populations. Because indoor and personal SO_2 concentrations are generally much lower than outdoor or ambient measurements, individuals that spend most of their time indoors, such as older adults, are not anticipated to be vulnerable to high SO_2 exposures, though in some cases they may be more susceptible to the effects of these exposures than the general population due to preexisting health factors.

Other individuals with increased vulnerability include those who spend a lot of time outdoors at increased exertion levels, for example outdoor workers and individuals who exercise or play outdoor sports. Exercise may cause an increase in uptake of SO_2 resulting from an increase in ventilation rate and accompanying shift from nasal to oronasal breathing. Children, who generally spend more time playing outdoors, may qualify as both a susceptible population

due to their developing physiology and as a vulnerable population since ambient SO_2 concentrations are several-fold higher than indoor concentrations.

Residential location is not as strong of a predictor of exposure vulnerability for SO_2 as for traffic-related pollutants, because meteorological conditions have a greater impact on pollutant plume direction from primary point sources such as coal-fired power plants.

Social economic status (SES) is a known determinant of health and there is evidence that SES modifies the effects of air pollution (Makri and Stilianakis, 2007; O'Neill et al., 2003). Both higher exposures to air pollution and greater susceptibility to its effects may contribute to a complex pattern of risk among those with lower SES. Conceptual frameworks have been proposed to explain the relationship between SES, susceptibility and exposure to air pollution. Common to these frameworks is the consideration of the broader social context in which people live and its effect on health in general (Gee and Payne-Sturges, 2004; O'Neill et al., 2003), as well as on maternal and child health (Morello-Frosch and Shenassa, 2006), and asthma (Wright et al., 2007) specifically. Multilevel modeling approaches that allow parameterization of community level stressors such as increased life stress, as well as individual risk factors, are considered by these authors. In addition, statistical methods that allow for temporal and spatial variability in exposure and susceptibility, have been discussed in the recent literature (Jerrett and Finkelstein, 2005; Kunzli, 2005).

Most studies to date have examined modification by SES indicators on the association between mortality and PM (Finkelstein et al., 2003; Jerrett et al., 2004; Martins et al., 2004; O'Neill et al., 2003; Romieu et al., 2004) or other indices such as traffic density, distance to roadway or a general air pollution index (Finkelstein et al., 2005; Ponce et al., 2005; Woodruff et al., 2003). However, modification of SO_2 associations has been examined in a few studies. For example, in a study conducted in 10 large Canadian cities, living in communities in which individuals have lower household education and income levels increased the individual's vulnerability to air pollution (Cakmak et al., 2006). These effects were statistically significant for several gaseous criteria pollutants, but not for SO_2. In addition, Finkelstein et al. (2003) evaluated neighborhood levels of income and air pollution in southern Ontario, Canada. They found that both income and SO_2 levels were associated with mortality differences. Specifically, among people with below-median income, the relative risk for those with above-median exposure to SO_2 was 1.18 (95% CI: 1.11, 1.26); the corresponding relative risk among subjects

with above-median income was 1.03 (95% CI: 0.83, 1.28). Overall, there is very limited evidence available from which conclusions on the human health effects from the interaction between SES and SO_2 can be drawn.

4.3. Potential Public Health Impacts

Exposure to ambient SO_2 is associated with a variety of outcomes including increases in respiratory symptoms, particularly among asthmatic children, and ED visits and hospital admissions for respiratory diseases among children and older adults (65+ years). In protecting public health, a distinction must be made between health effects that are considered "adverse" and those that are not. What constitutes an adverse health effect varies for different population groups. Some changes in healthy individuals are not viewed as adverse while those of similar type and magnitude in other susceptible individuals with preexisting disease are.

4.3.1. Concepts Related to Defining Adverse Health Effects

The American Thoracic Society (ATS) published an official statement titled "What Constitutes an Adverse Health Effect of Air Pollution?" (ATS, 2000a). This statement updated the guidance for defining adverse respiratory health effects that had been published 15 years earlier (Society, 1985), taking into account new investigative approaches used to identify the effects of air pollution and reflecting concern for impacts of air pollution on specific susceptible groups. In the 2000 update, there was an increased focus on quality of life measures as indicators of adversity and a more specific consideration of population risk. Exposure to air pollution that increases the risk of an adverse effect to the entire population is viewed as adverse, even though it may not increase the risk of any identifiable individual to an unacceptable level. For example, a population of asthmatics could have a distribution of lung function such that no identifiable single individual has a level associated with significant impairment. Exposure to air pollution could shift the distribution to lower levels that still do not bring any identifiable individual to a level that is associated with clinically relevant effects. However, this shift to a lower level of lung function would be considered adverse because individuals within the population would have diminished reserve function and, therefore, would be at increased risk if affected by another agent.

Reflecting new investigative approaches, the ATS statement also describes the potential usefulness of research into the genetic basis for disease, including responses to environmental agents that provide insights into the mechanistic basis for susceptibility and provide markers of risk status. Likewise, biomarkers that are indicators of exposure, effect, or susceptibility may someday be useful in defining the point at which one or an array of responses should be considered an adverse effect.

The 2006 Ozone AQCD (EPA, 2006) provided information helpful in defining adverse health effects associated with ambient O_3 exposure by describing the gradation of severity and adversity of respiratory-related O_3 effects. The definitions that relate to responses in impaired individuals are reproduced and presented here in Table 4-1. The severity of effects described in the tables and the approaches taken to define their relative adversity are valid and reasonable in the context of the new ATS (2000b) statement.

Table 4-1. Gradation of individual responses to short-term SO_2 exposure in individuals with impaired respiratory systems.

FUNCTIONAL RESPONSE	NONE	SMALL	MODERATE	LARGE
FEV_1 change	Decrements of < 3%	Decrements of 3 - 10%	Decrements of 10 - 20%	Decrements of > 20%
Nonspecific bronchial responsiveness[a]	Within normal range	Increases of < 100%	Increase of < 300%	Increases of > 300%
Airway resistance (sRaw)	Within normal range (±20%)	sRaw increased < 100%	sRaw increased up to 200% or up to 15 cm $H_2O \cdot s$	sRaw increased > 200% or more than 15 cm $H_2O \cdot s$
Duration of response	None	< 4 h	4 h - 24 h	> 24 h
SYMPTOMATIC RESPONSE	**NORMAL**	**MILD**	**MODERATE**	**SEVERE**
Wheeze	None	With otherwise normal breathing	With shortness of breath	Persistent with shortness of breath
Cough	Infrequent cough	Cough with deep breath	Frequent spontaneous cough	Persistent uncontrollable cough
Chest pain	None	Discomfort just noticeable on exercise or deep breath	Marked discomfort on exercise or deep breath	Severe discomfort on exercise or deep breath
Duration of response	None	< 4 h	4 h – 24 h	> 24 h
IMPACT OF RESPONSES	**NORMAL**	**MILD**	**MODERATE**	**SEVERE**
Interference with normal activity	None	Few individuals choose to limit activity	Many individuals choose to limit activity	Most individuals choose to limit activity
Medical treatment	No change	Normal medication as needed	Increased frequency of medication use or additional medication	Physician or emergency room visit

[a]An increase in nonspecific bronchial responsiveness of 100% is equivalent to a 50% decrease in PD20 or PD100.
This table is adapted from the 2006 Ozone AQCD (Table 8-3, page 8-68) (EPA, 26).

As assessed in detail in earlier chapters of this document and briefly recapitulated in preceding sections of this chapter, exposures to a range of SO_2 concentrations have been reported to be associated with increasing severity of health effects, ranging from respiratory symptoms to ED visits and hospital admission for respiratory causes. Respiratory effects associated with short-term SO_2 exposures have been by far the most extensively studied and most clearly shown to be causally related to SO_2 exposure. Such effects are observed among children, older adults, and persons with respiratory impairments.

4.3.2. Estimation of Potential Numbers of Persons in At-Risk Susceptible Population Groups in the United States

Although SO_2-related health risk estimates may appear to be small, they may be significant from an overall public health perspective due to the large numbers of individuals in the potential risk groups. Several subpopulations have been identified as possibly having increased susceptibility or vulnerability to adverse health effects from SO_2, including children, older adults, and individuals with preexisting pulmonary diseases. One consideration in the assessment of potential public health impacts is the size of various population groups that may be at increased risk for health effects associated with SO_2-related air pollution exposure. Table 4-2 summarizes information on the prevalence of chronic respiratory conditions in the U.S. population in 2004 and 2005 (NHIS, 2006a, 2006b).

Of most concern are those individuals with preexisting respiratory conditions, with approximately 10% of adults and 13% of children having been diagnosed with asthma and 6% of adults with COPD (chronic bronchitis and/or emphysema). As summarized in Section 3.1.3.5, human clinical studies indicate that a significant fraction (20-60%) of asthmatic individuals experience moderate or greater decrements in lung function as well as increased respiratory symptoms following peak (5-10 min) SO_2 exposures to concentrations of as low as 0.4-0.6 ppm (Table 3-1). Some sensitive asthmatics (5-20%) have been shown to experience moderate decrements in lung function at concentrations between 0.2 and 0.3 ppm. Among asthmatics, both the magnitude of SO_2-induced decrements in lung function as well as the percent of individuals affected have been shown to increase with increasing exposure concentrations between 0.2 and 1.0 ppm.

In addition, subpopulations based on age group also comprise substantial segments of the population that may be potentially at risk for SO_2-related health impacts. Based on U.S. Census data from 2000, about 72.3 million (26%) of the U.S. population are under 18 years of age, 18.3 million (7.4%) are under 5 years of age, and 35 million (12%) are 65 years of age or older. Hence, large proportions of the U.S. population are included in age groups that are considered likely to have increased susceptibility and vulnerability for health effects from ambient SO_2 exposure. For example, Figure 4-6 demonstrates that the SO_2-related excess risk for asthma is, on average, 50% higher among children when compared to risk estimates that include all ages with a 10 ppb increase in 24-h avg SO_2 concentration.

Table 4-2. Prevalence of selected respiratory disorders by age group in the United States (2004 [U.S. adults] and 2005 [U.S. children] National Health Interview Survey).

