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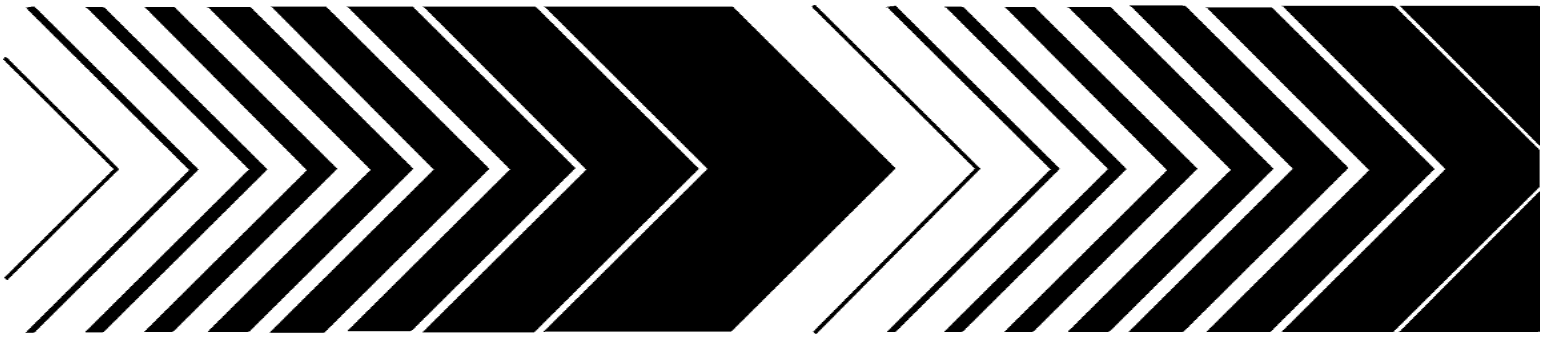
Air Quality Criteria for Particulate Matter

Volume II

Notice

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.



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National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

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This document is an external review draft for review purposes only and does not constitute U.S. Environmental Protection Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Preface

National Ambient Air Quality Standards (NAAQS) are promulgated by the United States Environmental Protection Agency (U.S. EPA) to meet requirements set forth in Sections 108 and 109 of the U.S. Clean Air Act (CAA). Sections 108 and 109 require the EPA Administrator: (1) to list widespread air pollutants that may reasonably be expected to endanger public health or welfare; (2) to issue air quality criteria for them which assess the latest available scientific information on nature and effects of ambient exposure to them; (3) to set "primary" NAAQS to protect human health with adequate margin of safety and to set "secondary" NAAQS to protect against welfare effects (e.g., effects on vegetation, ecosystems, visibility, climate, manmade materials, etc); and (5) to periodically (every 5-yrs) review and revise, as appropriate, the criteria and NAAQS for a given listed pollutant or class of pollutants.

The original U.S. NAAQS for particulate matter (PM), issued in 1971 as "total suspended particulate" (TSP) standards, were revised in 1987 to focus on protecting against human health effects associated with exposure to ambient PM less than 10 microns ($\leq$ 10 μm) that are capable of being deposited in thoracic (tracheobronchial and alveolar) portions of the lower respiratory tract. Later periodic reevaluation of newly available scientific information, as presented in the last previous version of this "Air Quality Criteria for Particulate Matter" document published in 1996, provided key scientific bases for PM NAAQS decisions published in July 1997. More specifically, the PM_{10} NAAQS set in 1987 (150 $\mu g/m^3$, 24-h; 50 $\mu g/m^3$, annual ave.) were retained in modified form and new standards (65 $\mu g/m^3$, 24-h; 15 $\mu g/m^3$, annual ave.) for particles $\leq$ 2.5 μm ($PM_{2.5}$) were promulgated in July 1997.

This First External Review Draft of revised Air Quality Criteria for Particulate Matter assesses new scientific information that has become available since early 1996 through mid-1999. Extensive additional pertinent information is expected to be published during the next 6 to 9 months (including results from a vastly expanded U.S. EPA PM Research program and from other Federal and State Agencies, as well as other partners in the general scientific community) and, as such, the findings and conclusions presented in this draft document must be considered only provisional at this time. The present draft is being released for public comment and review by the Clean Air Scientific Advisory Committee (CASAC) mainly to obtain comments on the

organization and structure of the document, the issues addressed, and the approaches employed in assessing and interpreting the thus far available new information on PM exposures and effects. Public comments and CASAC review recommendations will be taken into account, along with newly available information published or accepted for peer-reviewed publication by April/May 2000, in making further revisions to this document for incorporation into a Second External Review Draft. That draft is expected to be released in June 2000 for further public comment and CASAC review (September 2000) in time for final revisions to be completed by December 2000). Evaluations contained in the present document will be drawn upon to provide inputs to associated PM Staff Paper analyses prepared by EPA's Office of Air Quality Planning and Standards (OAQPS) to pose options for consideration by the EPA Administrator with regard to proposal and, ultimately, promulgation by July 2000 of decisions on potential retention or revision of the current PM NAAQS.

This document was prepared and reviewed by experts from Federal and State government agencies, academia, industry, and NGO's for use by EPA in support of decision making on potential public health and environmental risks of ambient PM. It describes the nature, sources, distribution, measurement, and concentrations of PM in both the outdoor (ambient) and indoor environments and evaluates the latest data on the health effects in exposed human populations, as well as environmental effects on: vegetation and ecosystems; visibility and climate; manmade materials; and associated economic impacts. Although not intended to be an exhaustive literature review, this document is intended to assess all pertinent literature through mid-1999.

The National Center for Environmental Assessment – Research Triangle Park, NC (NCEA-RTP) acknowledges the contributions provided by authors, contributors, and reviewers and the diligence of its staff and contractors in the preparation of this document.

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CHAPTER 6. EPIDEMIOLOGY OF HUMAN HEALTH EFFECTS FROM AMBIENT PARTICULATE MATTER

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CHAPTER 8. INTEGRATIVE SYNTHESIS OF KEY POINTS: PM EXPOSURE, DOSIMETRY, AND HEALTH RISKS

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6. EPIDEMIOLOGY OF HUMAN HEALTH EFFECTS FROM AMBIENT PARTICULATE MATTER

6.1 INTRODUCTION

Epidemiology studies linking community ambient PM concentrations to adverse health effects played an important role in the 1996 PM Air Quality Criteria Document (PM AQCD), and continue to play an important role. Those studies are indicative of measurable excesses in pulmonary function decrements, respiratory symptoms, hospital and emergency department admissions, and mortality being associated with ambient levels of $PM_{2.5}$, PM_{10}, and other indicators of PM exposure. The more recent epidemiologic studies reviewed in this chapter generally identify more cities and extend the earlier findings. Therefore, the main emphasis in this chapter has shifted from a detailed discussion of the findings in the individual studies (as contained in the 1996 PM AQCD) to a greater emphasis here on integrating and interpreting the findings in the body of evidence provided by the newer studies, as well as those reviewed in 1996.

Several hypotheses may be proposed, based on the earlier evidence:

Hypothesis 0: Exposure to ambient PM at current levels cannot cause adverse health effects in susceptible sub-populations, even in the presence of other environmental factors such as weather conditions or the presence of other air pollutants;

Hypothesis 1: Exposure to ambient PM or some component at current levels is associated with adverse health effects in some susceptible sub-population.

Hypothesis 1 has many alternative forms. Those of greatest interest in this chapter concern the circumstances under which the adverse health effects may be manifested, typically the occurrence of adverse health effects in association with either a specific form or component of ambient PM, or with specific environmental co-factors (such as weather or co-pollutants) along with PM exposure. These circumstances can markedly affect the approaches taken to the synthesis of epidemiology studies from different sites. Table 6-1 illustrates several of the possible variants of Hypothesis 1:

TABLE 6-1. ALTERNATIVE VERSIONS OF HYPOTHESIS 1 THAT MAY AFFECT THE SYNTHESIS OF EPIDEMIOLOGY STUDIES

Alternative Hypotheses	Adverse Health Effects Depend Only on Ambient PM, Independent of Co-Factors	Adverse Health Effects Depend on Ambient PM Concentrations as Well as Co-Factors
Adverse Health Effects Depend Only on Ambient PM Size Range and Concentration	Adverse health effects from ambient PM at a given concentration are the same in all sites with the same PM size range	Adverse health effects from PM are different in sites where PM has different co-factors with the same PM size range and concentration.
Adverse Health Effects Depend on PM With Specific Physical Properties or Composition, and on Concentration	Adverse health effects from PM are different at sites where PM has different physical properties or composition with the same PM size range and concentration.	Adverse health effects from PM are different in sites where PM has different physical properties, composition, or co-factors, even at the same PM size range concentrations.

If row 1, column 1 in Table 6-1 occurs, it is feasible to combine information from all epidemiology studies of a common design concerning a specific health effect of PM at all sites. The estimated PM effect depends only on the size range in the study, and is assumed to be independent of the PM chemical components or physical characteristics within that size range, and independent of the levels of co-pollutants or the occurrence of certain weather variable ranges with which the PM levels are associated. The implicit assumption of a single quantitatively similar effect of PM of any composition at all sites appears to be present in a number of published research syntheses or meta-analyses. This is important in evaluating the consistency of the quantitative effects (concentration-response) across different studies or different sites. While some studies may show a positive and statistically significant adverse health effect of the PM index being evaluated, others may show statistically non-significant effects. The different findings may suggest a substantive reason for grouping sites by PM components or by environmental co-factors. Statistically positive or non-positive PM health effects may be attributable to the presence or absence of a particular PM component, or to the

presence or absence of a specific environmental co-factor, and may help to define a quantitative relationship to the component or the environmental co-factor.

If row 1, column 2 applies, then it may be informative to group sites with some commonality, such as the presence of significant specific sources, specific mixtures of co-pollutants, common weather patterns, or even common demographic factors that affect exposure and toxicity. Examples referred to below include location ('eastern' U.S. versus 'western' U.S., 'central-eastern Europe' versus 'western' Europe) and source types (gasoline combustion mobile sources, diesel combustion sources, fossil fuel power plants, metal smelters or factories, crustal particles, sea salt particles, other organic particle sources, biotoxins, etc., as discussed in Chapters 5 and 7).

Row 2 considers the possibility that site-to-site or study-to-study differences in outcome may depend on properties of the ambient PM itself, independent of or in addition to its mass concentration. These may include chemical composition (acids, metals, oxidants) or physical properties (number concentration or surface area) of the PM, or even of gaseous pollutants adhering to particles. In the row 2, column 2 case, it might only be appropriate to evaluate sites with common distributions of air pollution, weather, and population.

The epidemiology studies presented here should be regarded in combination with the ambient concentration studies in Chapter 4, the human exposure studies in Chapter 5, and the toxicology studies in Chapter 7. The contribution of the epidemiology studies is to identify whether specific adverse health effects occur in susceptible human populations that are likely to have been exposed to relevant levels of ambient PM. Chapter 8 provides a more detailed causal synthesis indicating (a) that personal exposure to ambient PM does occur and (b) that the biological effects may be similar to those observed in free-living human populations.

Types of Epidemiology Studies Reviewed

A concise definition of the various types of epidemiology studies used here is given in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996) and in most epidemiology texts; it is not repeated here. Briefly, the epidemiology studies are divided into *morbidity* studies and *mortality* studies. The morbidity studies include a wide range of health endpoints, such as changes in pulmonary function tests (PFT), reports of respiratory symptoms, self-medication in asthmatics, medical visits, low birthweight infants, and hospitalization. *Mortality* studies from

many causes have provided the most unambiguous evidence of a clearly adverse endpoint, and are sufficiently numerous to be discussed in detail.