CHRONIC CONDITION/DISEASE ADULTS (18+ YEARS)	AGE (YEARS)					
	ALL ADULTS		18-44	45-64	65-74	75+
	CASES ($\times 10^6$)	%	%	%	%	%
Respiratory Conditions: Asthma	14.4	6.7	6.4	7.0	7.5	6.6
COPD: Chronic Bronchitis	8.6	4.2	3.2	4.9	6.1	6.3
COPD: Emphysema	3.5	1.7	0.3	2	4.9	6.0
CHRONIC CONDITION/DISEASE CHILDREN (<18 YEARS)	**ALL CHILDREN**		**0-4**	**5-11**	**12-17**	
	CASES ($\times 10^6$)	**%**	**%**	**%**	**%**	
Respiratory Conditions	6.5	8.9	6.8	9.9	9.6	

Source: National Center for Health Statistics (2006a,b)

Evidence indicates that several groups are potentially at increased risks from SO_2 exposures compared to the average population. Susceptible subgroups include individuals with preexisting disease, especially asthma, and children and older adults. Other individuals with potentially increased vulnerability include those who spend a lot of time outdoors at increased exertion levels (e.g., outdoor workers, children, individuals who exercise or play sports) and those in proximity to large uncontrolled or poorly controlled sources. The considerable size of the population groups at risk indicates that exposure to ambient SO_2 could have a potentially significant impact on public health in the United States, with the greatest public health risks for the smaller subset of susceptible individuals exposed to relatively high peak SO_2 concentrations.

Chapter 5. Summary and Conclusions

Previous chapters present the most policy-relevant information related to the review of the NAAQS for SO_x, which are 0.14 ppm averaged over a 24-hour period not to be exceeded more than once per year, and 0.030 ppm annual arithmetic mean, with SO_2 as the indicator. This chapter summarizes and integrates key findings from atmospheric sciences, ambient air data analyses, exposure assessment, dosimetry, and health evidence. The EPA framework for causal determinations described in Chapter 1 has been applied to the body of evidence in order to judge the scientific data about exposure to SO_x and health effects in a two-step process. This framework draws from similar efforts across the Federal government and the wider scientific community, especially from the recent NAS Institute of Medicine document *Improving the Presumptive Disability Decision-Making Process for Veterans* (IOM, 2007). The first step is to determine the weight of evidence in support of causation at relevant pollutant exposures and characterize the strength of any resulting causal classification. The EPA framework applied here employs a five-level hierarchy for causal determination to be consistent with the *Guidelines for Carcinogen Risk Assessment* (EPA, 2005):

- Sufficient to infer a causal relationship
- Sufficient to infer a likely causal relationship (i.e., more likely than not)
- Suggestive but not sufficient to infer a causal relationship
- Inadequate to infer the presence or absence of a causal relationship
- Suggestive of no causal relationship

The second step evaluates the quantitative evidence regarding the concentration-response relationships including levels and exposure durations at which effects are observed. These two steps characterize the health effects of SO_x and levels at which effects may occur.

5.1. Emissions and Ambient Concentrations of SO_2

Anthropogenic SO_2 is emitted mainly by fossil fuel combustion (chiefly coal and oil) and metal smelting. The largest source of emissions is from elevated point sources such as the stacks of power plants and industrial facilities. Since 1990, in response to controls applied under the Acid Rain Program (EPA, 2006), SO_2 emissions from these sources have declined substantially.

Emissions demonstrate a strong gradient increasing from west to east, owing to the high concentration of SO_2-emitting electric generating utilities in the Ohio River Valley and regions to the south. PRB levels of SO_2 are estimated to be in the range of a few hundredths of a ppb (< 1% of typical ambient levels) across most of the United States, though much higher values are found in areas affected by volcanic or geothermal activity or in areas affected by episodic transport of high concentration plumes from Asia and Europe.

The levels of the current primary NAAQS for SO_x are 0.14 ppm for 24-h avg SO_2 concentrations and 0.03 ppm for an annual avg SO_2 concentration. Exceedances in recent years have become rare, as the mean 24-h and annual avg SO_2 concentrations in the United States for the years 2003 to 2005 were ~4 ppb, with 99th percentile values of ~25 ppb for the 24-h avg, and ~15 ppb for both the 99^{th} percentile and max values of the annual avg. Mean 1-h max concentrations in these years were ~13 ppb, with a 99^{th} percentile value of ~120 ppb and maximum value of ~700 ppb. The large differences between 99^{th} percentile and maximum values for the shorter term averages suggest that the maxima are strongly limited spatially and temporally and are not a major determinant of the mean values. The nonuniform spatiotemporal distribution of 5-min data, which are voluntarily supplied from a very few monitors without a specific regulatory mandate makes them very difficult to use quantitatively for determining concentrations and exposures at this very short time duration.

5.2. Health Effects of SO_2

Evaluation of the health evidence, with consideration of issues related to atmospheric sciences, exposure assessment, and dosimetry, led to the conclusion that it is *sufficient to infer a causal relationship between respiratory morbidity and short-term exposure to* SO_2. This conclusion is supported by the consistency, coherence, and plausibility of findings observed in human clinical studies with 5-10 min exposures, epidemiological studies mostly using 24-h avg exposures,7 and animal toxicological studies using exposures of minutes to hours.

The respiratory health effects of SO_2 are consistent with the mode of action of SO_2 as it is currently understood. The immediate effect of SO_2 on the respiratory system is bronchoconstriction. This response is mediated by chemosensitive receptors in the tracheobronchial tree. These receptors trigger reflexes at the central nervous system level resulting in bronchoconstriction, mucus secretion, mucosal vasodilation, cough, and apnea

followed by rapid shallow breathing. In some cases, local nervous system reflexes also may be involved. Asthmatics are more sensitive to the effects of SO_2 likely resulting from preexisting inflammation associated with this disease. This inflammation may lead to enhanced release of mediators, alterations in the autonomic nervous system and/or sensitization of the chemosensitive receptors. These biological processes are likely to underlie the respiratory symptoms; exacerbations of airways inflammation, reactivity, and responsiveness; and decreased lung function observed in response to SO_2 exposure.

The strongest evidence for this causal relationship comes from human clinical studies reporting respiratory symptoms and decreased lung functions following peak exposures of 5-10 min duration to SO_2 at concentrations which have sometimes been measured in ambient air for similarly short-time durations. These effects are particularly evident among exercising asthmatics, with some sensitive asthmatics (5-20%) experiencing moderate or greater decrements in lung function at SO_2 concentrations as low as 0.2-0.3 ppm (see Table 5-1). At concentrations

Table 5-1. Key health effects of short-term exposure to SO_2 observed in human clinical studies.

CONCENTRATION	EXPOSURE	EFFECTS	STUDIES
0.2-0.3 ppm	5-10 min	Moderate to large reductions in FEV_1 and increases in specific airway resistance (sRaw) observed among some asthmatic adults (5-20%) during moderate to heavy exercise. Bronchial responsiveness to SO_2 may be enhanced when preceded by exposure to O_3. Limited evidence of SO_2-induced increases in respiratory symptoms.	Bethel et al. (1985); Horstman et al. (1986); Koenig et al. (1990); Linn et al. (1983, 1987; 1988; 1990); Schachter et al. (1984); Sheppard et al. (1981); Trenga et al. (2001)
	1-6 h	Enhanced sensitivity to an inhaled allergen following exposure to SO_2 with NO_2 in resting asthmatics. No evidence of respiratory symptoms or decrements in lung function in resting asthmatics or healthy adults. Some weak and inconsistent evidence to suggest that SO_2 exposure may lead to changes in heart rate variability.	Devalia et al. (1994) ; Routledge et al. (2006); Rusznak et al. (1996); Tunnicliffe et al. (2001, 2003)
0.4-0.5 ppm	1-10 min	Decrements in lung function clearly demonstrated in asthmatics during exercise with significant interindividual variability in response (approximately 30% of asthmatics experienced moderate or greater decrements in lung function). Effects observed within 1-5 min of exposure generally not enhanced by increasing exposure duration. Respiratory symptoms (e.g., wheezing, chest tightness) observed at concentrations as low as 0.4 ppm and have been shown to increase with increasing exposure concentrations.	Balmes et al. (1987); Gong et al. (1995); Horstman et al. (1986); Koenig et al. (1983); Linn et al. (1983, 1987); Magnussen et al. (1990); Schachter et al. (1984); Sheppard et al. (1981); Trenga et al. (1999)
	~1-h	Decrements in lung function among asthmatics following 10 min of exercise at the end of a 60-75 min exposure are statistically significant, but less severe than effects observed following a 10 min period of exercise at the start of the exposure.	Linn et al. (1987); Roger et al. (1985)
0.6-1.0 ppm	1-10 min	Clear and consistent SO_2-induced increases in respiratory symptoms observed among exercising asthmatics. Moderate to large decrements in lung function demonstrated in 35-60% of asthmatics. Respiratory effects attributed to SO_2 among asthmatics during exercise may be diminished after cessation of exercise, even with continued SO_2 exposure. No respiratory effects reported in healthy, non-asthmatics.	Balmes et al. (1987); Gong et al. (1995); Hackney et al. (1984); Horstman et al. (1986, 1988); Koenig et al. (1983); Linn et al. (1987; 1988; 1990); Roger et al. (1985); Schachter et al. (1984)
	1-6 h	Decrements in lung function among asthmatics following 5-10 min of exercise at the end of a 1-6 h exposure are statistically significant, but less severe than effects observed following a 5-10 min period of exercise at the start of the exposure.	Linn et al. (1984 ; 1987); Hackney et al. (1984) ; Roger et al. (1985)

≥ 0.4 ppm, a greater percentage (20-60%) of asthmatics experience SO_2-induced decrements in lung function, which are frequently accompanied by respiratory symptoms. A clear concentration-response relationship has been demonstrated following exposures to SO_2 at concentrations between 0.2 and 1.0 ppm, both in terms of severity of effect and percentage of asthmatics adversely affected. Animal toxicological studies have also reported bronchoconstiction with short-term exposures of 0.5 to 1 ppm SO_2 (see Table 5-2).