The most commonly used study designs are *cross-sectional*, *panel, time series, and prospective cohort* studies. Cross-sectional studies evaluate subjects at a 'point' in time, where measurements of health status, pollution exposure, and individual covariates are observed simultaneously. When summary statistics are used to compare either health outcomes or exposure indices for different populations, the study is called an *ecological* or *semi-ecological* study. *Panel* studies follow the health outcomes of the same individuals over several time points. *Prospective cohort* studies follow a group of initially recruited individuals over a long period of time, where some events (such as the date of death of a subject) may be determined individually with great precision. To contrast these study designs, individuals in a prospective cohort study may have their vital status monitored over a long period of time, whereas symptoms may be recorded daily only in the first few months of the study and PFT measurements made initially and after 3, 6, and 12 years of follow-up (as in the Harvard Six Cities cohort). *Time-series* studies, as referred to in this document, usually involve aggregate-level outcomes, such as the daily number of deaths in a community, or the daily count of hospital admissions or emergency department visits, over a large number of days. Time-series studies require different analytical strategies than the other study designs. A few recent analyses have examined *case-control* designs.

Studies with individual-level outcome data, covariates, and PM exposure indices would be preferred, whatever the design. Individual-level exposure data are the most commonly missing component. Community-level air pollution concentrations are usually substituted as surrogate indices of population exposures, and the evidence presented in Chapter 5 suggests that exposure to PM_{10} and $PM_{2.5}$ of ambient origin, and to sulfates, is adequately characterized by community-level measurements. Substantial efforts to develop individual long-term exposure indices for a prospective cohort study have been reported by Abbey et al. (1991, 1995, 1999; Beeson et al., 1998) for the California Adventist Health Study of Smog (AHSMOG).

The strengths and weaknesses of the study designs have been discussed in some detail in (U.S. Environmental Protection Agency, 1996). In general, prospective cohort and panel studies would be preferred because of the individual-level information. However, time series studies allow valid inferences about short-term responses to changes in environmental factors in exposed

populations, and are considered very informative, provided that the environmental factors (such as co-pollutants) are not too highly correlated with the PM exposure index.

Selection of Studies for Detailed Review

Numerous papers on PM epidemiology have been published since the 1996 PM AQCD. Those papers selected here as being most clearly relevant to this NAAQS review are described in greater detail in the text of this chapter, and the others are included in tables where appropriate. Some of the criteria for selecting relevant literature for text discussion include consideration as to whether a given study:

1. Presents PM indices previously considered: PM_{10}, fine or coarse PM_{10} fractions;
2. Presents analyses with informative new PM indices such as nitrates or ultrafines;
3. Presents information on health endpoints not previously considered;
4. Presents new information on multiple pollutant analyses;
5. Presents new information on long-term effects, mortality displacement;
6. Presents new information on health effects of specific PM constituents.

The present chapter is organized as follows. After this brief introduction, Section 6.2 examines the case for causal inference based on studies of morbidity as a health endpoint. Section 6.3 examines the case for causal inference based on studies of PM effects on mortality, the most clearly adverse effect. Section 6.4 discusses a variety of issues related to the inferences that can be drawn from the studies reviewed in Sections 6.2 and 6.3. Section 6.5 briefly reviews some of the general and methodological issues in inferring causal relationships from the large number of epidemiology studies reviewed here. The overall findings of this Chapter are then summarized in Section 6.6.

6.2 MORBIDITY EFFECTS OF PARTICULATE MATTER EXPOSURE

This morbidity section is presented in sub sections, dealing with: (a) short-term PM exposure effects on lung function and respiratory symptoms in asthmatics and non-asthmatics; (b) long-term PM exposure effects on lung function and respiratory symptoms; (c) effects of short-term PM exposure on the incidence of respiratory and other medical visits and hospital admissions, and (d) effects of ambient PM exposure on acute cardiovascular morbidity.

For consistency with the prior PM Criteria Document (U.S. Environmental Protection Agency, 1996), the pollutant increments utilized here to report Relative Risks (RR's) or Odds Ratios for various health effects are: for PM_{10}, 50 $\mu g/m^3$; for $PM_{2.5}$, 25 $\mu g/m^3$; for $SO_4^=$, 155 nmoles/m^3 (=15 $\mu g/m^3$); and, for H^+, 75 nmoles/m^3 (=3.6 $\mu g/m^3$, if as H_2SO_4).

6.2.1 Short Term Effects on Lung Function and Respiratory Symptoms

In the 1996 PM AQCD, the available respiratory disease studies used a wide variety of designs examining pulmonary function and respiratory symptoms in relation to PM_{10}. The models for analysis varied and the populations included several different subgroups. Pulmonary function studies were suggestive of short term effects resulting from particulate exposure. Peak expiratory flow rates showed decreases in the range of 2 to 5 l/min resulting from an increase of 50 $\mu g/m^3$ in PM_{10} or its equivalent, with somewhat larger effects in symptomatic groups such as asthmatics. Studies using FEV_1 or FVC as endpoints showed less consistent effects. The chronic pulmonary function studies were less numerous than the acute studies and the results were inconclusive.

The available acute respiratory symptom studies included several different endpoints, but typically presented results for: (1) upper respiratory symptoms, (2) lower respiratory symptoms, or (3) cough. These three respiratory symptom endpoints had similar general patterns of results. The odds ratios were generally positive, the 95% confidence intervals for about half of the studies were statistically significant (i.e., the lower bound exceeded 1.0). As part of the Six Cities studies, three analyses done for different time periods suggested a chronic effect of PM exposure on respiratory disease. Chronic cough, chest illness, and bronchitis showed positive associations with PM for the earlier surveys. One study was strongly suggestive of an effect on bronchitis from acidic particles or from other PM.

The earlier studies of morbidity health outcomes of PM_{10} exposure on asthmatics were limited in terms of conclusions that could be drawn because of the few available studies on asthmatic subjects. Lebowitz et al. (1987) reported a relationship with TSP exposure and productive cough in a panel of 22 asthmatics but not for peak flow or wheeze. Pope et al. (1991) studied respiratory symptoms in two panels of asthmatics in the Utah Valley. The 34 asthmatic school children panel yielded estimated odd ratios of 1.28 (1.06, 1.56) for lower respiratory illness and the second panel of 21 subjects aged 8 to 72 for LRI of 1.01 (0.81, 1.27) for exposure

to PM_{10}. Ostro et al. (1991) reported no association for $PM_{2.5}$ exposure in a panel of 207 adult asthmatics in Denver; but, for a panel of 83 asthmatic children age 7 to 12 in central Los Angeles, reported a relationship of shortness of breath to O_3 and PM_{10} but could not separate the effect of the two pollutants. These few studies did not indicate a consistent relationship for PM_{10} exposure and health outcome in asthmatics.

Several new studies of short term PM exposure effects on lung function and respiratory symptoms have been published since early 1996. Most of these studies followed a panel of subjects over one or more periods. Daily lung function and/or respiratory symptoms were associated with changes in ambient PM_{10} and/or $PM_{2.5}$. Lung function was usually measured daily with many studies including forced expiratory volume (FEV), forced vital capacity (FVC) and peak expiratory flow rate (PEF). Some analyses included both morning and afternoon measurements. A large variety of respiratory symptoms were measured, including cough, phlegm, difficulty breathing, wheeze, and bronchodilator use. Finally, several measures of particulate matter were used including PM_{10}, $PM_{2.5}$, TSP, British Smoke (BS), and sulfate fraction of ambient PM.

These various studies are discussed in the following text and tables. Studies providing quantitative information can often add more understanding of possible relationships between PM exposure and health outcomes. Data on physical and chemical aspects of ambient particulate levels, especially for PM_{10} and $PM_{2.5}$ and smaller size fractions are a focus of discussion. Additionally, new studies are discussed that present potential new insights or that examine health outcome effects and/or exposure measures not studied as much in the past.

This section is organized around discussion of PM effects on lung function, respiratory symptoms, and related pulmonary outcomes. The acute studies are split into two groups: panels of asthmatics and panels of non-asthmatics. The lung function studies are not split from the respiratory symptom studies because many of the studies included both endpoints. To facilitate a quantitative synthesis of outcomes, studies are placed into homogeneous groupings and their results are presented as shown. Note that some unique study results need to be discussed in that they may examine an aspect which no other study has, such as number of particles or 1-h and 8-h PM averages.

The following section contains a quantitative synthesis of several studies. The combination of differing endpoints and differing lag-times in the analyses resulted in a large number of

potential analyses for each study. Authors may have tended to choose and report results for those models that gave the strongest effects. In an attempt to present these studies in an organized manner, specific analyses were selected based on the following criteria (which also may minimize potential bias of reported results):

(1) Peak flow was used as the primary lung function measurement of interest. While FEV_1 would be a good measure, peak flow is most often measured in these panel studies.

(2) Only cough, phlegm, difficulty breathing, wheeze, and bronchodilator use were summarized as measures of respiratory symptoms.

(3) Summaries focused on those studies presenting results in terms of PM_{10} and $PM_{2.5}$ and smaller PM.

(4) The analyses were also restricted to include a short term lag (zero or one day) a longer term lag (two to five day), and a moving average analysis. If both zero and one day lag analyses were presented, the zero day lag analysis was selected for all but the AM peak flow measurements, and here for longer term lags, the measure which came closest to being an average of two to five days was selected.

(5) Studies were included only if they modeled individual responses. A few studies modeled group rates and this flaw is also known as the "panel data problem" (Neuhaus and Kalbfleisch, 1998).

Whenever three or more studies of a similar endpoint were available, the results were combined using a random effects model (Hedges and Olkin, 1985). Tests for homogeneity are also reported.

A few of the analyses included more than one pollutant in the model at the same time. However, while the number of such studies was too small to allow for any meaningful conclusions, these results are discussed due to the importance of considering co-pollutants. The summary from this section reflects the above organization.

6.2.1.1 Short Term Effects on Lung Function and Respiratory Symptoms In Asthmatics

Ostro et al. (1995) followed 87 African-American children, ages 7-12 years with confirmed asthma for at least 6 weeks. Four subjects were dropped because of concerns about the accuracy of responses, leaving 83 subjects. Most subjects lived in central and south-central Los Angeles, CA. Analyses were done using "daily reporting of respiratory symptoms including cough,

shortness of breath, and wheeze" as the dependent variables and the pollutants of TSP, sulfates, nitrates, ozone, SO_2, NO_2, and PM_{10} as the independent variables. PM_{10} from 3 downtown LA sites had a mean of 56 $\mu g/m^3$ (range 19 to 101 $\mu g/m^3$). General logistic regression models were used with generalized estimating equation (GEE) corrections for autocorrelation. Significant relationships were found between shortness of breath and PM_{10} or ozone, with symptoms estimated to increase about 9% per each 10 $\mu g/m^3$ increase in PM_{10}. The authors examined other symptoms and found no significant associations, but results were not reported.

Peters et al. (1997a) studied 89 children, aged 6 to 14 years, with asthma in Sokolov, Czech Republic. The subjects kept diaries and measured peak flow for seven months during the winter of 1991-92. Aerometric measurements included PM_{10}, SO_2, TSP, sulfate, and particle strong acidity. PM_{10} was measured at one central site, with a mean of 55 $\mu g/m^3$ and a max of 171 $\mu g/m^3$. The analysis was done using linear regression for the pulmonary function data and logistic regression for binary outcomes. First order autocorrelations were observed and corrected for using polynomial distributed lag structures. Only weak associations were reported between the measures of particulate pollution and lung function or respiratory symptoms. Although the magnitudes of effect were still weak, there were associations for both morning and evening PEF. This was a wintertime study in an area with relatively high SO_2 (median 46 $\mu g/m^3$) and so, not unexpectedly, in comparison to PM_{10}, sulfate effects on PEF and symptoms were similar and slightly larger for some models.

In a further analysis, Peters et al. (1997b) compared children with mild asthma who were either taking β-agonist medications (31 subjects) or not taking them (51 subjects) during the winter of 1991-92 in Sokolov, Czech Republic. Those taking such medications had more severe asthma than those not taking them. For the relationship between PEF and 5-day mean sulfate (interquartile range of 6.5 $\mu g/m^3$), effects were larger for the medicated subjects (–5.62, 95% CI –9.93 to –1.30 L/min) as compared with unmedicated subjects (–1.35, 95% CI –3.69 to 0.99 L/min). Effects of the same day sulfate were small and non significant.

Gielen et al. (1997) studied 61 children aged, 7 to 13 years, living in Amsterdam, The Netherlands during the summer of 1995. Seventy-seven percent of the children were taking asthma medication and the others were hospitalized for respiratory problems. Peak flow measurements were taken twice daily and respiratory symptoms were recorded by the parents in a diary. PM_{10} was measured at one city site with a mean of 30.5 $\mu g/m^3$. Associations of air

pollution were evaluated using time series analyses. The analyses adjusted for pollen counts, time trend, and day of week. The studies found relationships with ozone and PM_{10}. Stronger associations were found for black smoke (BS) than for PM_{10}, in relation to PEF, symptoms and bronchodilator use. The authors hypothesized that BS may be a better surrogate for fine particles emitted by diesel engines or for other chemicals that may be the causal components in PM.

Romieu et al. (1997) studied 65 children with mild asthma aged 5-13 years living in the southwest area of Mexico City, Mexico. During the study period, maximum daily 1-h ozone ranged from 40 to 390 ppb (mean 196 ppb SD = 78 ppb) and PM_{10} daily average ranged from 12 to 126 $\mu g/m^3$ ($\bar{x}$ =`54.2 $\mu g/m^3$). Pollutant measurement were made at a local site. Morning and evening peak flow measurements were made and respiratory symptoms were recorded by the parents in a daily diary. Peak flow measurements were standardized for each person and a model was fitted using GEE methods. The model included terms for minimum temperature.
An autoregressive logistic regression model using GEE methods was used to analyze the presence of respiratory symptoms. The strongest relationships were found between ozone and the respiratory symptoms.

Peters et al. (1996) studied two mild/moderate asthma panels in Erfurt and Weiman, Germany and in Sokolov, Czech Republic from September 1990 thru June 1992 for health outcomes in relation to pollutant exposure. During that period, TSP was measured at 3 central sites. From January 10 through June 1992, PM_{10} was also measured. The panels consisted of 102 adults and 155 children aged 7 to 15 years. Mean levels of PM_{10} in Erfurt, for the winter 1991-92 was 64 $\mu g/m^3$. The panelists recorded daily symptom, medication intake and PEF.
A linear regression analysis was conducted. The dominate air pollutant was SO_2. An increase of 52 $\mu g/m^3$ PM_{10} was associated with a 0.43% decrease in evening PEF for children with asthma. Because of the small observed effects and the pollutants being highly correlated, separation of contributions of individual air pollutants was difficult.

Three studies attempted to relate lung function or respiratory symptoms to particles smaller than $PM_{2.5}$. Peters et al. (1997c) studied 27 non-smoking adult asthmatics living in Erfurt, Germany during the winter season 1991-92. The study measured particulate fractions over a range of sizes from ultrafine (<0.1 μm in diameter) to fine (0.1 to 2.5 μm), including PM_{10} at one site. A 5-day mean level of 60 $\mu g/m^3$ PM_{10} was observed. Morning and evening peak flow were measured and a diary was used to record the presence of cough. An autoregressive model was

used to analyze the deviations in the individual peak flow values. The model included terms for time trend, temperature, humidity, and wind speed and direction. The strongest effects on peak flow were found with the ultrafine particles although the confidence intervals were significantly overlapping. The symptom information was analyzed using multiple logistic regression analysis. The authors reported no association between PM and phlegm or dyspnea, but estimates and standard errors were not given. The Peters et al. (1997c) study is unique for two reasons: (1) they studied the size distribution of particles in the range 0.01 to 2.5 μm, and (2) they examined the number of particles. They report that the health effects of 5 day means of the number of ultrafine particles were larger than those of the mass of fine particles, and that the size distribution of ambient particles helps elucidate the properties of ambient aerosol responses for health effects.

Pekkanen et al. (1997) studied 39 asthmatic children, aged 7-12 years, living in Kuopio, Finland for 57 days in early 1994. Changes in peak flow measurements were analyzed using a linear first-order autoregressive model. The study measured particulate fractions at a local site over a range of sizes from ultrafine to fine, including PM_{10}. Particulate measurements included both particles <0.03 μm in diameter, 0.03 to 0.1, 0.1 to 0.32, and 0.32 to 1.0 μm in diameter. The number of particles was also determined by size. The mean PM_{10} level was 18 $\mu g/m^3$. Decrements in peak flow were found to be related with all measures of particulate matter after adjusting for minimum temperature. The results were quite variable across zero to 3 day lags, showing no particular pattern across size. Results for two day lags tended to be larger than other lags. Similar results were found for evening PEFR except that the one day lags tended to show a stronger relationship. In contrast to the findings of Peters et al. (1997c) discussed above, PM_{10} was more consistently associated with PEF across the different lags, and gave the only models that were statistically significant (with the exception of BS). The authors note that the different particle size fractions were highly intercorrelated and that future studies should aim at obtaining data where these intercorrelations are lower.

Timonen and Pekkanen (1997) studied 74 asthmatic children and 95 children with dry cough ages 7-12 in Kuopio, Finland, during the winter of 1994. PM_{10} levels were a mean of 18 $\mu g/m^3$, 25 to 75 percentile, 10-23 $\mu g/m^3$. Linear regression analyses with autoregressive parameters for PEF data and logistic regression models for binary symptom data were performed.

A significant association for morning PEF and PM_{10} was found, but not for evening PEF. No clear or consistent trends in association between air pollution and symptoms was observed.

Tiittanen et al. (1999) studied 49 children with chronic respiratory symptoms (age 8-13 years) for six weeks in the spring of 1995. Particulate measurements included both ultrafine particles (<0.1 μm in diameter) and fine particles (0.1 to 1.0 μm in diameter). No consistent differences in effects by particle diameter on morning and evening PEFR were found. Similarly, no consistent differences in effects by particle diameter on the incidence of cough were found.

Delfino et al. (1998) examined the relationship of adverse asthma symptoms (bothersome or interfered with daily activities or sleep) to O_3 and PM_{10} in a southern California community in the air inversion zone (1200-2100 ft) with high O_3 and low PM (R = 0.3). The region was initially chosen for study to examine effects of high ambient O_3 with less co-pollutant confounding from PM. A panel of 25 asthmatics ages 9-17 were followed daily, August through October, 1995 (N=1,759 person-days excluding 1 subject without symptoms). The highest 24-hour PM_{10} mean was only 54 $\mu g/m^3$, in contrast to the median of 1-hr maximums (56 $\mu g/m^3$). Longitudinal regression analyses utilized the GEE model controlling for autocorrelation, day of week, outdoor fungi and weather. Asthma symptoms were significantly associated with both outdoor O_3 and PM_{10} in single pollutant- and co-regressions, with 1-hr and 8-hr maximum PM_{10} having larger effects than the 24-hr mean. This aspect of this study reporting particle effects from 1-hr and 8-hr maximum PM_{10} as compared with the standard metric of 24-hr means makes these results unique. The author notes that particle effects may be determined by factors not entirely dependent on mass and/or 24-hr averages and thus may miss important short-term excursions, during peak exposure periods.

Vedal et al. (1998) studied 206 children (aged 6 to 13 years) living in Port Alberni, BC. The authors chose this town of 30,000 on Vancouver Island to maximize the spatial relationship of a central air monitor to subject activities and to minimize the influence of co-pollutants such as ozone, SO_2 or acid aerosol, which were low in the region. PM_{10} levels ranged from 0.2 to 159.0 $\mu g/m^3$ (median 22.1 $\mu g/m^3$). Major sources of PM in the region were a pulp and paper mill, and residential wood burning. Seventy-five children had physician-diagnosed asthma, 57 had an exercise-induced fall in FEV_1, 18 children with airway obstruction, and 56 children without any symptoms. Peak flow was measured twice daily and respiratory symptom data were obtained from diaries. An autoregressive model was fitted to the data using GEE methods.

Covariates included temperature, humidity, and precipitation. In general, PM_{10} was associated with changes in both peak flow and respiratory symptoms. The objective of the study was to compare the acute effects of inhalable particles on PEF and respiratory symptoms in asthmatic versus nonasthmatic children. Even though levels of PM_{10} were low (only 1.2% of days > 100 $\mu g/m^3$), PEF was inversely, and cough positively, associated with PM_{10} among children with diagnosed asthma, but not among the other groups of children.

Segala et al. (1998) studied children, aged 7-15 years, living in Paris, France. The study was separated into substudies of 43 mild asthmatics and 43 moderate asthmatics, followed from November 15, 1992 to May 9, 1993. Peak flow was measured three times a day and respiratory symptoms and as-needed-bronchodilator use were recorded daily in a diary by parents. The study measured SO_2, NO_2, PM_{13} (instead of PM_{10}) at four stations, and British smoke. A PM_{13} mean level of 34.2 $\mu g/m^3$ was reported with a range of 8.8 to 95.0 $\mu g/m^3$. Covariates in the model included temperature and humidity. An autoregressive model was fitted to the data using GEE methods. There were no significant associations for PM_{13} and prevalent symptoms in mild asthmatics. For an increase of 50 $\mu g/m^3$ the odds ratio for β-agonist inhaler use in moderate asthmatics ranged from 3 to 5 for PM_{13} lags 0 to 3 days and all were statistically significant. A subpopulation analysis of the 21 mild asthmatic subjects not taking regularly scheduled corticosteroids or β-agonists showed a significant effect of lag 4 PM_{13} on 2-transformed morning PEF. Effects were less related to PM_{10} than those found related to the other pollutants. Only selected results from selected panels were given.

Neukirch et al. (1998) studied the effect of particulate air pollution on 40 non-smoking mild to moderate adult asthmatics in Paris. The study was conducted from September to December, 1992, and was analyzed using group rates. Generalized estimating equations were used to adjust for autocorrelation in the data. The study found some relationships between PM_{13} and nocturnal cough, shortness of breath, and peak flow. Only selected results were given, making the study difficult to evaluate.

Romieu et al. (1996) studied 71 children with mild asthma aged 5-7 years living in the northern area of Mexico City, Mexico. Morning and evening peak flow measurements were made and respiratory symptoms were recorded by the parents in a daily diary. During the study period, maximum daily one hour ozone ranged from 40 to 370 ppb (mean 190 ppb, SD = 80 ppb). The 24 hour average PM_{10} levels measured at one site ranged from 29 to

363 $\mu g/m^3$ (mean 166.8 $\mu g/m^3$, SD 72.8 $\mu g/m^3$). For 53 percent of the study days, PM_{10} levels exceeded 150 $\mu g/m^3$. Peak flow measurements were standardized for each person and a model was fitted using GEE methods. The model included terms for minimum temperature. Peak flow was found to be strongly related to PM_{10}. This greater effect may be due to relatively higher levels of pollution in Mexico City and the fact that none of the subjects were on medication. An autoregressive logistic regression model was used to analyze the presence of respiratory symptoms. An increase of 20 $\mu g/m^3$ PM_{10} was related to an 8 percent increase in lower respiratory illness.

Hiltermann et al. (1998) studied 270 adult asthmatic patients from an out-patient clinic in Leiden, The Netherlands, during July 3 to October 6, 1995. Peak flow was measured twice daily and respiratory symptom data were obtained from diaries. An autoregressive model was fitted to group prevalence of outcomes rather than individual repeated measures. Covariates included temperature and day of week. PM_{10}, ozone, and NO_2 were associated with increases in respiratory symptoms. During the study, PM_{10} levels measured at one central site never exceeded 98 $\mu g/m^3$ (mean 39 $\mu g/m^3$). Shortness of breath and nocturnal asthma were weakly associated with PM_{10}. The results of this paper were not included in the analysis tables presented later because individual responses were not modeled.