A larger body of evidence supporting this determination of causality comes from numerous epidemiological studies reporting associations with respiratory symptoms, ED visits, and hospital admissions with short-term SO_2 exposures, generally of 24-h avg. Almost all of these studies were conducted in areas where the maximum ambient 24-h avg SO_2 concentration was consistently below the current 24-h avg NAAQS level of 0.14 ppm. Important new multicity studies and several other studies have found an association between 24-h avg ambient SO_2 concentrations and respiratory symptoms in children, particularly those with asthma. Furthermore, limited epidemiological evidence indicates that atopic children and adults may be at increased risk for SO_2-induced respiratory symptoms. Generally consistent associations also were observed between ambient SO_2 concentrations and ED visits and hospitalizations for all respiratory causes, particularly among children and older adults (≥ 65 years), and for asthma. The SO_2-related changes in ED visits or hospital admissions for respiratory causes ranged from -5% to 20% excess risk. Results of experiments in laboratory animals support these observations. Studies in animals sensitized with antigen demonstrated that repeated exposure to SO_2 levels as low as 0.1 ppm exacerbated allergic responses including mucin production, airway inflammation and airway hyperresponsiveness. These responses are consistent with exacerbation of asthma in humans.

The consistency and internal coherence of the epidemiological evidence for respiratory effects associated with short-term exposure to SO_2 are illustrated in Figures 5-1 and 5-2, which present effect estimates for respiratory symptoms, ED visits, and hospitalizations in children. Associations between short-term ambient SO_2 concentrations and respiratory symptoms, ED visits, and hospitalizations are largely positive, with several of the more precise effect estimates (suggestive of greater study power) indicating statistical significance. The epidemiological findings of asthma symptoms with 24-h avg SO_2 exposures are generally coherent with increases

Table 5-2. Key respiratory health effects of exposure to SO_2 in animal toxicological studies.

REFERENCE	EXPOSURE	SPECIES	EFFECTS
LUNG FUNCTION			
Amdur et al. (1983)	1 ppm SO_2 for 1-h	Male Hartley guinea pigs	An 11% increase in pulmonary resistance and 12% decrease in dynamic compliance were observed. Neither effect persisted into the 1-h period following exposure. No effects were observed for breathing frequency, tidal volume, or min volume.
Conner et al. (1985)	1 ppm (2.62 mg/m^3); nose only; 3-h/day for 6 days; animals evaluated for up to 48-h following exposure	Hartley guinea pig, male, age not reported, 250-320 g, n = ≤18 group/time point	No effect was observed on residual volume, functional reserve capacity, vital capacity, total lung capacity, respiratory frequency, tidal volume, pulmonary resistance, pulmonary compliance, diffusing capacity for carbon monoxide or alveolar volume at 1- or 48-h after last exposure.
Barthélemy et al. (1988)	0.5 or 5 ppm (1.3 or 13.1 mg/m^3); intratracheal; 45 min	Rabbit, sex not reported, adult, mean 2.0 kg, n = 5-9/group; rabbits were mechanically ventilated	Lung resistance increased by 16% and 50% in response to 0.5 and 5 ppm SO_2, respectively. Bivagotomy had no effect on 5 ppm SO_2-induced increases in lung resistance (54% increase before vagotomy and 56% increase after vagotomy). Reflex bronchoconstrictive response to phenyldiguanide (intravenously administered) was eliminated by exposure to SO_2 but SO_2 had no effect on lung resistance induced by intravenously-administered histamine. The study authors concluded that (1) vagal reflex is not responsible for SO_2-induced increase in lung resistance at 45 min and (2) transient alteration in tracheobronchial wall following SO_2 exposure may have reduced accessibility of airway nervous receptors to phenyldiguanide.
LUNG INJURY, INFLAMMATION AND MORPHOLOGY			
Conner et al. (1989)	1 ppm (2.62 mg/m^3); nose only 3-h/day for 5 days; bronchoalveolar lavage performed daily	Hartley guinea pig, male, age not reported, 250-320 g, n = 4	No change in numbers of total cells and neutrophils, protein levels or enzyme activity in lavage fluid following SO_2 exposure.
Park et al. (2001)	0.1 ppm (0.26 mg/m^3); whole body; with and without exposure to ovalbumin, 5-h/day for 5 days	Dunkin-Hartley guinea pig, male, age not reported, 250-350 g, n = 7-12/group	After bronchial challenge, the ovalbumin/SO_2-exposed group had significantly increased eosinophil counts in BAL fluids compared with all other groups, including the SO_2–only group. The bronchial and lung tissue of the ovalbumin/SO_2–exposed group showed infiltration of inflammatory cells, bronchiolar epithelial damage, and mucus and cell plug in the lumen.
Li et al. (2007b)	2 ppm (5.24 mg/m^3), with and without exposure to ovalbumin, 1-h/day for 7 days	Wistar rats, male, age not reported	Increased number of inflammatory cells in BALfluid, increased levels of MUC5AC and ICAM-1 and an enhanced histopathological response compared with those treated with ovalbumin or SO_2 alone
Conner et al. (1985)	1 ppm, 3-h/day/6 day. Evaluated up to 72-h postexposure	Male Hartely guinea pigs	No alveolar lesions.
Smith et al. (1989)	1 ppm, 5-h/day, 5 day/wk up to 4 and 8 mos	Male Sprague-Dawley rats	Increased bronchial epithelial hyperplasia and number of nonciliated epithelial cells observed at 4 mos.
AIRWAY HYPERRESPONSIVENESS AND ALLERGY			
Riedel et al. (1988)	0.1, 4.3, or 16.6 ppm (0, 0.26, 11.3, or 43.5 mg/m^3); whole body; 8-h/day for 5 days; animals were sensitized to ovalbumin on the last 3 days of exposure	Perlbright-White Guinea pig, female, age not reported, 300-350 g, n = 5 or 6/group (14 controls)	Bronchial provocation with ovalbumin was conducted every other day for 2 wks, starting at 1 wk after the last exposure. Numbers of animals displaying symptoms of bronchial obstruction after ovalbumin provocation was increased in all SO_2 groups compared to air-exposed groups. Anti-ovalbumin antibodies (IgG total and IgG1) were increased in BAL fluid and serum of SO_2-exposed compared to air-exposed controls, with statistical significance obtained for IgG total in BAL fluid at ≥4.3 ppm SO_2 and in serum at all SO_2 concentrations. Results indicate that in this model, subacute exposure to even low concentrations of SO_2 can potentiate allergic sensitization of the airway.
Park et al. (2001)	0.1 ppm (0.26 mg/m^3); whole body; with and without exposure to ovalbumin; 5-h/day for 5 days	Dunkin-Hartley guinea pig, male, age not reported, 250-350 g, n = 7-12/group	After bronchial challenge, the ovalbumin/SO_2-exposed group had significantly increased enhanced pause (indicator of airway obstruction) compared with all other groups, including the SO_2 group. Study authors concluded that low level SO_2 may enhance the development of ovalbumin-induced asthmatic reactions in guinea pigs.

in symptoms reported in asthmatics in human clinical studies with 5-10 min exposures; it is possible that these epidemiological associations are determined in large part by peak exposures within a 24-h period. The effects of SO_2 on respiratory symptoms, lung function, and airway inflammation observed in the human clinical studies using peak exposures further provides a basis for a progression of respiratory morbidity resulting in increased ED visits and hospital admissions. Collectively, these findings provide biological plausibility for the observed associations between ambient SO_2 levels and ED visits and hospitalizations for all respiratory diseases and asthma, notably in children and older adults (≥ 65 years).

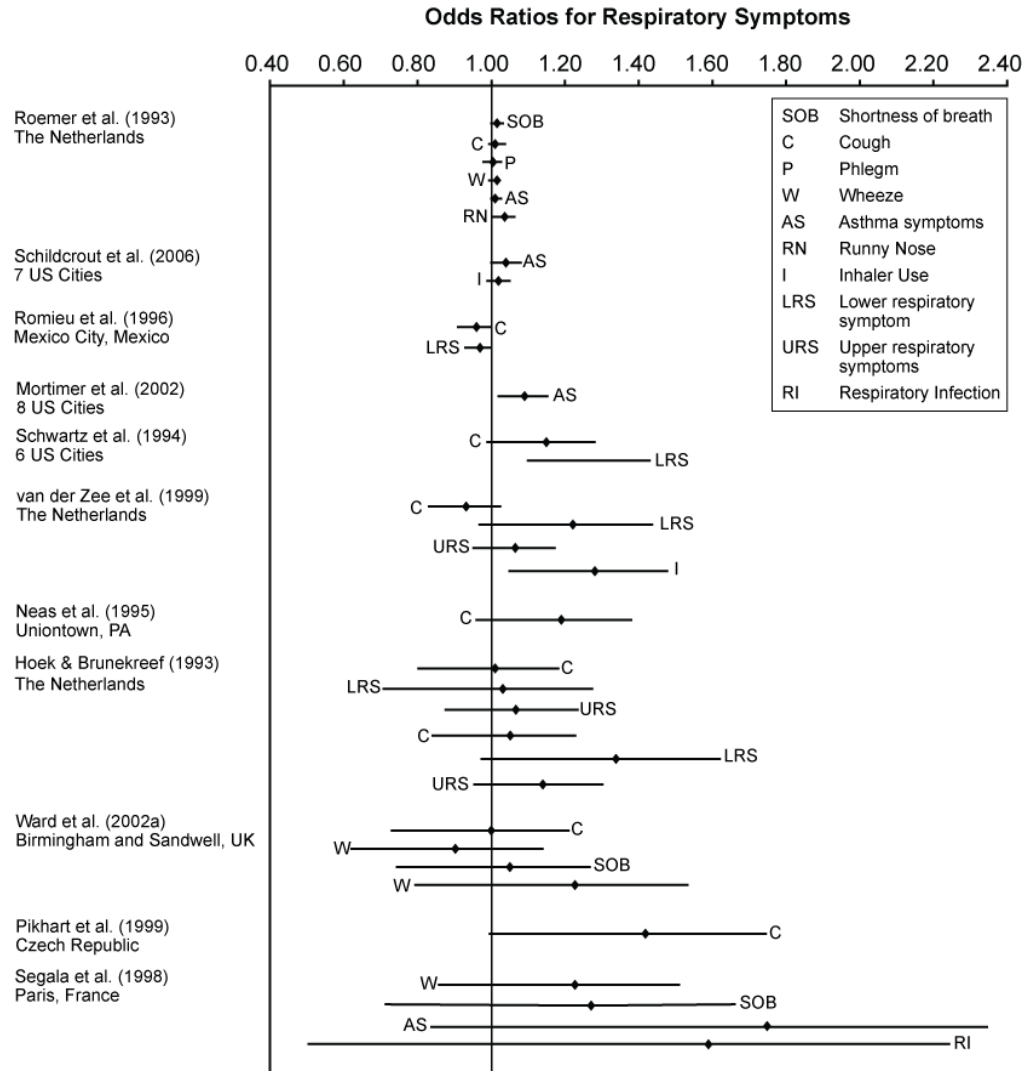

Figure 5-1. Odds ratios (95% CI) for the association between short-term exposures to ambient SO_2 and respiratory symptoms in children. Odds ratios are standardized per 10-ppb increase in

24-h avg SO_2 level. Studies are generally presented in the order of increasing width of the 95% CI.

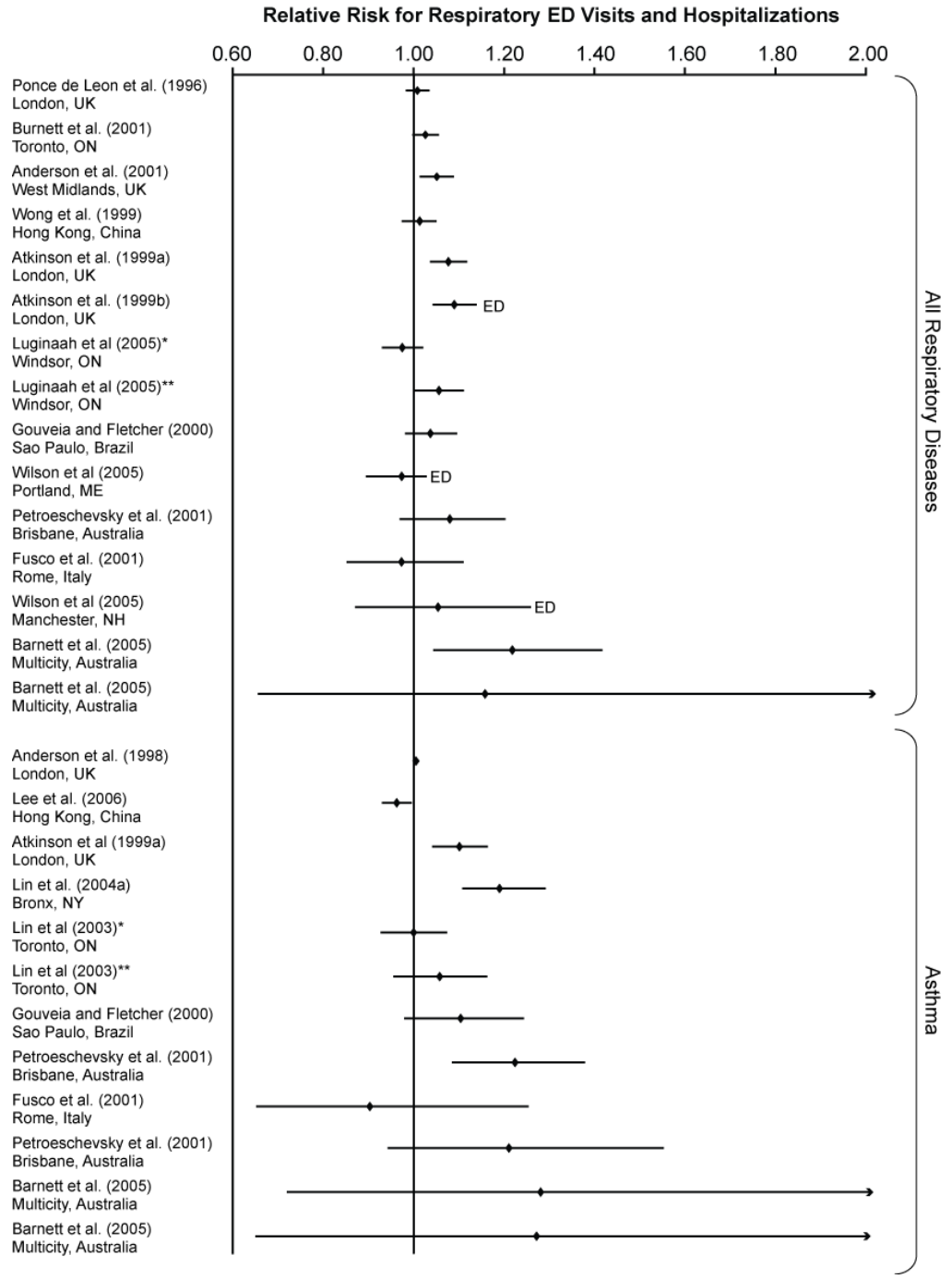

Figure 5-2. Relative risks (95% CI) for the association between short-term exposures to ambient SO_2 and emergency department (ED) visits/hospitalizations for all respiratory diseases and asthma in children. Relative risks are standardized per 10-ppb increase in 24-h avg SO_2 level. The

studies are generally presented in the order of increasing width of the 95% CI. For Luginaah et al. (2005) and Lin et al. (2003), risk estimates for males (*) and females (**) are shown separately.

Overall, the epidemiological evidence for respiratory morbidity is consistent, with associations reported in studies conducted in numerous locations using a variety of methodological approaches. In the epidemiological studies that assessed potential confounding by copollutants using multipollutant models, SO_2 effect estimates were generally robust to the inclusion of copollutants, including PM, O_3, CO, and NO_2, suggesting that the observed effects of SO_2 on respiratory endpoints occur independent of the effects of other ambient air pollutants.

Intervention studies provide additional evidence that supports a causal relationship between SO_2 exposure and respiratory health effects. The proposition that intervention studies can provide strong support for causal inferences was emphasized by Hill (1965). Two notable studies conducted in several cities in Germany and in Hong Kong reported that decreases in SO_2 concentrations were associated with improvements in respiratory symptoms. In eastern Germany, a decrease in the prevalence of respiratory symptoms was correlated with a steep decline in ambient SO_2 concentrations of more than 90% from 1992-1993 to 1998-999. During this study period, decreases in other ambient air pollutants, including ~60% lower TSP concentrations, also occurred in these cities. In Hong Kong, respiratory health improved with similarly large reductions in SO_2 of up to 80% in the polluted district but with much smaller reductions in TSP (less than 20%) compared with those in the cities in eastern Germany. The possibility remains that these health improvements may be partially attributable to declining concentrations of air pollutants other than SO_2, most notably PM or constituents of PM. Animal toxicological studies have reported that interactions of SO_2 and PM may lead to transformation of SO_2 to other sulfur-containing compounds which may have more potent biological effects; thus the improvements in respiratory health may be jointly attributable to declines in both SO_2 and PM.

The draft ISA also evaluates the evidence of other health outcomes and exposure durations. For short-term exposure to SO_2 and mortality, the evidence was found to be suggestive but not sufficient to infer a casual relationship. Recent epidemiological studies have consistently reported positive associations between mortality and SO_2, with slightly larger effect estimates observed for respiratory mortality compared to cardiovascular mortality. However, the SO_2 effect estimates were generally reduced after adjusting for copollutants in the regression models, indicating some extent of confounding among these pollutants. The evidence between short-term

SO_2 exposure and cardiovascular effects, and morbidity and mortality with long-term SO_2 exposures is inadequate to infer a causal relationship. The key conclusions on the health effects of SO_2 exposure are briefly summarized in Section 5.5.

5.3. Interpretation of the Epidemiological Evidence

This section highlights some key considerations for the evaluation of epidemiological evidence in this draft ISA. As discussed above, clinical studies provide the strongest evidence that short-term SO_2 exposure is associated with respiratory morbidity. Numerous epidemiological studies report associations for a broader range of respiratory health outcomes, at lower concentrations than the clinical studies, at levels below the current standard. There is, however, uncertainty about the magnitude of the epidemiological effects estimates. Several sources of uncertainty and the implications for risk assessment are discussed below.

Although the numerous epidemiological studies provide supportive evidence in making a causal determination for the effect of SO_2 on respiratory health, much uncertainty remains in the magnitude of the effect estimates related to ambient SO_2 exposures. Exposure measurement error is a key source of this uncertainty as there are questions about the extent to which concentrations measured by the regulatory ambient monitoring network typically used in epidemiological studies can accurately represent an individual's exposure to SO_2 of ambient origin. Factors contributing to exposure measurement error include the spatial variation in ambient SO_2, variation in time-activity patterns and the infiltration characteristics of microenvironments, as well as instrument error in the ambient and personal monitors.

SO_2 monitors currently deployed in the regulatory monitoring networks are adequate to determine compliance with current standards, since both the 24-h avg and annual standards are substantially above the operating limit of detection of these monitors. However, these monitors are inadequate for accurate and precise measurements at or near the current ambient mean 24-h avg SO_2 levels of ~4 ppb. Also, typical 24-h avg personal SO_2 exposures are often below the detection limit of commonly deployed passive SO_2 monitors. Therefore, the association between ambient concentrations and personal exposure may be inadequately characterized in recent studies at lower ambient concentrations.

For community time-series and short-term panel epidemiological studies using daily SO_2 concentrations from ambient monitors, these exposure and analytical measurement errors would

tend to bias the effect estimate towards the null, leading to uncertainty in accurately quantifying the magnitude of the effect. In long-term exposure studies, the variable ambient measurement and exposure error could also result in bias, but the extent and direction of this bias is unclear.