The Pollution Effects on Asthmatic Children in Europe (PEACE) study developed methodology for assessing the relationship between short-term changes in air pollution and in acute changes in the health status of children with chronic respiratory symptoms (Roemer et al., 1998). Children with chronic respiratory symptoms (i.e., a positive answer to one of several selected questions) were selected into the panels. The symptom with one of the larger selection percentages was dry cough (range over sample of study communities 29 to 92% [22/75; 84/91] with most values over 50%). The symptom that would most typify selection of asthmatics was doctor-diagnosed asthma (2 to 59% [1/63; 43/72] with most about 20%) (Kotesovec et al., 1998; Clench-Aas et al., 1998; Haluszka et al., 1998; Kalandidi et al., 1998; Forsberg et al., 1998; Beyer et al., 1998). Thus, while asthmatics were included in the subject pool, the overall panels by city tended to have a small percent of asthmatics. The group as a whole did not characterize effects on asthmatics as much as those with chronic respiratory disease, especially cough. The PEACE study was a multi-center study of PM_{10}, BS, SO_2, and NO_2 on respiratory health of children with chronic respiratory symptoms (Roemer et al., 1998). Mean PM_{10} levels measured

at locals sites ranged from 11.2 to 98.8 $\mu g/m^3$ over the 28 sites. Results from individual centers were reported by Kotesovec et al. (1998), Kalandidi et al. (1998), Haluszka et al. (1998), Forsberg et al. (1998), Clench-Aas et al. (1998), and Beyer et al. (1998). These studies modeled group rates and are an example of the panel data problem mentioned earlier.

Roemer et al. (1998, 1999) summarized the results for asthmatic patients in the PEACE studies. Phlegm was not related to PM_{10} levels for lags of zero, one or two days. Furthermore, no relationship was found with the seven day mean. The results for lower respiratory disease were similar to phlegm.

The above studies are summarized in Tables 6-2 thru 6-13. These tables examine peak flow, symptoms, and medication use for 50 $\mu g/m^3$ for PM_{10} and 25 $\mu g/m^3$ for $PM_{2.5}$. The tables are split by zero to one-day lags and two-to 5-day lags. Also included in the tables (except for those with only 2 studies) are results of meta-analyses of the combined results of all the studies summarized in a given table, using an Empirical Bayes Model Chi-square for Homogenity.

6-2. EFFECT OF 50 $\mu g/m^3$ PM_{10} ON EVENING PEAK FLOW (L/MIN) IN ASTHMATICS LAGGED ZERO OR ONE DAY

Study	Description	Change in PFR per 50 $\mu g/m^3$	Standard Error of Change	95% Confidence Interval
Gielen et al. (1997)	61 children aged 7 to 13 years living in Amsterdam, The Netherlands	-0.30	0.99	-2.24, 1.64
Romieu et al. (1997)	65 children aged 5-13 years living south of Mexico City	-1.55	2.11	-5.69, 2.59
Peters et al. (1997c)	27 non-smoking adults living in Erfurt, Germany	-0.37	0.74	-1.82, 1.08
Pekkanen et al. (1997)	39 children aged 7-12 years living in Kuopio, Finland	-0.35	2.02	-4.31, 3.61
Peters et al. (1997a)	89 children aged 6-14 living in Sokolov, Czech Republic	-0.92	0.53	-1.96, 0.12
Romieu et al. (1996)	71 children aged 5-7 years living north of Mexico City	-2.95	1.52	-5.93, 0.03
COMBINED	Meta-analysis using an Empirical Bayes Model Chi-square for homogeneity = 2.89, p = .716	-0.82*	0.38	-1.57, -0.07

*$p < 0.05$

TABLE 6-2A. EFFECT OF 50 $\mu g/m^3$ PM_{10} ON MORNING PEAK FLOW (L/MIN) IN ASTHMATICS LAGGED ZERO OR ONE DAY

Study	Description	Change in PFR per 50 $\mu g/m^3$	Standard Error of Change	95% Confidence Interval
Romieu et al. (1997)	65 children aged 5-13 years living south of Mexico City	-0.65	2.37	-5.30, 3.99
Peters et al. (1997c)	27 non-smoking adults living in Erfurt, Germany	-1.30**	0.54	-2.36, -0.24
Pekkanen et al. (1997)	39 children aged 7-12 years living in Kuopio, Finland	-2.71	1.97	-6.57, 1.15
Peters et al. (1997a)	89 children aged 6-14 living in Sokolov, Czech Republic	-0.84*	0.40	-1.62, -0.06
Timonen and Pekkanen (1997)	45 urban children age 7-12 years living in Kuopio, Finland	2.93	2.07	-1.13, 6.99
Timonen and Pekkanen (1997)	40 suburban children age 7-12 years living near Kuopio, Finland	-5.55	2.87	-11.18, 0.08
Romieu et al. (1996)	71 children aged 5-7 years living north of Mexico City	-2.95	1.52	-5.93, 0.03
COMBINED	Meta-analysis using an Empirical Bayes Model Chi-square for homogeneity = 9.33, p = .156	-1.11**	0.32	-1.74, -0.48

*p < 0.05
**p < 0.01

TABLE 6-3. EFFECT OF 50 $\mu g/m^3$ PM_{10} ON EVENING PEAK FLOW (L/MIN) IN ASTHMATICS LAGGED TWO TO FIVE DAYS

Study	Description	Change in PFR per 50 $\mu g/m^3$	Standard Error	95% Confidence Interval
Gielen et al. (1997)	61 children aged 7 to 13 years living in Amsterdam, The Netherlands	-2.32	1.55	-5.36, 0.72
Romieu et al. (1997)	65 children aged 5-13 years living south of Mexico City	-0.04	2.17	-4.29, 4.23
Peters et al. (1997c)	27 non-smoking adults living in Erfurt, Germany	-2.31*	1.13	-4.53, -0.10
Pekkanen et al. (1997)	39 children aged 7-12 years living in Kuopio, Finland	0.14	3.63	-6.98, 7.26
Peters et al. (1997a)	89 children aged 6-14 living in Sokolov, Czech Republic	-1.34	0.76	-2.83, 0.15
Segala et al. (1998)	21 asthmatic children aged 7-15 years living in Paris, France	-0.62	0.46	-1.52, 0.28
Romieu et al. (1996)	71 children aged 5-7 years living north of Mexico City	-3.65*	1.81	-7.20, -0.10
COMBINED	Meta-analysis using an Empirical Bayes Model Chi-square for homogeneity = 2.89, p = .717	-1.21**	0.39	-1.98, -0.44

*p < 0.05
**p < 0.01

TABLE 6-4. EFFECT OF 25 $\mu g/m^3$ $PM_{2.5}$ ON EVENING PEAK FLOW IN ASTHMATICS LAGGED ZERO OR ONE DAY

Study	Description	Change in PFR per 25 $\mu g/m^3$	Standard Error of Change	95% Confidence Interval
Peters et al. (1997c)	27 non-smoking adults living in Erfurt, Germany	-1.38	0.71	-2.77, 0.01
Romieu et al. (1996)	71 children aged 5-7 years living north of Mexico City	-1.98	2.39	-6.66, 2.70

TABLE 6-5. EFFECT OF 25 $\mu g/m^3$ $PM_{2.5}$ ON EVENING PEAK FLOW IN ASTHMATICS LAGGED TWO TO FIVE DAYS

Study	Description	Change in PFR per 25 $\mu g/m^3$	Standard Error	95% Confidence Interval
Peters et al. (1997c)	27 non-smoking adults living in Erfurt, Germany	-2.18*	0.82	-3.79, -0.57
Romieu et al. (1996)	71 children aged 5-7 years living north of Mexico City	-2.55	2.70	-7.84, 2.74

*$p < 0.01$

TABLE 6-6. EFFECT OF 50 $\mu g/m^3$ PM_{10} ON COUGH IN ASTHMATICS LAGGED ZERO OR ONE DAY

Study	Description	Odds Ratio for Event per 50 $\mu g/m^3$	Standard Error of Log-Odds Ratio	95% Confidence Interval
Gielen et al. (1997)	61 children aged 7 to 13 years living in Amsterdam, The Netherlands	2.19	0.531	0.77, 6.20
Romieu et al. (1997)	65 children aged 5-13 years living south of Mexico City	1.21	0.046	1.11, 1.32
Peters et al. (1997c)	27 non-smoking adults living in Erfurt, Germany	1.01	0.026	0.96, 1.06
Romieu et al. (1996)	71 children aged 5-7 years living north of Mexico City	1.21*	0.047	1.10, 1.33
Peters et al. (1997a)	89 children aged 6-14 living in Sokolov, Czech Republic	1.01	0.032	0.95, 1.08
Vedal et al. (1998)	206 children aged 6 to 13 years living in Port Alberni, British Columbia	1.40	0.150	1.04, 1.88
COMBINED	Meta-analysis using an Empirical Bayes Model Chi-square for homogeneity = 32.71, $p < .001$	1.12*	0.046	1.03, 1.23

* $p < 0.05$

TABLE 6-7. EFFECT OF 50 $\mu g/m^3$ PM_{10} ON COUGH IN ASTHMATICS LAGGED TWO TO FIVE DAYS

Study	Description	Odds Ratio for Event per 50 $\mu g/m^3$	Standard Error of Log-Odds Ratio	95% Confidence Interval
Gielen et al. (1997)	61 children aged 7 to 13 years living in Amsterdam, The Netherlands	2.19	0.787	0.47, 10.24
Romieu et al. (1997)	65 children aged 5-13 years living south of Mexico City	1.21*	0.047	1.10, 1.33
Peters et al. (1997c)	27 non-smoking adults living in Erfurt, Germany	1.08	0.026	1.03, 1.14
Romieu et al. (1996)	71 children aged 5-7 years living north of Mexico City	1.27*	0.086	1.07, 1.50
Peters et al. (1997a)	89 children aged 6-14 living in Sokolov, Czech Republic	1.10*	0.031	1.03, 1.17
Vedal et al. (1998)	206 children aged 6 to 13 years living in Port Alberni, British Columbia	1.40*	0.108	
COMBINED	Meta-analysis using an Empirical Bayes Model Chi-square for homogeneity = 16.17, p = .006	1.15**	0.032	1.08, 1.23

*p < 0.05
**p < 0.01

TABLE 6-8. EFFECT OF 50 $\mu g/m^3$ PM_{10} ON PHLEGM IN ASTHMATICS LAGGED ZERO OR ONE DAY

Study	Description	Odds Ratio for Event per 50 $\mu g/m^3$	Standard Error of Log-Odds Ratio	95% Confidence Interval
Romieu et al. (1997)	65 children aged 5-13 years living south of Mexico City	1.10	0.095	0.91, 1.33
Peters et al. (1997c)	27 non-smoking adults living in Erfurt, Germany	1.10*	0.037	1.02, 1.18
Romieu et al. (1996)	71 children aged 5-7 years living north of Mexico City	1.10	0.085	0.93, 1.30
Peters et al. (1997a)	89 children aged 6-14 living in Sokolov, Czech Republic	1.13*	0.043	1.04, 1.23
Vedal et al. (1998)	206 children aged 6 to 13 years living in Port Alberni, British Columbia	1.28	0.200	0.86, 1.89
COMBINED	Meta-analysis using an Empirical Bayes Model Chi-square for homogeneity = 0.80, p = .938	1.11**	0.026	1.06, 1.17

* p < 0.05
**p < 0.01

TABLE 6-9. EFFECT OF 50 $\mu g/m^3$ PM_{10} ON PHLEGM IN ASTHMATICS LAGGED TWO TO FIVE DAYS

Study	Description	Odds Ratio for Event per 50 $\mu g/m^3$	Standard Error of Log-Odds Ratio	95% Confidence Interval
Romieu et al. (1997)	65 children aged 5-13 years living south of Mexico City	1.00	0.074	0.86, 1.16
Peters et al. (1997c)	27 non-smoking adults living in Erfurt, Germany	1.05	0.096	0.87, 1.27
Romieu et al. (1996)	71 children aged 5-7 years living north of Mexico City	1.05	0.096	0.87, 1.27
Peters et al. (1997a)	89 children aged 6-14 living in Sokolov, Czech Republic	1.12*	0.037	1.04, 1.20
Vedal et al. (1998)	206 children aged 6 to 13 years living in Port Alberni, British Columbia	1.40*	0.156	1.03, 1.90
COMBINED	Meta-analysis using an Empirical Bayes Model Chi-square for homogeneity = 0.80, p = .938	1.09**	0.031	1.03, 1.16

*p < 0.05
**p < 0.01

TABLE 6-10. EFFECT OF 50 $\mu g/m^3$ PM_{10} ON DIFFICULTY IN BREATHING IN ASTHMATICS LAGGED ZERO OR ONE DAY

Study	Description	Odds Ratio for Event per 50 $\mu g/m^3$	Standard Error of Log-Odds Ratio	95% Confidence Interval
Romieu et al. (1997)	65 children aged 5-13 years living south of Mexico City	1.18*	0.046	1.08, 1.29
Ostro et al. (1995)	83 African-American children living in central Los Angeles	1.71**	0.180	1.20, 2.43
Romieu et al. (1996)	71 children aged 5-7 years living north of Mexico City	1.05	0.096	0.87, 1.27
COMBINED	Meta-analysis using an Empirical Bayes Model Chi-square for homogeneity = 0.80, p = .938	1.18	0.043	1.08, 1.28

*p < 0.05
**p < 0.01

TABLE 6-11. EFFECT OF 50 $\mu g/m^3$ PM_{10} ON DIFFICULTY IN BREATHING IN ASTHMATICS LAGGED TWO TO FIVE DAYS

Study	Description	Odds Ratio for Event per 50 $\mu g/m^3$	Standard Error of Log-Odds Ratio	95% Confidence Interval
Romieu et al. (1997)	65 children aged 5-13 years living south of Mexico City	1.21	0.058	1.08, 1.36
Romieu et al. (1996)	71 children aged 5-7 years living north of Mexico City	1.05	0.150	0.78, 1.41

TABLE 6-12. EFFECT OF 50 $\mu g/m^3$ PM_{10} ON BRONCHODILATOR USE IN ASTHMATICS LAGGED ZERO OR ONE DAY

Study	Description	Odds Ratio for Event per 50 $\mu g/m^3$	Standard Error of Log-Odds Ratio	95% Confidence Interval
Gielen et al. (1997)	61 children aged 7 to 13 years living in Amsterdam, The Netherlands	0.94	0.237	0.59, 1.50
Peters et al. (1997c)	27 non-smoking adults living in Erfurt, Germany	1.06	0.094	0.88, 1.27

TABLE 6-13. EFFECT OF 50 $\mu g/m^3$ PM_{10} ON BRONCHODILATOR USE IN ASTHMATICS LAGGED TWO TO FIVE DAYS

Study	Description	Odds Ratio for Event per 50 $\mu g/m^3$	Standard Error of Log-Odds Ratio	95% Confidence Interval
Gielen et al. (1997)	61 children aged 7 to 13 years living in Amsterdam, The Netherlands	2.90*	0.242	1.80, 4.66
Peters et al. (1997c)	27 non-smoking adults living in Erfurt, Germany	1.23	0.128	0.96, 1.58

*$p < 0.01$

The results of the peak flow analyses consistently show small decrements for both PM_{10} and $PM_{2.5}$. The results were shown for both morning (AM) and evening (PM) peak flow The effects using two to five day lags averaged about the same as did the zero to one day lags, but the

effects seen were slightly less consistent. None of the studies provided analyses which were able to separate out the effects of PM_{10} and $PM_{2.5}$ from other pollutants, nor were they able to distinguish the effects between PM_{10} and $PM_{2.5}$.

The effects on respiratory symptoms also tended to be positive although they were much less consistent. Most studies showed increases in cough, phlegm, difficulty in breathing, and bronchodilator use, although these increases were generally not statistically significant. Bronchodilator use was the only endpoint that appeared to be more strongly related to the longer lag times, but this result is based on three studies.

6.2.1.2 Short Term Effects on Lung Function and Respiratory Symptoms in Non-Asthmatics

Roemer et al. (1993) studied acute respiratory symptoms in a panel of 73 Dutch children with chronic respiratory symptoms in the winter of 1990-91 living in Wageningen and Bennekom, The Netherlands. Exposure measurements included SO_2, NO_2, and PM_{10}. PM_{10} measured at a central site exceeded 110 $\mu g/m^3$ on six days over the 3 month study period. Daily measurements of peak flow were made twice a day. A diary was used to measure the occurrence of acute respiratory symptoms and medication use. A time series analysis was performed using the SAS procedure, AUTOREG, using the Yule-Walker estimation method. Both morning and evening peak flow measurements were marginally significant in their relationship to PM_{10}, BS and SO_2 levels. PM_{10} was also associated with increased bronchodilator use.

Hoek and Brunekreef (1994) studied 1079 children living in four non-industrial communities in The Netherlands. The study was conducted during the three winters of 1987-88, 1988-89, and 1989-90. Pollutants measured included SO_2, NO_2, PM_{10}, sulfate fraction, nitrate fraction, and acid aerosol. PM_{10} levels were low (mean 45, range 14-126 $\mu g/m^3$). A first order autoregressive model, which contained temperature as a covariate, found a weak association between most pollutants and peak flow but no relationship with respiratory symptoms.

Hoek et al. (1998) summarized and reanalyzed results from several other studies reported in the literature, including those on asymptomatic children in the Utah Valley of Utah (Pope et al., 1991), children in Bennekom, The Netherlands (Roemer et al., 1993), children in Uniontown, PA (Neas et al., 1995), and children in State College, PA (Neas et al., 1996). The point of the reanalysis was to show an alternative method for summarizing peak flow studies, that is, relative

odds for a substantial 10% decrease in peak flow. Hoek et al. (1998) conducted a different type of analysis on peak flow data, the results of which become much more readily interpretable from a clinical point of view: most PEF studies have looked at changes in population mean PEF in response to air pollution findings, effects on the order of a few percentage points over a relevant pollution concentration range. The small changes seen are within the circadian variation everybody experiences every day, which is not associated with the symptomatology. Hoek et al. (1998) shows that these small changes in the population mean PEF are accompanied by significantly increased percentages of subjects experiencing large PEF changes (of more than 10% or more than 20% of their habitual level). Such relatively large changes can be associated with symptoms and with the need to use bronchodilators, which makes this analysis more coherent with findings of increased respiratory symptoms and relief medication use also found to be associated with air pollution. Significant decreases in peak flow were found to be related to increases in PM_{10} for models using data from the five panels. The analyses were done using a first-order autoregressive model with adjustments for time trend and ambient temperature. Co-pollutant models showed effects of ozone and PM_{10} to be largely independent.

Schwartz et al. (1994) also summarized results from several studies, including the "Six Cities study" (Ferris et al., 1979) and the asymptomatic patients from the Utah Valley study (Pope et al., 1992). Autoregressive logistic models were fitted using GEE methods. The symptoms of cough, lower respiratory disease, cough, and upper respiratory disease were found to be associated with PM_{10}, SO_2, and ozone.

Roemer et al. (1998, 1999) summarized the results for patients selected for cough in the PEACE studies. Phlegm was not related to PM_{10} levels for lags of zero, one or two days. Furthermore, no relationship was found with the seven day mean. The results for lower respiratory disease were similar to phlegm.

Linn et al. (1998) report the outcome of a study of 30 volunteer Los Angeles area residents with severe chronic obstructive pulmonary disease (COPD), relating pollutant levels (PM_{10}, $PM_{2.5}$, O_3, NO_2) to health outcomes (blood pressure, lung function, arterial blood oxygen saturation). The authors report that LA area monitoring stations appeared to give meaningful estimates of PM exposures outdoors at the homes of the COPD subjects studied with respect to temporal as well as spatial variations but note that on the whole, their findings provide only weak support that personal exposures track ambient background PM levels. They found the following:

(1) daily mean diastolic blood pressure increased significantly with same-day or previous day 24 hr-mean PM_{10} at the nearest monitoring stations, (2) no significant relationships with blood pressure were found for outside home $PM_{2.5}$, (3) some analyses of lung function versus subject-oriented PM measurements showed statistically significant negative relationships, but were usually eliminated by excluding 2 or 3 "outlying" subjects, and (4) arterial blood oxygen saturation showed no significant relationships. The authors suggest caution in interpreting the study.

Harré et al. (1997) studied 40 subjects aged over 55 years with COPD living in Christchurch, New Zealand. The study was conducted during the winter of 1994. Subjects completed diaries twice daily as well as their peak flow measurement. Pollutants measured included SO_2, NO_2, PM_{10}, and CO. Local PM_{10} measures exceeded 120 $\mu g/m^3$ five times during the study period. A log-linear regression model with adjustment for first order autocorrelation was used to analyze the peak flow data and a Poisson regression model was used to analyze the symptom data. Few significant associations between the health endpoints and the pollutants were found.

Boezen et al. (1999) studied 632 children aged 7 to 11 years of age during three winters (1992-95) in The Netherlands. The analyses were performed on two subpopulations: the 36 percent of children with no bronchial hyperresponsiveness and total IGE of 60 kU/L or less, and the remaining 64 percent without. Lung function was measured as the dichotomous variable: a decrease of 10 percent or more. Upper and lower respiratory symptoms were also measured. The PM_{10} readings ranged from 4.7 to 145.6 $\mu g/m^3$. A logistic regression model was used to analyze the data. Autocorrelation was adjusted for using the AR macro (SAS version 6.12). No consistent relationships were found between the health endpoints and PM_{10} levels.

Korrick et al. (1998) studied the effect of short-term changes in pollution on adult hikers on Mt. Washington, NH. Ozone levels were measured at two sights near the top of the mountain and $PM_{2.5}$ was measured near the base of the mountain. Both linear and non-linear regression models were used to assess the effect of pollution on lung function. Logistic regression was used to assess the effect on the odds of having a decline of greater than 10 percent in lung function. No estimates were given for the effect of $PM_{2.5}$ but it was stated that $PM_{2.5}$ did not affect the coefficient for ozone.

Naeher et al. (1999) studied 473 non-smoking women (ages 19 to 43 years) in Virginia over the 1995 and 1996 summers. Subjects took peak flow measurements twice a day for two weeks each summer. A regional monitoring site measured $PM_{2.5}$, PM_{10}, sulfate, strong acid (H+), hourly ozone, and meteorological variables. The data were analyzed using a mixed model assuming a linear regression term for each subject. These terms were assumed to be random and normally distributed and were estimated using SAS proc MIXED. Morning changes in peak flow were related to current day H+ and $PM_{2.5}$. Ozone was related to changed in evening peak flow.

Tables 6-14 through 6-17 examine outcomes for studies of non-asthmatics. Again, results of meta-analyses of combined results from the studies summarized in each table are also provided.

TABLE 6-14. EFFECT OF 50 $\mu g/m^3$ PM_{10} ON PEAK FLOW (L/MIN) IN NON-ASTHMATICS LAGGED ZERO OR ONE DAY

Study	Description	Change in PFR per 50 $\mu g/m^3$	Standard Error of Change	95% Confidence Interval
Hoek and Brunkreef (1994)	73 children aged 6-12 years with respiratory symptoms in the Netherlands	-0.42*	0.15	-0.71 , -0.1260
Hoek et al. (1998)	39 asymptomatic children in the Utah Valley	-0.33*	0.11	-0.55 , -0.11
Hoek et al. (1998)	67 children in Bennekom, the Netherlands	-0.45	1.05	-2.51, 1.61
Hoek et al. (1998)	83 children in Uniontown, PA	-0.95	1.60	-4.09 , 2.19
Hoek et al. (1998)	108 children in State College, PA	-0.15	1.45	-2.99, 2.69
Harré et al. (1997)	40 adults aged 55+ years with COPD living in Christchurch, New Zealand	-0.86	0.75	-2.33, 0.61
COMBINED	Meta-analysis using an Empirical Bayes Model Chi-square for homogeneity = 1.12, p = 0.952.	-0.38*	0.09	-0.56, -0.20

*$p < 0.05$

TABLE 6-15. EFFECT OF 50 $\mu g/m^3$ PM_{10} ON COUGH IN NON-ASTHMATICS LAGGED ZERO OR ONE DAY

Study	Description	Odds Ratio for Event per 50 $\mu g/m^3$	Standard Error of Log-Odds Ratio	95% Confidence Interval
Hoek and Brunkreef (1994)	73 children aged 6-12 years with respiratory symptoms in the Netherlands	0.94	0.255	0.57, 1.55
Schwartz et al. (1994)	Six Cities Study	1.39*	0.145	1.05, 1.85
Schwartz et al. (1994)	39 asymptomatic children in the Utah Valley	1.36*	0.120	1.07, 1.72
COMBINED	Meta-analysis using an Empirical Bayes Model Chi-square for homogeneity =, p = .	1.31*	0.088	1.10, 1.56