Another factor that contributes to uncertainty in estimating the SO_2-related effect from epidemiological studies is that SO_2 is one component of a complex air pollution mixture including various other components, e.g., PM and NO_2, known to affect respiratory health.

As a consequence of these uncertainties, the epidemiological observations of SO_2 health effects can be interpreted in several ways which are not mutually exclusive. First, the reported SO_2 effect estimates in epidemiological studies may reflect independent SO_2 effects on respiratory health. This is supported by evidence from human clinical studies which indicate that peak exposures (5-10 min) to SO_2 at levels as low as 0.2-0.3 ppm are capable of eliciting respiratory responses in some sensitive asthmatics. Because pure SO_2 does not appear alone in real-world ambient conditions but rather is part of a pollutant mixture, it is difficult to relate these peak exposures in the human clinical studies unequivocally to the 24-h avg SO_2 concentrations typically assessed in epidemiological studies. It is possible that higher, shorter-term concentrations of SO_2 may be driving the observed associations in epidemiological studies. Among the limited number of epidemiological studies evaluating the concentration-response function, several reported a linear relationship across the entire range of concentrations, suggesting the lack of a population effects threshold. However, other studies found that a marked increase in SO_2-related respiratory health effects was only observed at higher concentrations (above 90^{th} percentile values).

A second interpretation is that ambient SO_2 may be serving as an indicator of complex ambient air pollution mixtures sharing the same source as SO_2 (i.e., combustion of sulfur-containing fuels or metal smelting). Other components of mixed emissions from these sources include trace elements such as vanadium, nickel, selenium, and arsenic. Distinguishing effects of individual pollutants in multipollutant regression models is made difficult by the possibility that a given air pollutant may be acting as a surrogate for a less-well-measured or unmeasured pollutant, or that several pollutants may all be acting as surrogates for the same mixtures of pollutants. Therefore, reported SO_2-related effects may represent those of the overall mixture or other chemical components within the mixture. However, analysis of ambient data compiled monthly for the years 2003 to 2005 showed that SO_2 concentrations were uncorrelated with SO_4^{2-}

in 12 CMSAs having multiple monitors. Moreover, in multipollutant models adjusted for PM indices, SO_2 effect estimates were generally found to be robust.

A third interpretation is that in situations of complex pollution mixtures, copollutants may enhance the toxic capability of SO_2 or that SO_2 may influence the toxicity of copollutants. Findings from animal toxicological studies demonstrate that the effects of SO_2 may be exacerbated when aerosol particles act as carriers and deliver sulfur-containing compounds more effectively to the lower respiratory tract. The synergism observed with combined exposure to SO_2 and PM in the animal toxicological studies provides supportive evidence for the SO_2-related respiratory effects observed under ambient conditions in the epidemiological studies.

5.4. Susceptible and Vulnerable Populations

Evidence from epidemiological and human clinical studies has indicated that certain subgroups within the population are more susceptible and/or vulnerable to the effects of SO_2 exposure. There is substantial evidence from epidemiological and human clinical studies indicating that asthmatics are more susceptible to respiratory health effects from SO_2 exposures than the general public. Limited epidemiological evidence further suggests that children and older adults ($\geq$ 65 years) are more susceptible to the adverse respiratory effects associated with ambient SO_2 concentrations when compared to the general population. A number of potentially susceptible groups, including obese individuals, individuals in a chronic pro-inflammatory state like diabetics, and children born prematurely or with low birth weight (< 2,500 grams), may experience increased adverse effects associated with exposure to air pollution, but these relationships have not been examined specifically in relation to SO_2. The differential effects of air pollution among genetically diverse subpopulations have been examined for a number of GST genes and other genotypes. While limited in number, these studies provide some insight into a potential genetic role in the determination of susceptibility to air pollution.

Human clinical studies have clearly shown that exercising asthmatics are at greatest risk of experiencing adverse respiratory effects related to SO_2 exposure. Oronasal breathing during exercise increases vulnerability as it allows a larger fraction of inhaled SO_2 to reach the lower airways. Therefore, individuals with increased vulnerability for SO_2-related respiratory health effects include those who spend time outdoors at increased exertion levels, for example children, outdoor workers, and individuals who exercise or play sports.

5.5. Conclusions

The important findings of this draft ISA on the health effects of SO_2 exposure, including the levels at which effects are observed, are briefly summarized in Table 5-3. Also summarized are conclusions drawn in the previous review for comparison.

Collectively, the epidemiological, human clinical, and animal toxicological data support the finding of a causal relationship between short-term exposure to SO_2 and respiratory morbidity. Observed associations between SO_2 exposure and an array of respiratory outcomes, including respiratory symptoms, lung function, airway inflammation, airway hyperresponsiveness, and ED visits and hospitalizations from the human clinical, animal toxicological, and epidemiological studies, in combination, provide clear and convincing evidence of consistency, specificity, temporal and biologic gradients, biological plausibility, and coherence.

Human clinical studies provide strong evidence of respiratory morbidity among asthmatics following peak exposures (5-10 min) to SO_2 concentrations $\geq$ 0.4 ppm, with some evidence of respiratory effects at concentrations as low as 0.2 ppm in the most sensitive asthmatics. In the epidemiological studies, the SO_2-related respiratory effects were consistently observed in areas where the maximum ambient 24-h avg SO_2 concentration was below the current 24-h avg NAAQS level of 0.14 ppm (Tables 5-4 and 5-5). Potentially susceptible and vulnerable subgroups include asthmatics, children, older adults, and individuals who spend a lot of time outdoors at increased exertion levels.

In addition to respiratory morbidity related to short-term exposure to SO_2, studies of other health outcomes and exposure durations were also evaluated in this draft ISA. The evidence is suggestive but not sufficient to infer a causal relationship between short-term exposure to SO_2 and mortality. The evidence linking short-term SO_2 exposure and cardiovascular effects, and morbidity and mortality with long-term exposures to SO_2 is inadequate to infer a causal relationship.

Table 5-3. Key findings on the health effects of SO_2 exposure

Short-Term Exposure: RESPIRATORY MORBIDITY
Sufficient to infer a causal relationship

RESPIRATORY SYMPTOMS

Previous Conclusion: Among exercising asthmatics, there is a clear, statistically significant increase in respiratory symptoms following peak exposures (5-10 min) to 0.6-1.0 ppm SO_2. Significant, but less severe symptoms are associated with peak SO_2 exposures at concentrations of 0.4-0.5 ppm in human clinical studies.

In the epidemiological studies, an association with aggravation of bronchitis is consistently obsserved at 24-h avg SO_2 levels of 0.19 to 0.23 ppm and in some cases at levels below 0.19 ppm.

Current Conclusion: Recent human clinical studies provide additional evidence of respiratory symptoms in asthmatics following peak exposures (5-10 min) with exercise to 0.5 ppm SO_2. Statistically significant increases in respiratory symptoms are observed at SO_2 concentrations of as low as 0.4 ppm, with the severity of symptoms shown to increase with increasing concentration between 0.4 and 0.6 ppm.

Epidemiological studies provide consistent evidence of an association between ambient SO_2 exposure and increased respiratory symptoms in children, particularly those with asthma or chronic respiratory symptoms. Multicity studies have observed these associations at a median range of 17 to 37 ppb (75th percentile: ~25 to 50) across cities for 3-h avg SO_2 and 2.2 to 7.4 ppb (90th percentile: 4.4 to 14.2) for 24-h avg SO_2.

In contrast, the epidemiological evidence on the association between SO_2 and respiratory symptoms in adults are generally mixed, with some showing positive associations and others finding no relationship at current ambient levels.

LUNG FUNCTION

Previous Conclusion: Bronchoconstriction has been found to be the most sensitive indicator of lung function effects following acute exposure to SO_2. Guinea pigs were found to be the most sensitive species, with bronchoconstriction observed using 0.16 ppm SO_2. In human clinical studies, ≤ 10-20% of exercising asthmatic individuals experience large decrements in lung function (i.e., sRaw increases ≥ 200% or FEV_1 decreases ≥ 20%) following 5-10 min exposures to SO_2 concentrations of 0.2-0.5 ppm. At 0.6-1.0 ppm SO_2, ≥ 20-25% of exercising asthmatics are similarly affected.

Small, reversible declines in lung function in children are observed in epidemiological studies at levels of 0.10 to 0.18 ppm but not at levels of 0.04 to 0.08 ppm.

Current Conclusion: Evaluation of the human clinical evidence focused on moderate or greater decrements in lung function in exercising asthmatics. SO_2-induced increases in sRaw (≥ 100%) or decreases in FEV_1 (≥ 15%) following 5-10 min exposures are observed in 5-10% of individuals at 0.2 ppm, 10-20% of individuals at 0.3 ppm, and 20-60% of individuals at 0.4-1.0 ppm.

The results are inconsistent for the association between 24-h avg SO_2 and lung function in children and adults in the epidemiological studies.

AIRWAYS INFLAMMATION

Previous Conclusion: No overall conclusion.

Current Conclusion: A limited number of health studies have evaluated the effect of SO_2 on airway inflammation. One human clinical study observed an SO_2-induced increase in sputum eosinophil counts in exercising asthmatics 2 h after a 10 min exposure to 0.75 ppm SO_2. The results of this study provide some evidence that SO_2 may elicit an allergic inflammatory response in the airways of asthmatics which extends beyond the short time period typically associated with SO_2 effects.

Animal toxicological studies suggest that repeated exposures to SO_2, at concentrations as low as 0.1 ppm in guinea pigs, may exacerbate inflammatory responses in allergic animals.

AIRWAYS RESPONSIVENESS

Previous Conclusion: No conclusions in the previous review.

Current Conclusion: Animal toxicological evidence suggests that repeated exposures to SO_2, at concentrations as low as 0.1 ppm in guinea pigs, can exacerbate airway responsiveness following allergic sensitization. In a human clinical study, concurrent exposure (6 h) to 0.2 ppm SO_2 and 0.4 ppm NO_2 has been observed to enhance airway responsiveness to an inhaled antigen among resting asthmatics. These findings are consistent with the very limited epidemiological evidence that suggests that exposure to SO_2 may lead to airway hyperresponsiveness in atopic individuals.

ED VISITS/HOSPITALIZATIONS

Previous Conclusion: No conclusions in the previous review.

Current Conclusion: Epidemiological studies provide evidence of an association between ambient SO_2 concentrations and ED visits and hospitalizations for all respiratory causes, particularly among children and older adults (age 65+ years), and for asthma. The SO_2 effect estimates ranged from a 5% decreased risk to a 20% excess risk per 10- ppb increase in 24-h avg SO_2, with the large majority of studies suggesting an increase in risk. These effects were observed in studies with mean 24-h avg concentrations as low as 4 ppb, but two studies evaluating the concentration-response function observed that a marked increase in SO_2-related effects was only observed higher concentrations (above 90^{th} percentile values).

Short-Term Exposure: CARDIOVASCULAR MORBIDITY

Inadequate to infer the presence or absence of a causal relationship

CARDIOVASCULAR EFFECTS; ED VISITS/ HOSPITALIZATIONS

Previous Conclusion: No conclusions in the previous review.

Current Conclusion:There was some suggestive evidence of an association between 24-h avg SO_2 exposure and heart rate variability in the epidemiological studies, but the evidence from two human clinical studies with were weak and inconsistent. Some epidemiological studies have observed positive associations between ambient SO_2 concentrations and ED visits or hospital admissions for cardiovascular diseases, but results are not consistent across studies and the SO_2 effect estimate was generally not robust to copollutant adjustment.

Short-Term Exposure: MORTALITY

Suggestive but not sufficient to infer a casual relationship

NONACCIDENTAL AND CARDIOPULMONARY MORTALITY

Previous Conclusion: Epidemiological studies based on historical air pollution episodes observed the clearest mortality associations when both black smoke (BS) and SO_2 concentrations were at high levels (24-h avg values exceeding 1,000 $\mu g/m^3$ [~400 ppb for SO_2]). Later studies observed that an increased risk of mortality was associated with exposure to BS and SO_2 levels in the range 0.19 to 0.38 ppm. Because of the high colinearity between BS and SO_2 levels, it is difficult to readily separate the effects of these pollutants on mortality.

Current Conclusion: Recent epidemiological studies have consistently reported positive associations between mortality and SO_2, often at mean 24-h avg levels < 10 ppb. The range of SO_2 excess risk estimates for nonaccidental mortality is 0.4 to 2% per 10 ppb increase in 24-h avg SO_2 in several multicity studies and meta-analyses. SO_2 effect estimates for respiratory mortality were generally larger than the cardiovascular mortality estimates, suggesting a stronger association of SO_2 with respiratory mortality compared to cardiovascular mortality. The SO_2 effect estimates were generally reduced when copollutants were added in the model, indicating some extent of confounding among these pollutants.

Long-Term Exposure: RESPIRATORY MORBIDITY

Inadequate to infer the presence or absence of a causal relationship

RESPIRATORY SYMPTOMS AND LUNG FUNCTION

Previous Conclusion: The limited available epidemiological data indicated associations between respiratory illnesses and symptoms and persistent exposures to SO_2 in areas with long-term averages exceeding 0.04 ppm.

Current Conclusion: Several epidemiological studies that examined the effects of long-term exposure to SO_2 on asthma, bronchitis, and respiratory symptoms observed positive associations in children. While the evidence is suggestive, the variety of outcomes examined and the inconsistencies in the observed results make it difficult to assess the direct impact of long-term exposure of SO_2 on respiratory symptoms. The epidemiological and animal toxicological evidence generally do not indicate that long-term exposure to SO_2 has a detrimental effect on lung function.

Long-Term Exposure: OTHER MORBIDITY

Inadequate to infer the presence or absence of a causal relationship

CARCINOGENIC EFFECTS

Previous Conclusion: Epidemiological evidence did not substantiate the hypothesized links between SO_2 or other SO_x and cancer, though there was some animal toxicological evidence that led to the conclusion that SO_2 may be considered a suspect carcinogen/cocarcinogen.

Current Conclusion: Animal toxicological studies indicate that SO_2 at high concentrations may cause DNA damage but fails to induce carcinogenesis, cocarcinogenesis, or tumor promotion. Epidemiological studies did not provide evidence that long-term exposure to SO_2 is associated with an increased incidence of or mortality from lung cancer.

PRENATAL AND NEONATAL OUTCOMES

Previous Conclusion: No conclusions in the previous review.

Current Conclusion: Epidemiological studies on birth outcomes have found suggestive positive associations between SO_2 exposure and low birth weight. However, the inconsistent results across trimesters of pregnancy and the lack of evidence to evaluate confounding by copollutants limit the interpretation of these studies.

Long-Term Exposure: MORTALITY

Inadequate to infer the presence or absence of a causal relationship

NONACCIDENTAL AND CARDIOPULMONARY MORTALITY

Previous Conclusion: The available studies on the effects of long-term exposure to SO_2 on mortality were all ecological cross-sectional studies which did not take into consideration potential confounders. In addition, it was concluded that effects from PM and SO_2 could not be distinguished in these studies.

Current Conclusion: Two major U.S. epidemiological studies observed associations between long-term exposure to SO_2 and mortality, but several other U.S. and European cohort studies did not observe an association. The relative risks ranged from 0.97 to 1.07 per 5-ppb increase in the long-term average SO_2. Evaluation of these studies is further limited by the inability to distinguish potential confounding by copollutants and uncertainties regarding the geographic scale of analysis.

Table 5-4. Effects of short-term exposure to SO_2 on respiratory symptoms among children.

STUDY	POPULATION	MEAN CONCENTRATION	SO_2 (ppb) 98TH%	SO_2 (ppb) 99TH%	SO_2 (ppb) RANGE	SO_2 (ppb) UPPER %TILE	STANDARDIZED ODDS RATIO (95% CI)[a]
United States							
Schildcrout et al. (2006) Multicity, North America Seattle, WA; Baltimore, MD; St. Louis, MS (Nov 1993–Aug 1995); Denver, CO; San Diego, CA (Nov 1993–Jul 1995); Toronto, ON (Dec 1993–Jul 1995); Boston, MA (Jan 1994–Sep 1995) No SO_2 data available in Albuquerque, NM	Asthmatic children (n = 990)	24-h avg: 2.2-7.4 (range of city-specific medians)	NR	NR	NR	75th: 3.1, 10.7 90th: 4.4, 14.2 (range in city specific estimates)	Asthma symptoms: SO_2 alone: 1.04 (1.00, 1.08), 3-day sum SO_2 & NO_2: 1.04 (1.00, 1.09), 3-day sum SO_2 & PM_{10}: 1.04 (0.99, 1.08), 3-day sum
Schwartz et al. (1994) Multicity, United States Watertown, MA (Apr-Aug 1985); Kingston-Harriman, TN; St. Louis, MO (Apr-Aug 1986); Steubenville, OH; Portage, WI (Apr-Aug 1987); Topeka, KS (Apr-Aug 1988)	Children in grades 2-5 (n = 1,844)	24-h avg: 4.1 (median)	NR	NR	NR	75th: 8.2 90th: 17.9 Max: 81.9	Cough incidence: SO_2 alone: 1.15 (1.02-1.31), 4-day avg SO_2, adjusting for PM_{10}: 1.08 (0.93, 1.25), 4-day avg SO_2, adjusting for NO_2: 1.09 (0.94, 1.30), 4-day avg
Neas et al. (1995) Uniontown, PA Summer 1990	Children in grades 4-5 (n = 83)	12-h avg: 0.2 5.9 overnight 14.5 daytime	NR	NR	IQR: 11.1	Max: 44.9	Evening cough: 1.19 (1.00, 1.42), lag 12-h
Mortimer et al. (2002) Multicity, United States Bronx, NY; East Harlem, NY; Baltimore, MD; Washington, DC; Detroit, MI; Cleveland, OH; Chicago, IL; St. Louis, MO (Jun-Aug 1993)	Asthmatic children, aged 4-9 (n = 846)	3-h avg: 22 (shown in figure)	NR	NR	0-75 ppb (shown in graph)	NR	Asthma symptoms: SO_2 alone (8 cities): 1.19 (1.06, 1.35), lag 1-2 SO_2, adjusting for O_3 & NO_2 (7 cities): 1.19 (1.04, 1.37), lag 1-2 SO_2, adjusting for O_3, NO_2 & PM_{10} (3 cities):1.23 (0.94, 1.62), lag 1-2
Europe							
Timonen and Pekkanen (1997) Kuopio (urban and suburban) Finland Winter 1994	Children 7-12 yrs with asthma or cough symptoms (n = 169)	24-h avg: 2.3	NR	NR	NR	75th: 2.7 Max: 12.3	Upper respiratory symptoms: 2.71 (1.19, 6.17), lag 0 3.17 (1.21, 8.78), lag 1
Ward et al. (2002) Birmingham and Sandwell, UK Jan-Mar 1997 May-Jul 1997	Children, age at enrollment 9 yrs (n = 162)	24-h avg: Median 5.4, Winter 4.7, Summer	NR	NR	2, 18 Winter 2, 10 Summer	NR	Cough: Winter: 0.59 (0.25, 1.40), Summer: 0.90 (0.49, 1.66) Shortness of breath: Winter: 0.59 (0.32, 1.09), Summer: 0.81 (0.30, 2.17) Wheeze: Winter: 0.79 (0.38, 1.63), Summer: 0.77 (0.28, 2.08) (7-day avg lag for above)