*$p < 0.05$

TABLE 6-16. EFFECT OF 50 $\mu g/m^3$ PM_{10} ON LOWER RESPIRATORY ILLNESS IN NON-ASTHMATICS LAGGED ZERO OR ONE DAY

Study	Description	Odds Ratio for Event per 50 $\mu g/m^3$	Standard Error of Log-Odds Ratio	95% Confidence Interval
Hoek and Brunkreef (1994)	73 children aged 6-12 years with respiratory symptoms in the Netherlands	1.00	0.172	0.71, 1.40
Schwartz et al. (1994)	Six Cities Study	2.03*	0.206	1.36, 3.04
Schwartz et al. (1994)	39 asymptomatic children in the Utah Valley	1.21	0.187	0.84, 1.75
Boezen et al. (1999)	167 children aged 7-11 years living in The Netherlands	1.02	0.100	0.84, 1.24
COMBINED	Meta-analysis using an Empirical Bayes Model Chi-square for homogeneity = 10.23, p = 0.017	1.211	0.128	0.94, 1.56

*$p < 0.05$

TABLE 6-17. EFFECT OF 50 $\mu g/m^3$ PM_{10} ON UPPER RESPIRATORY ILLNESS IN NON-ASTHMATICS LAGGED ZERO OR ONE DAY

Study	Description	Odds Ratio for Event per 50 $\mu g/m^3$	Standard Error of Log-Odds Ratio	95% Confidence Interval
Hoek and Brunkreef (1994)	73 children aged 6-12 years with respiratory symptoms in the Netherlands	1.00	0.089	0.84, 1.19
Schwartz et al. (1994)	Six Cities Study	1.39	0.186	0.97, 2.00
Schwartz et al. (1994)	39 asymptomatic children in the Utah Valley	1.03	0.166	0.74, 1.43
Boezen et al. (1999)	167 children aged 7-11 years living in The Netherlands	1.01	0.033	0.94, 1.07
COMBINED	Meta-analysis using an Empirical Bayes Model Chi-square for homogeneity = 2.76, p = .251	1.02	0.031	0.96, 1.08

The results of the peak flow analyses consistently show small decrements for increases in PM_{10}. The results are similar to those found for asthmatics. There were no studies that gave results for $PM_{2.5}$, and no studies gave results for longer lag times.

Studies not meeting the criteria for discussion above are summarized in Tables 6-18 and 6-19. Many excellent studies are included in these tables without further discussion. These studies provide supporting evidence for the conclusions reached from the studies selected for text discussion.

6.2.1.3 Discussion of Co-Pollutant Studies

A small number of short-term PM exposure respiratory studies considered multiple pollutants in the same model. These are described individually.

Delfino et al. (1998) found that the presence of ozone in a model with PM_{10} reduced slightly the effect of PM_{10} on asthma symptoms. However, all terms that were significant without ozone in the model remained significant with ozone added to the model.

TABLE 6-18. OTHER ASTHMATIC PANEL STUDIES

Study	Design	Model Type	Other Pollutants	Other Covariates	Results
Thurston et al. (1997)	Three 5-day summer camps with 166 asthmatic children conducted in 1991, 1992, 1993 measuring symptoms and change in lung function (morning to evening)	Linear regression for lung function, Poisson regression for symptoms and bronchodilator use in relation to sulfate, with random subject effects.	Ozone, H+	Pollen, daily maximum temperature,	Sulfate and ozone were related to both respiratory symptoms and bronchodilator use.
Agócs et al. (1997)	A panel of 60 asthmatic children was followed for two months in Budapest, Hungary	A mixed model relating TSP to the morning and evening PEFR measurements was used	SO_2	time trend, day of week, temperature, humidity	No significant relationships with TSP were found
Güntzel et al. (1996)	An asthma reporting system was used in connection with pollutant monitoring in Switzerland from the fall of 1988 to the fall of 1990	A Box-Jenkins ARIMA time series model was used to relate asthma to TSP	Ozone, SO_2, NO_2	Temperature	No significant relationships were found
Taggart et al. (1996)	A panel of 38 adult asthmatics were followed from July 17 to September 22, 1993 in northern England	A generalized linear model was used to relate pollutants to bronchial hyperresponsiveness	SO_2, NO_2	Temperature	Small effects were seen in relation to NO_2 and black smoke
Delfino et al. (1996)	A panel of 12 asthmatic children with symptomatic asthma living in San Diego, CA were followed during the early fall of 1993.	A random effects model was fitted to ordinal symptom scores and bronchodilator use in relation to 24-hour $PM_{2.5}$.	O_3	Temperature, relative humidity, fungal spores, and day of week.	Symptoms and bronchodilator use were associated with 12-hour personal ozone measurements, but not stationary outdoor monitor data on 1-hour maximum ozone or 24-hour $PM_{2.5}$. Fungal spores were associated with symptoms and inhaler use.

TABLE 6-18 (cont'd). OTHER ASTHMATIC PANEL STUDIES

Study	Design	Model Type	Other Pollutants	Other Covariates	Results
Defino et al. (1997)	A panel of 9 adults and 13 children were followed during the late spring of 1994 in a semi-rural area of San Diego County at the inversion zone elevation of around 1,200 feet.	A random effects model was fitted to ordinal symptom scores, bronchodilator use, and PEF in relation to 24-hour PM_{10}.	O_3	Temperature, relative humidity, fungal spores, day of week	Although PM_{10} never exceeded 51 $\mu g/m^3$, bronchodilator use was significantly associated with PM_{10} (0.152 inhaler puffs/10 $\mu g/m^3$; SE 0.064). Fungal spores were associated with all respiratory outcomes.
Hiltermann et al. (1997)	Sixty outpatient asthmatics were examined for nasal inflammatory parameters in The Netherlands from July 3 to October 6, 1995.	The association of log transformed inflammatory parameters to 24-h PM_{10} were analyzed for using a linear regression model.	O_3	Mugwort-pollen	An association of inflammatory parameters in nasal lavage of patients with intermittent to severe persistent asthma with ambient ozone and allergen exposure was observed, but not with exposure to PM_{10}.

TABLE 6-19. OTHER NON-ASTHMATIC PANEL STUDIES

Study	Design	Model Type	Other Pollutants	Other Covariates	Results
Spektor et al. (1991)	Monthly time series analysis of pulmonary function	Not given	SO_2, O_3	Height, weight	Pulmonary function related to PM_{10}
Studnicka et al. (1995)	Three panels of 16 to 19 day duration measured at a summer camp	Linear regression of lung function allowing for repeated measures	H+, sulfate, ammonia, ozone	Temperature, humidity, pollen	Pulmonary function related to H+ but not to PM_{10}
Scarlett et al. (1996)	154 school children had pulmonary function measured daily for 31 days	Separate autoregressive models for each child were pooled	PM_{10}, ozone, NO_2	Pollen, machine, operator, time of day, time trend	PM_{10} was related to changes in FEV and FVC
Gordian et al. (1996)	Outpatient visits for upper respiratory symptoms were related to ambient PM_{10} levels	An autoregressive Poisson model was fitted to detrended pollution and meteorological data	CO	Weekday, temperature	Upper respiratory symptoms were associated with increased PM_{10} levels
Cuijpers et al. (1994)	Summer episode study in Maastrucht, The Netherlands PM_{10} measured.	Paired t tests were used for pulmonary function tests, methods for respiratory symptoms not given	SO_2, NO_2, BS, ozone, H+	none in model	Small decreases in lung function were found
Awasthi et al. (1996)	A cohort of 664 preschool children were followed for two weeks each in northern India	Ordinary least squares was used to relate a respiratory symptom complex to suspended particulate matter	SO_2, nitrates	Coal, wood, kerosene	A significant regression coefficient between PM and symptoms was found
Miyao et al. (1993)	Japanese national health insurance records were correlated with suspended particulate matter	Pearson correlation	SO_2, NO_2	cedar and cyprus pollen	No significant correlation with particulate matter was found
Long et al. (1998)	428 participants with mild airway obstruction in a health study were surveyed during a pollution episode	Gender specific odds ratios of symptoms were calculated for differing PM_{10} levels using the Breslow-Day test	TSP, VOC		Cough, wheezing, chest tightness, and shortness of breath were all increased during the episode
Boezen et al. (1998)	75 symptomatic and asymptomatic adults near Amsterdam were surveyed during the winter of 1993-1994 for three months	An autoregressive logistic model was used to relate PM_{10} to respiratory symptoms, cough, and phlegm.	SO_2, NO_2	Daily minimum temperature, time trend, day of week	No relationship was found with pulmonary function. Some significant relationships with respiratory disease were found in subpopulations
Linn et al. (1996)	269 school children in Southern California were surveyed twice daily for one week in the fall, winter and spring for two years	A repeated measures analysis of covariance was used to fit an autoregressive model	NO_2, ozone	Year, season, day of week, temperature	Morning FVC was significantly decreased as a function of PM_5 and NO_2

Timonen and Pekkanen (1997) found a relationship between PM_{10} and decreases in morning peak flow for lags of two days or for a four day mean. When NO_2 was added to the model, the coefficients for PM_{10} remained essentially unchanged.

Romieu et al. (1997) found a significant relationship between peak flow and respiratory symptoms as dependent variables and ozone and PM_{10} as independent variables in asthmatic children in Mexico City. When both ozone and PM_{10} were included in the model, the significance of ozone increased. PM_{10} was not significant in this study and it remained so after the inclusion of ozone. Romieu et al. (1996) in a separate study found an effect of $PM_{2.5}$ on peak flow. This effect remained after the inclusion of ozone in the model.

Studnika et al. (1995) observed decreases in FEV_1 as a function of H+ and PM_{10} levels in children participating in a summer camp. The coefficients for PM_{10} remained relatively constant with the inclusion of H+ in the model.

Gold et al. (1999) found that both $PM_{2.5}$ and ozone were related to changes in morning peak flow. The combined effect of the two pollutants was somewhat larger than the effect of each pollutant individually in the model, but was less than the sum of the two separate effects.

Although these studies are not definitive about the effects of multiple pollutants, it does appear that the pollutants considered in these models act somewhat independent of each other. There were no cases where the statistical significance was eliminated by the inclusion of co-pollutants.

6.2.2 Long-Term Exposure Effects on Lung Function and Respiratory Symptoms

A small number of studies have been published recently which looked at the effects of long-term PM exposure on lung function and respiratory illness. Some of these did not relate effects directly to PM_{10} or $PM_{2.5}$.

Dockery et al. (1996) examined respiratory health effects among 13,369 white children, aged 8 to 12 years, from 24 communities in the United States and Canada. A two-stage logistic regression model was used to adjust for potential confounding from gender, history of allergies, parental asthma, parental education, and smoking in the home. The city-specific range in the annual pollutant means from local monitors were 14.9 $\mu g/m^3$ for $PM_{2.1}$ and 17.3 $\mu g/m^3$ for PM_{10}.

Although the endpoint of bronchitis was significantly related to fine particulate sulfates, no endpoints were related to PM_{10} levels.

Abbey et al. (1998) studied associations between lung function measures collected in 1997 and estimated 20-year exposure to respirable particulates, suspended sulfates, ozone, and PM_{10} in 1391 non smoking seventy-day adventist, throughout CA. Increased frequency of days where PM_{10} exceeded 100 $\mu g/m^3$ was associated with a decrement in FEV in males whose parents had asthma, bronchitis, emphysema, or hay fever. No other effects were seen in any other subgroups.

Braun-Fahrländer et al. (1997) studied the impact of long-term exposure to air pollution on respiratory symptoms and illnesses in a cross-sectional study of school children (aged 6 to 15 years), living in ten different communities in Switzerland. Air pollution measurements included PM_{10}, NO_2, SO_2, and ozone. Local PM_{10} measurements yielded annual PM_{10} means in the ten communities ranging from 10 to 33 $\mu g/m^3$. Symptoms were analyzed using a logistic regression model that included the covariates of family history of respiratory and allergic diseases, number of siblings, parental education, indoor fuels, passive smoking, and others. The endpoints of chronic cough, bronchitis, wheeze and conjunctivitis symptoms were all related to the various pollutants. The collinearity of the pollutants prevented any causal separation.