STUDY	POPULATION	MEAN CONCENTRATION	SO_2 (ppb) 98TH%	SO_2 (ppb) 99TH%	SO_2 (ppb) RANGE	SO_2 (ppb) UPPER %TILE	STANDARDIZED ODDS RATIO (95% CI)[a]
Segala et al. (1998) Paris, France Nov 1992-May 1993	Children 7-15 yrs with physician-diagnosed asthma (n = 84)	24-h avg: 8.3 (5.2)	NR	NR	1.7-32.2	NR	Prevalent asthma: 1.32 (1.08, 1.62), lag 0 1.26 (0.93, 1.71), lag 1 Prevalent shortness of breath: 1.17 (0.53, 2.62), lag 0 1.21 (0.99, 1.49) lag 1 Incident asthma 1.73 (1.15, 2.60), lag 0 1.60 (1.01, 2.53), lag 1 Incident wheeze 1.22 (0.95, 1.58), lag 0 1.13 (0.68, 1.88), lag 1
Boezen et al. (1998) Amsterdam and Meppel (urban and rural), the Netherlands Winter 1993-1994	Children 7-11 yrs, with and w/o BHR and high serum concentrations of total IgE (n = 632)	24-h avg: Means: 1.7, 8.7; Medians: 1.4, 8.3 (range in city-specific estimates)	NR	NR	1.9, 23.6	NR	Among children with BHR and relatively high serum total IgE - lower respiratory symptoms: 1.27 (1.09, 1.49), lag 0 1.25 (1.06, 1.48), lag 1 1.69 (1.26, 2.28), 5-day avg
Roemer et al. (1993) Wageningen, the Netherlands Winter 1990-1991	Children 6-12 yrs with chronic respiratory conditions (n = 73)	24-h avg 1-h max	NR	NR	0, 40.4 (24-h avg)	Max: 56.5 (1-h max)	Asthma attack: 1.79 (1.35, 2.38). 7-day avg Wheeze: 1.97 (1.42, 2.72), 7-day avg Waken with symptoms: 1.79 (1.12, 2.87), 7-day avg Shortness of breath: 1.48 (1.06, 2.07), 7-day avg Cough: 1.97 (1.03, 3.77), 7-day avg
Hoek and Brunekreff (1993) Wageningen, the Netherlands Winter 1991	Children 7-11 yrs, nonurban area (n = 112)	24-h avg	NR	NR	NR	Max: 40.4	Cough: 1.22 (0.20, 7.39), lag 0 0.25 (0.04, 1.65), lag 1 3.67 (0.002, 7.331.974), 7-day avg Lower resp symptoms: 1.82 (0.14, 24.3), lag 0 0.33 (0.02, 6.05), lag 1 0.005 (0.0, 44.7), 5-day avg

STUDY	POPULATION	MEAN CONCENTRATION	SO_2 (ppb) 98TH%	SO_2 (ppb) 99TH%	SO_2 (ppb) RANGE	SO_2 (ppb) UPPER %TILE	STANDARDIZED ODDS RATIO (95% CI)[a]
Van der Zee et al. (1999) Urban and nonurban areas The Netherlands 3 winters, 1992-1995	Children 7-11 yrs, with and without chronic respiratory symptoms (n = 633)	24-h avg: 1.4, 8.8 (range in city-specific medians)	NR	NR	NR	Max: 6.5, 58.5 (range in city-specific maximums)	Lower respiratory symptoms, urban, SO_2 alone: 1.22 (1.01, 1.46), lag 0 1.14 (0.95, 1.38), lag 1 1.34 (0.98, 1.82), 5-day avg Lower respiratory symptoms, urban, SO_2, adjusting for PM_{10}: 1.18 (0.96, 1.45), lag 0 1.03 (0.83, 1.27), lag 1 1.08 (0.72, 1.63), 5-day avg Lower respiratory symptoms, nonurban: 0.94 (0.79, 1.12), lag 0 0.94 (0.78, 1.13), lag 1 1.10 (0.75, 1.63), 5-day avg Cough, urban: 0.93 (0.84, 1.03), lag 0 1.08 (0.98, 1.19), lag 1 1.08 (0.89, 1.30) 5-day avg Cough, nonurban: 1.05 (0.96, 1.15), lag 0 0.98 (0.90, 1.08), lag 1 1.04 (0.83, 1.30), 5-day avg

[a]24-h avg SO_2 and 12-h avg SO_2 standardized to 10- ppb incremental change; 3-h avg SO_2 standardized to 20-ppb incremental change; and 1-h max SO_2 standardized to 40-ppb incremental change. NR = Not Reported BHR = Bronchial Hyperresponsiveness

Table 5-5. Effects of short-term SO_2 exposure on emergency department visits and hospital admissions for respiratory outcomes.

STUDY	POPULATION	MEAN CONCENTRATION	SO_2 (ppb) 98TH%	SO_2 (ppb) 99TH%	SO_2 (ppb) RANGE	SO_2 (ppb) UPPER %TILE	STANDARDIZED ODDS RATIO (95% CI)[a]
EMERGENCY DEPARTMENT VISITS – ALL RESPIRATORY							
UNITED STATES							
Wilson et al. (2005) Portland, ME Jan 1998-Dec 2000 Manchester, NH Jan 1996-Dec 2000	≈ 84,000 ED visits	1-h max: Portland: 11.1 (9.1) Manchester: 16.5 (14.7)	NR	NR	NR	NR	Portland: All ages: 8% (3, 11) 0-14: -2.6% (-10.3, 2.7) 15-64: 11% (5.4, 13.9) 65+: 16.8% (8.2, 25.8) Manchester: All ages: 0% (-3, 5) 0-14: 0% (8, 8) 15-64: 0% (-3, 5) 65+: 8% (6, 23)
Tolbert et al. (2007) Atlanta, GA Jan 1993-Dec 2004	> 1,000,000 ED visits for all respiratory causes	1-h max: 14.9	NR	NR	1.0 - 149.0	75th: 20.0 90th: 35.0	0.75% (-0.75, 2.3)

STUDY	POPULATION	MEAN CONCENTRATION	SO_2 (ppb) 98TH%	SO_2 (ppb) 99TH%	SO_2 (ppb) RANGE	SO_2 (ppb) UPPER %TILE	STANDARDIZED ODDS RATIO (95% CI)[a]
Peel et al. (2005) Atlanta, GA Jan 1993-Aug 2000	484,830 ED visits, all ages from 31 hospitals	1-h max: 16.5 (17.1)	NR	NR	NR	90th: 39.0	1.6% (-0.6, 3.8)
EUROPE							
Atkinson et al. (1999a) London, UK Jan 1992-Dec 1994	98,685 ED visits from 12 hospitals	24-h avg: 8.0 (2.9)	NR	NR	2.8, 30.9	50th: 7.4 90th: 11.7	All Ages: 4.2% (1.1, 7.4) 0-14: 9.0% (4.4, 13.8) 15-64:4.0% (-0.3, 8.5) 65+: -2.7% (-5.4, 3.3)
EMERGENCY DEPARTMENT VISITS – ASTHMA							
UNITED STATES							
Ito et al. (2007) New York, NY Jan 1999-Dec 2002	Asthma ED visits, all ages from 11 hospitals	24-h avg: 7.8 (4.6)	NR	NR	NR	75th: 10 95th: 17	35% (23%, 51%)
NY Department of Health (2006) Bronx & Manhattan, NY Jan 1999-Dec 2000	Asthma ED visits among children from 22 hospitals	24-h avg : 11 (7.2)	NR	NR	NR	NR	5-day moving average: Manhattan: -1% (-12, 12) Bronx: 11% (6, 17)
Jaffe et al. (2003) Cincinnati, OH Cleveland, OH Columbus, OH Jul 1991-Jun 1996	4,416 ED visits for asthma, age 5-34	24-h avg: Cincinnati: 13.5 (9.4) Cleveland: 14.7 (9.5) Columbus: 4.2 (3.2)	NR	NR	Cincinnati: 0.6, 49.6 Cleveland: 0.98, 62.8 Columbus 0, 21.4	NR	Cincinnati: 17.3% (4.7, 30.8) Cleveland: 3.1% (-3.8, 10.7) Columbus: 13.1% (-14.2, 48.6) All Cities: 6.2% (0.5, 11.6)
Wilson et al. (2005) Portland, ME Jan 1998-Dec 2000 Manchester, NH Jan 1996-Dec 2000	≈ 84,000 ED visits	1-h max: Portland: 11.1 (9.1) Manchester: 16.5 (14.7)	NR	NR	NR	NR	Portland: All ages: 11.0% (0.0, 19.7) 0-14: 5.4% (-12.8, 25.8) 15-64: 11% (0, 22.7) 65+: 11.0% (-15.2, 48.4) Manchester: All ages: 5.4% (-2.6, 16.8) 0-14: 19.7% (-2.6, 51.8) 15-64: 2.7% (-7.8, 13.9) 65+: 11.0% (-28.8, 77.2)
Peel et al. (2005) Atlanta, GA Jan 1993-Aug 2000	Asthma ED visits, all ages and 2-18 yrs from 31 hospitals	1-h max: 16.5 (17.1)	NR	NR	NR	90th: 39.0	0.2% (-3.2, 3.4)