Ackermann-Liebrich et al. (1997) studied the long-term effect of air pollution in a cross-sectional population-based sample of Swiss adults aged 18 to 60 years. Air pollutants monitored by local authorities in each of eight regions included SO_2, NO_2, TSP, ozone, and PM_{10}. Annual PM_{10} means ranged from 10.1 to 33.4 $\mu g/m^3$. A random sample of 2,500 adults in each region was drawn from registries of the local inhabitants. The natural logarithm of FVC and FEV_1 was regressed against the natural logarithms of height, weight, age, gender, atopic status, and pollutant variables. The estimated regression coefficient for PM_{10} versus FVC was -0.0345 with 95 percent confidence intervals of -0.0407 to-0.0283. The corresponding value for FEV_1 was -0.0160 with 95 percent confidence interval of -0.0225 to -0.0095. Thus, a 10 $\mu g/m^3$ increase in PM_{10} was estimated to lead to an estimated 3.4 percent decrease in FVC and 1.6 percent decrease in FEV_1.

Von Mutius et al. (1995) studied 9 to 11 year old school children living in Leipzig, East Germany. Parents filled out a respiratory disease questionnaire. The presence of respiratory symptoms was confirmed by a physician. After controlling for parental education, passive smoke exposure, temperature, and humidity, the odds ratio for developing upper respiratory illness was

1.62 with 95 percent confidence limits of 1.08 to 2.45. PM was measured by beta-absorption. The same effects were seen when the other pollutants were used as the independent variable.

Raizenne et al. (1996) examined the health effects of exposure to acidic air pollution among children living in 24 communities in the United States and Canada. Parents of the children (aged 8 to 12) completed a self-administered questionnaire. Pulmonary function measurements were taken at the end of the pollution monitoring period. These measurements were analyzed using a two-stage regression analysis that adjusted for age, gender, height, and weight. Although decreases in lung function were highly related to particle strong acidity, they were also related to PM_{10}. The particle strong acidity range over the study areas was 43.4 nmol/m^3.

To study whether chronic effects of ozone exposure can be observed in an unselected cohort of 1,150 children, Frischer et al. (1999) prospectively followed a cohort of primary school children in Austrian counties by repeated measurements of lung function between January 1994 and December 1996. This unique study observed during the 3 yr time period small but consistent decrements in lung function in a cohort of children with ambient ozone exposure. They report that for PM_{10}, a positive effect was seen for winter exposure, which was completely confounded by temperature. Tager (1999) comments that in this study the data indicated that summertime PM_{10} was associated with decreased growth of MEF_{50} (maximum expiratory flow at 50% of vital capacity). However, the more important comment of Tager (1999) is that cross-sectional studies are fraught with too many methodological problems, and should be abandoned as a design strategy and that the approach taken by Frischer et al. (1999) offers a practical study design that should be emulated. Such shorter term prospective studies of young children will help develop a more substantive database through which more accurate estimates of effects of ambient air pollution on lung function growth can be obtained.

Lewis et al. (1998) studied 3,023 primary school children in New South Wales. Particulate and sulfur dioxide measures were collected from January 1993 to December 1993. Children in each of the nine areas were chosen to be within 3 km of a monitoring station. Night cough, chest colds, and wheeze were found to be related to PM_{10} levels.

Peters et al. (1999a) studied 12 southern California communities with differing levels of pollution. In each community, 150 students in grades 4 and 7 were enrolled. The study was conducted in 1993, but pollution estimates were based on the years 1986-1990. Several

respiratory illness rates were related to PM_{10} levels including the presence of asthma, bronchitis, cough, or wheeze. None of the symptoms were significantly related to PM_{10}. Peters et al. (1999b) also studied the effect of PM_{10} on lung function in the same population. Forced vital capacity and mid-maximal flow rate were negatively related to PM_{10} levels, but FEV_1 and peak flow were not. All results tended to show a negative effect of PM_{10}.

Three other studies related long-term PM_{10} exposure to PM_{10}. Jammes et al. (1998) compared lung function at two sites (suburbs and downtown Marseilles) and found some differences. Zemp et al. (1999) studied the effect of PM_{10} on respiratory symptoms in eight communities in Switzerland and found that PM_{10} was related to differences in rates of chronic phlegm, breathlessness, and dyspnea in never smokers. Results for ex-smokers and current smokers tended to show smaller effects. McDonnell et al. (1999) looked at a cohort of 3,091 non-smokers in southern California (AHSMOG Study). Most of the analyses were done using ozone as the pollutant of interest, and the inclusion of PM_{10} in the analyses had little effect on the coefficients for ozone.

Goren et al. (1999) studied school children (ages 7 to 13 years) who resided in two communities where one community had quarries and a cement factory as PM sources, while the other community was geographically near but divided from the sources by two valleys and two hills. Pollutants measured included only TSP and, for a limited time, PM_{10}. Both pulmonary function measurements and respiratory symptom data were obtained by standard methods in the spring of 1995. While geographically close the socioeconomics status of the populations differed significantly and was thus controlled for the logistic regression analyses. Approximately 16% of PM_{10} levels exceeded 150 $\mu g/m^3$ in the source-exposed community. TSP levels in the adjacent community were about 30 to 60% of those in the source-exposed community. The source community had a PEF decrement of 97.03% predicted, while the adjacent community was at 99.80% with a $p = 0.0326$ for the difference. While not significant, positive OR's were found for the symptoms such as a cough without cold.

Other new studies examined long term pollutant effects but did not use PM_{10} or $PM_{2.5}$ as the PM measure (De Kok et al., 1996; Chen et al., 1998; and Zejda et al., 1996).

Overall, the results of the chronic studies are not consistent. Some studies show effects for some endpoints, but other studies fail to find the same effects. It is generally more difficult to find a gradient in long term exposures, whereas short term studies need only find an area with

occasional high exposures. For this reason it is not surprising that the studies show less consistency than the acute exposure studies.

6.2.3 Effects of Short-Term PM Exposure on the Incidence of Respiratory Medical Visits and Hospital Admissions

6.2.3.1 Introduction

Potentially the most severe morbidity measure evaluated with regard to PM exposure is hospitalization. Hospital emergency department (ED) visits represent a somewhat less severe, but related, outcome that has also been studied in relation to air pollution. In addition, doctors visits also represent a related health measure that, although even less studied, is also relevant to those who also suffer severe health effects, but captures a different population than ED visits: those who choose to visit a private doctor, rather than attend an emergency department. This latter category of pollution affected persons can represent a large population, yet one that is largely unobserved, due to the usual lack of centralized data regarding doctors' visits. Indeed, we are often limited in such epidemiologic studies to "looking under the lamp post" for effects in data that are routinely collected, but which may miss many cases of adverse effects that are just as severe, but are not included in the routine health care record keeping system at hospitals.

This section evaluates present knowledge regarding the epidemiologic associations of hospitalizations and medical visits with ambient PM exposure. It intercompares various PM components vis-à-vis their relative associations with adverse health effects, as well as their respective extents of coherence in the PM associations exhibited across related measures of adverse health effects. In the following discussions, the focus for quantitative intercomparisons is on studies and results considering PM metrics that quantitatively measure mass or a specific mass constituent, i.e.: PM_{10}, $PM_{2.5}$, sulfates ($SO_4^{=}$), or acidic aerosols (H^+). Study results for other related PM metrics (e.g., Black Smoke; BS) are also considered, but only qualitatively, primarily with respect to their coherence or lack of coherence with studies using the mass or composition metrics measured in North America. In order to consider the potentially confounding effects of other co-existing pollutants, study results for the various PM metrics are presented both for: (1) the case when the PM metric is the only pollutant in the model; and, (2) the case where a second pollutant, ozone, is also included in the model (as ozone has been shown by most past studies to be the most important co-pollutant affecting respiratory

admissions). Results from models with more than two pollutants included simultaneously are not used for quantitative estimates of coefficient size or statistical strength, due to increased likelihood of bias and variance inflation due to multi-collinearity of various pollutants (e.g., see Harris, 1975).

6.2.3.2 Summary and Implications of Studies Assessed in the 1996 PM AQCD

In the 1996 PM AQCD, it was found that both COPD and pneumonia hospitalization studies showed moderate, but statistically significant, relative risks in the range of 1.06 to 1.25 per increase of 50 $\mu g/m^3$ in PM_{10} or its equivalent. There was a suggestion of a relationship between ambient PM_{10} and heart disease admissions, but the estimated effects were smaller than the effects for other endpoints. While a substantial number of hospitalizations for respiratory illnesses occur in those >65 years of age, there are also numerous hospitalizations for those under 65 years of age. Several of the hospitalization studies restricted their analysis by age of the individuals, but did not explicitly examine younger age groups. One exception noted was Pope (1991), who reported an increase in hospitalization for Utah Valley children (aged 0 to 5) for monthly numbers of admissions in relation to PM_{10} monthly averages, as opposed to daily admissions in relation to daily PM levels used in other studies.

Studies examining acute associations between indicators of components of fine particles (e.g., British smoke, BS; sulfates, $SO_4^=$; and acidic aerosols, H^+) and hospital admissions were also reported as finding significant relationships. While sulfates were especially predictive of health effects, it was not clear whether the sulfate-related effects were attributable to their acidity, or to the broader effects of associated combustion-related fine particles, in general.

6.2.3.3 Key New Respiratory Medical Visits Studies

As discussed above, medical visits include both hospital emergency department (ED) visits and doctors' office visits. As in the past CD's, most of the available morbidity studies discussed below are of ED visits and their associations with air pollution, but new studies look at the primary care setting such as a study conducted in Paris, France which looks at doctors' visits to patients in that city. This provides a new insight into the scope of air pollution's effects on severe morbidity.

Delfino and colleagues (1997) examined the association between air pollution and emergency department (ED) visits in Montreal, Canada from June through September 1992 and 1993. Air pollutants measured included: O_3, PM_{10}, $PM_{2.5}$, the $SO_4^=$ fraction of $PM_{2.5}$, and aerosol strong acidity (H^+). Temporal trends, autocorrelation, and weather were controlled for in time-series regressions. For 1992, no significant associations with ER visits were found, but 33% of the particulate data were missing. For 1993, only H^+ was significant for children less than 2 years of age, despite very low levels of aerosol acidity (mean effect of 4 nmol/m^3= 5.0%: CI = 0.4-9.6%). There were no significant associations between air pollution and ED visits for persons 2-64 yrs. of age. For patients over 64 yrs. of age, 1-h maximum O_3, PM_{10}, $PM_{2.5}$, and $SO_4^=$ were all positively associated with respiratory visits ($p < 0.02$). Effects of particles in the older adults were smaller than for O_3, with mean effect sizes of 16% (CI = 4-28%), 12% (CI = 2-21%) and 6% (CI = 1-12%) for PM_{10}, $PM_{2.5}$, and $SO_4^=$, respectively. Ozone and PM_{10} levels never exceeded 67 ppb and 51 μg/m^3, respectively.

Delfino et al. (1998) examined the relationship between the number of daily ED visits for respiratory illnesses and outdoor air pollution in Montreal, Quebec (June-August, 1989-1990). Air pollutants measured included 1- and 8-h maximum ozone (O_3) and estimated $PM_{2.5}$. Seasonal and day-of-week trends, autocorrelation, temperature, and relative humidity were addressed in-time series regressions. Although O_3 levels never exceeded the U.S. National Ambient Air Quality Standard (NAAQS) of 120 ppb (maximum day, 106 ppb), statistically significant ($P < 0.01$) relationships were found between respiratory ER visits for patients over the age of 64 with both 1- and 8-h maximum O_3 measured 1 day prior to the ER visit day during the 1989 summer. There was an association between respiratory ER visits for the elderly and estimated $PM_{2.5}$ lagged 1 day (0.1 visit/μg/m^3 $PM_{2.5}$, $P < 0.07$), but this was found to be confounded by both temperature and O_3. Direct $PM_{2.5}$ measurements were only available every sixth day, and the estimated $PM_{2.5}$ was derived from daily measurements of Coefficient of Haze (CoH), O_3, NO_x, barometric pressure, and RH corrected light extinction coefficient (B_{ext}) derived from visibility data. The authors noted that, because of this, their estimated $PM_{2.5}$ metric "should obviously be viewed as an indicator of the level of photochemical smog rather than as an accurate measurement of $PM_{2.5}$". The authors concluded that their findings confirmed the impression that, while air quality standards may protect the respiratory health of the general population, this is not the case for especially susceptible subgroups such as the elderly.