STUDY	POPULATION	MEAN CONCENTRATION	SO_2 (ppb) 98TH%	SO_2 (ppb) 99TH%	SO_2 (ppb) RANGE	SO_2 (ppb) UPPER %TILE	STANDARDIZED ODDS RATIO (95% CI)[a]
EUROPE							
Atkinson et al. (1999a) London, UK Jan 1992-Dec 1994	98,685 ED visits from 12 hospitals	24-h avg: 8.0 (2.9)	NR	NR	2.8, 30.9	50th: 7.4 90th: 11.6	All ages: 7.4% (2.3, 12.8) 0-14: 15.0% (7.1, 23.5) 15-64: 6.3% (-0.8, 13.8)
Hajat et al. (1999) London, UK Jan 1992-Dec 1994	General practitioner visits for asthma	24-h avg: All yr: 8.0 (2.9) Warm: 7.7 (2.4) Cool: 8.3 (3.4)	NR	NR	NR	All yr: 90th: 11.6 Warm: 90th: 10.7 Cool: 90th: 12.4	All ages: 6.6% (1.3, 11.9) 0-14: 6.6% (-1.0, 14.7) 15-64: 5.2% (-1.5, 12.3) 65+: 7.2% (-4.3, 20.1)
Boutin-Forzano et al. (2004) Marseille, France Apr 1997-Mar 1998	549 ED visits for asthma	24-h avg: 8.5	NR	NR	0.0, 35.3	NR	3-49 yrs: 0.6% (-1.4, 2.7)
Galan et al. (2003) Madrid, Spain Jan 1995-Dec 1998	4,827 ED visits for asthma	24-h avg: 8.9 (5.8)	NR	NR	1.9, 45.6	50th: 7.0 75th: 11.8 90th: 16.5	All ages: 4.9% (-4.2, 15.0)
Tenias et al. (1998) Valencia, Spain Jan 1993-Dec 1995	734 ED visits for asthma	24-h avg: 10.0 Cold: 11.9 Warm: 8.2 1-h max: 21.2 Cold: 24.3 Warm: 18.1	NR	NR	NR	24-h avg: 50th: 9.8 75th: 12.9 95th: 16.0 1-h max: 50th: 19.6 75th: 27.1 95th: 35.8	> 14 yrs: 13.9% (-7.0, 39.4)
Sunyer et al. (1997) Multicity, Europe Barcelona, Spain; Helsinki, Finland; Paris, France; London, UK Jan 1986-Dec 1992	All ED visits for asthma	24-h avg: Barcelona: 15.4 Helsinki: 6.0 London: 11.6 Paris: 8.6	NR	NR	Barcelona: 0.8, 60.2 Helsinki: 1.1, 35.7 London: 3.4, 37.6 Paris: 0.4, 82.3	NR	0-14 yrs: 3.2% (-0.2, 6.8) 15-64: 0.2% (-2.2, 2.6)
Castellsague et al. (1995) Barcelona, Spain Jan 1986-Dec 1989	ED visits for asthma from 4 hospitals	24-h avg: Summer: 15.3| Winter: 19.5	NR	NR	NR	Summer: 50th: 13.5 75th: 20.3 95th: 30.8 Winter: 50th: 18.4 75th: 25.2 95th: 35.3	15-64 yrs, summer: 5.5% (-2.1, 13.8) 15-64 yrs, winter: 2.1% (-4.2, 9.0)
HOSPITAL ADMISSIONS – ALL RESPIRATORY							
UNITED STATES							

STUDY	POPULATION	MEAN CONCENTRATION	SO_2 (ppb) 98TH%	SO_2 (ppb) 99TH%	SO_2 (ppb) RANGE	SO_2 (ppb) UPPER %TILE	STANDARDIZED ODDS RATIO (95% CI)[a]
Schwartz (1995) New Haven, CT Tacoma, WA Jan 1988-Dec 1990	≈ 13,470 Hospital admissions, ages 65+	24-h avg: New Haven: 29.8 Tacoma: 16.8	NR	NR	NR	New Haven: 75th: 37.6 90th: 59.8 Tacoma: 75th: 21.1 90th: 27.8	New Haven: 1.6% (1.1, 2.6) Tacoma: 3.2% (0.5, 6.2)
CANADA							
Fung et al. (2006b) Vancouver, BC Jun 1995-Mar 1999	≈ 41,000 respiratory admissions for elderly (65+ yrs)	24-h avg: 3.46 (1.82)	NR	NR	0.0, 12.5	NR	12.6% (4.1, 22.0)
Cakmak et al. (2006) Multicity, Canada Calgary, Edmonton, Halifax, London, Ottawa, Saint John, Toronto, Vancouver, Windsor, Winnipeg Jan 1993-Dec 2000	> 200,000 hospital admissions for all respiratory causes	24-h avg: 4.6	NR	NR	2.8, 10.2	NR	2.4% (1.1, 3.9)
Yang et al. (2003b) Vancouver, BC Jan 1986-Dec 1998	Respiratory hospital admissions among young children (< 3 yrs) and elderly (≥65 yrs)	24-h avg: 4.84 (2.84)	NR	NR	NR	75th: 6.25 100th: 24.00	< 3 yrs: 3% (-6, 15) 65+ yrs: 5.8% (0.0, 11.9)
*Burnett et al. (2001) Toronto, ON Jan 1980-Dec 1994	All respiratory admissions for young children (< 2 yrs)	1-h max: 11.8	NR	55	NR	75th: 15 95th: 32 100th: 110	11% (-0.3, 23.6)
Luginaah et al. (2005) Windsor, ON Apr 1995-Dec 2000	All respiratory admissions ages 0-14, 15-64, and 65+ from 4 hospitals	1-h max: 27.5 (16.5)	NR	NR	0, 129	NR	All ages, female: 2.1% (-0.7, 5.0) All ages, male: -2.5% (-5.3, 0.5) 0-14, female: 5.6% (0.6, 10.9) 0-14, male: -2.5% (-6.8, 1.9) 15-64, female: 1.6% (-3.7, 7.2) 15-64, male: -4.5% (-8.4, 5.8) 65+, female: 1.5% (-2.6, 5.8) 65+, male: -3.1% (-7.5, 1.5)

STUDY	POPULATION	MEAN CONCENTRATION	SO_2 (ppb) 98TH%	SO_2 (ppb) 99TH%	SO_2 (ppb) RANGE	SO_2 (ppb) UPPER %TILE	STANDARDIZED ODDS RATIO (95% CI)[a]
AUSTRALIA							
Barnett et al. (2005) Multicity, Australia/New Zealand Auckland, Brisbane, Canberra, Christchurch, Melbourne, Perth, Sydney Jan 1998-Dec 2001	All respiratory hospital admissions	24-h avg: Auckland: 4.3 Brisbane: 1.8 Christchurch: 2.8 Sydney: 0.9 1-h max: Brisbane: 7.6 Christchurch: 10.1 Sydney: 3.7 NA in Auckland, Canberra, Melbourne, and Perth	NR	NR	24-h avg: Auckland: 0, 24.3 Brisbane: 0, 8.2 Christchurch: 0, 11.9 Sydney: 0, 3.9 1-h max Brisbane: 0, 46.5 Christchurch: 0.1, 42.1 Sydney: 0.1, 20.2		1-4 yrs: 5.1% (0.0, 9.1) 5-14: 3.7% (-9.9, 19.5)
Petroeschevsky et al. (2001) Brisbane, Australia Jan 1987-Dec 1994	33,710 hospital admissions	24-h avg: 4.1 1-h max: 9.2	NR	NR	NR	NR	All ages: -5.9% (-12.4, 1.1) 0-14: 8.0% (-2.9, 20.1) 15-64: -21.6% (-34.4, -6.2)
EUROPE							
Oftedal et al. (2003) Drammen, Norway Jan 1994-Dec 2000	All respiratory hospital admissions	24-h avg: 1.1 (0.8)	NR	NR	NR	NR	All ages: 71.8% (15.5, 152.7)
Fusco et al. (2001) Rome, Italy Jan 1995-Oct 1997	All respiratory hospital admissions	24-h avg: 3.4 (2.2)	NR	NR	NR	50th: 3.0 75th: 4.5	All age: 1.6% (-4.9, 8.8) 0-14: -2.7% (-4.6, 10.8)
Llorca et al. (2005) Torrelavega, Spain Jan 1992-Dec 1995	Hospital admissions from one hospital	24-h avg: 5.0 (6.3)	NR	NR	NR	NR	All ages: 1.0% (-2.8, 4.7)
Anderson et al. (2001) West Midlands conurbation, UK Oct 1994-Dec 1996	Hospital admissions stratified by age	24-h avg: 7.2 (4.7)	NR	NR	1.9, 59.8	90th: 12.3	All ages: 1.4% (-0.8, 3.8) 0-14: 5.1% (1.6, 8.7) 15-64: -1.0% (-5.3, 3.7) 65+: -2.2% (-5.4, 1.2)
Atkinson et al. (1999a) London, UK Jan 1992-Dec 1994	165,032 hospital admissions	24-h avg: 8.0 (2.9)	NR	NR	2.8, 30.9	50th: 7.4 90th: 11.7	All ages: 3.0% (0.4, 5.6) 0-14: 7.7% (3.8, 11.7) 15-64: 2.8% (-1.2, 7.0) 65+: 3.3% (-0.1, 6.9)
Schouten et al. (1996) Multicity, The Netherlands Amsterdam, Rotterdam Apr 1977-Sep 1989	All respiratory hospital admissions	24-h avg: Amsterdam: 10.5 Rotterdam: 15.0 1-h max: Amsterdam: 24.4 Rotterdam: 37.2	NR	NR	NR	NR	Amsterdam: 15-64: -2.3% (-5.5, 0.9) 65+: 0.2% (-2.8, 3.3) Rotterdam: 15-64: -2.9% (-6.2, 0.5)

STUDY	POPULATION	MEAN CONCENTRATION	SO_2 (ppb) 98TH%	SO_2 (ppb) 99TH%	SO_2 (ppb) RANGE	SO_2 (ppb) UPPER %TILE	STANDARDIZED ODDS RATIO (95% CI)[a]
Spix et al. (1998) Multicity, Europe London, UK; Amsterdam & Rotterdam, the Netherlands; Paris, France; Milan, Italy Jan 1977-Dec 1991	All respiratory hospital admissions	24-h avg: London: 10.9 Amsterdam: 7.9 Rotterdam: 9.4 Paris: 8.6 Milan: 24.8	NR	NR	NR	NR	15-64 yrs: 0.5% (-0.4, 1.3) 65+: 1.1% (0.3, 2.4)
Dab et al. (1996) Paris, France Jan 1987-Sep 1992	Hospital admissions from 27 hospitals	All yr: 24-h avg: 11.2 1-h max: 22.5 Warm season 24-h avg: 7.6 1-h max: 16.1 Cold season 24-h avg: 15.1 1-h max: 29.4	NR	NR	NR	All yr: 24-h avg: 99th: 50.0 1-h max: 99th: 87.5 Warm season 99th: 18.5 1-h max: 99th: 50.3 Cold season 24-h avg: 99th: 56.0 1-h max: 99th: 100.9	All ages: 1.1% (0.1, 2.1)

[a]24-h avg SO_2 and 12-h avg SO_2 standardized to 10- ppb incremental change; 3-h avg SO_2 standardized to 20-ppb incremental change; and 1-h max SO_2 standardized to 40-ppb incremental change.

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