Lipsett et al. (1997) examined whether there was a relationship between ambient air pollution in Santa Clara County, CA and emergency room visits for asthma during the winters of 1988-89 through 1991-1992. ED records from three acute-care hospitals were abstracted to compile counts of daily visits for asthma and for a control diagnosis (gastroenteritis) for 3-mo periods during each winter. Air monitoring data included daily CoH and PM_{10}, as well as hourly NO_2 and O_3 concentrations. Daily CoH measurements were used to predict values for missing days of PM_{10} to develop a complete PM_{10} time series. Daily data were also obtained for temperature, precipitation, and relative humidity. In time-series analyses using Poisson regression, consistent relationships were found between ER visits for asthma and PM_{10}. Same-day NO_2 was also associated with asthma ED visits, while ozone was not. Because there was a significant interaction between PM_{10} and minimum temperature in this data set, estimates of relative risks (RR's) for PM_{10}-associated asthma ED visits were temperature-dependent. A 60 $\mu g/m^3$ change in PM_{10} (2-day lag) corresponded to RR's of 1.43 (95% CI = 1.18-1.69) at 20 degrees F, representing the low end of the temperature distribution, 1.27 (95% CI = 1.13-1.42) at 30 degrees F, and 1.11 (95% CI = 1.03-1.19) at 41 degrees F, the mean of the observed minimum temperature. ED visits for gastroenteritis were not significantly associated with any pollutant variable. Several sensitivity analyses, including use of robust regressions and of nonparametric methods for fitting time trends and temperature effects in the data, supported these findings. The authors conclude that these results demonstrate an association between ambient wintertime PM_{10} and exacerbations of asthma in an area where one of the principal sources of PM_{10} is residential wood combustion.

Pantazopoulou et al. (1995) examined short-term exposure effects of air pollution on morbidity in the greater Athens area during 1988. Data were collected on the daily number of emergency outpatient visits and admissions for cardiac and respiratory causes (diagnoses at time of admission) to all major hospitals. Measurements of air pollution included values for BS, CO, and NO_2. Statistical analysis was done using multiple linear regression models controlling for potential confounding effects of meteorological and chronological variables, separately for winter and summer. The daily number of emergency visits was related positively with the levels of the various air pollutants, but this association reached the nominal level of statistical significance only for NO_2 in winter. The number of emergency admissions for cardiac and respiratory causes was related to a statistically significant degree with all indices of air pollution during the winter.

Two studies examine medical visits of children in Brazil and Chile. Lin et al. (1999) report the association between air pollution and pediatric respiratory emergency visits (RESP) in São Paulo, Brazil, from May 1991 to April 1993. The average of ten centrally located stations were used to provide daily city-wide levels of SO_2, CO, PM_{10}, O_3, and NO_2. Poisson regression was employed on 5-day lagged moving average based on the outcome of preliminary analyses. Based on the results of this regression model, they reported a statistically significant association between PM_{10} and pediatric emergency admission due to respiratory diseases even while controlling for season, weather, and day of week (1.040; 95% CI 1.034-1.046). The inclusion of other pollutants in the model did not substantially modify the estimated coefficients of PM_{10}, suggesting that the pollutant has an independent effect on RESP (1.052, 95% CI 1.042-1.063). Further, quintile analysis of unadjusted PM_{10} data appears to have revealed a general concentration-response relationship. The author states that this outcome represents a serious public health problem for the children of São Paulo – noting that a large increase in the counts of respiratory emergency visits; more than 20% – can be observed for the most polluted days.

In Santiago, Chile, Ostro et al. (1999) studied cohorts of children 3-15 years of age and below age 2 for daily medical visits to primary health care clinics for either upper or lower respiratory symptoms in relation to PM_{10} and ozone measurements. For children under age 2, a 50 $\mu g/m^3$ change in PM_{10} was associated with a 4 to 12% increase in lower respiratory symptoms while the older group (3 to 15 years) ranged from 3 to 9%. The average of four stationary monitors located downtown within a 12 km^2 quadrilateral was used to obtain the daily concentrations of PM_{10} and O_3. The daily mean PM_{10} level was 108.6 $\mu g/m^3$ (min-max 18.5 to 380 $\mu g/m^3$). The magnitude of the effect of one pollutant was not impacted by the inclusion of a second pollutant in the model. Analyses of lag periods appeared to be most significant for single day lags and cumulative exposure over a 5-day period generated the strongest effect.

Stieb et al. (1996) examined the relationship of asthma emergency department (ED) visits to daily concentrations of air pollutants in Saint John, New Brunswick, CN. Data on ED visits with a presenting complaint of asthma (n = 1987) were abstracted for the period 1984-92 (May-September). Air pollution variables included: O_3, SO_2, NO_2, $SO_4^=$, and TSP. Weather variables included temperature, humidex, dew point, and relative humidity. Daily ED visit frequencies were prefiltered to remove day-of-week and long wave trend effects, and filtered values were regressed on air pollution and weather variables for the same day and the 3 previous

days. A positive, statistically significant ($p < 0.05$) association was observed between O_3 and asthma ED visits 2 days later. The O_3 effect was not significantly influenced by the addition of weather or other pollutant variables into the model or by exclusion of repeat ED visits. However, given the limited number of sampling days available for $SO_4^=$ and TSP (measured only once every sixth day of this study), the authors concluded "a particulate effect could not be ruled out".

Other recent medical visit studies for asthma include the following: Norris et al. (1999) examined emergency department visits by children (under the age of 18) to six hospitals for asthma and daily air pollutant data to include $PM_{2.5}$ levels in the inner city of Seattle, Washington over 15 months during 1995 and 1996. A semiparametric poisson regression model yielded significant association for $PM_{2.5}$ and CO. A change of 11 $\mu g/m^3$ in $PM_{2.5}$ was associated with a relative rate of 1.15 (95% CI 1.08 - 1.23). Yang et al. (1997) studied asthma emergency room visits and air pollution (CO, O_3, PM_{10}) in Reno, Nevada for the period 1992-1994. Total asthma visits were found to increase 33.7%, (95% CI range 6.0 - 61.5%) for every 100 ppb in the O_3 level. No association, for CO or PM levels with asthma ER visits were found. PM_{10} by β-method had a mean of 33.6 with a min/max of 2.17 to 157.32 $\mu g/m^3$ and 6-day Hi-Vol yielded a mean of 38.01, min 10.2 to max 119.17. Ozone average was 51.01 range 16 to 100 ppb. Daily average emergency visits for asthma averaged 1.75. In a bivariate analyses none of the three air pollutants was statistically significantly associated with ER asthma visits. The concentration of PM_{10} of CO, and O_3 were correlated. Choudhury et al. (1997) examined insurance claims data in Anchorage, Alaska for medical visits for asthma, bronchitis, and upper respiratory infection over a three year period in relation to 24-hr PM_{10} concentration. No other pollutants were examined. They concluded that fall is positively associated with asthma visits, but not winter, and suggest that PM_{10} levels are less during the winter when the ground is covered with snow and ice.

Garty et al. (1998) report a study in Israel of emergency room visits for acute asthma attacks of asthmatic children age 1 to 18 years for January 1 to December 31, 1993 in relation to pollutant levels. No significant correlation with concentration of particulate was observed. The authors comment that airborne particle levels (50% with size less than 10 μm fluctuated around a rather constant level without outstanding peaks or troughs. An exceptionally high incidence of ER visits of asthmatic children, observed during September, coincided with the beginning of the school year, possibly due to an increase in the number of viral illnesses. The correlation between ER visits and pollutants increased significantly when the September peak was excluded.

Tenías et al. (1998) studied the association between hospital emergency visits for asthma and air pollution (black smoke, SO_2, NO_2, O_3) in Valencia, Spain during the period 1994-95 using the APHEA analysis approach that takes into account potential confounding factors. For an increase in smoke of 10 $\mu g/m^3$ at lag 0 over the whole period a relative risk of 1.025 (95% CI.0. 981 to 1.072) was found, with higher rates in cold months versus warm months. Based on a three year series analysis during the cold months, when PM levels are highest, the relative risk estimated for an increase of 10 $\mu g/m^3$ (lag 0) was 1.049 (95% CI 1.008 to 1.093).

In London, Atkinson et al. (1999) studied the association between the number at daily visits to accident and emergency departments for respiratory complaints and measures of outdoor air pollution to include PM_{10}, NO_2, SO_2 and CO. They examined different age groups and reported the strongest association for children for visits for asthma, but were unable to separate the effects of PM_{10} and SO_2. Pollen levels did not influence the results.

Two studies examined methodological aspects of medical visit studies. Stieb et al. (1998a) examined the occurrence of bias and random variability in diagnostic classification of air pollution and daily cardiac respiratory emergency department visits such as asthma, COPD respiratory infection and cardiac. They concluded that there was no evidence of diagnostic bias in relation to daily air pollution levels. Stieb et al. (1998b) report that in a population of adults visiting an emergency department with cardiac respiratory disease, fixed site sulfate monitors appear to accurately reflect daily variability in average personal exposure to particulate sulfate, while particulate acid was not as well represented by fixed site monitors.

Minshew and Towle (1999) and Mulla et al. (1998) report health outcomes related to wildfires in Florida during June and July 1998. The frequency of selected conditions reported by hospital emergency rooms in Volusia and Flagler counties were reported for the same period of days in 1997 June 1 - July 6 to compare for the same time period during the wildfires in 1998. For example, asthma reports increased from 77 to 147; bronchitis from 28 to 65; and shortness of breath from 68 to 90, but no specific pollutant data were examined.

As mentioned at the outset of this section, there is also information from new studies that look at primary care setting doctor visits. Medina et al. (1997) examined short-term relationships between doctors' house calls and urban air pollution in Greater Paris for the period 1991-95. Poisson regressions were employed with nonparametric smoothing functions controlled for time trend, seasonal patterns, pollen counts, influenza epidemics, day-of-week, holidays, and weather.

The relationship between asthma house calls and air pollution was stronger for children. A relative risk of 1.32 [95% confidence interval (CI) = 1.17-1.47)] was observed for an increase from the 5th to the 95th percentile (7-51 $\mu g/m^3$) in daily concentrations of black smoke (BS). The risks for 24-hr sulfur dioxide, nitrogen dioxide, and PM_{13} levels were in the same range. Cardiovascular conditions were concluded to show weaker associations than angina pectoris/myocardial infarction. Eye conditions were exclusively related to ozone (relative risk of 1.17 (95% CI 1.02-1.33) for the BS range 7-51 $\mu g/m^3$). In two-pollutant models of asthma house calls that included BS with, successively, SO_2, NO_2, and O_3, only BS and O_3 effects remained stable. These results suggest that the widely documented air pollutant associations noted for hospital emergency department visits are also applicable to a wider population consulting their physician, rather than an emergency department.

Another published study looking at effects of air pollution on health in the primary care setting was conducted Hajat et al. (1999), who evaluated the relationship between daily General Practice (GP) doctor consultations for asthma and other lower respiratory disease (LRD) and air pollution in London, UK. Time-series analysis of daily numbers of GP consultations was performed, controlling for time trends, season factors, day of week, influenza, weather, pollen levels, and serial correlation. Consultation data were available for between 268,718 and 295,740 registered patients from 45-47 London practices contributing to the General Practice Research Database during 1992-94. Positive associations, weakly significant and consistent across lags, were observed between asthma consultations and NO_2 and CO in children, and PM_{10} in adults, and between other LRD consultations and SO_2 in children. The authors concluded that there are associations between air pollution and daily concentrations for asthma and other lower respiratory disease in London. In children, the authors identified the most important pollutants to be NO_2, CO, and SO_2. In adults, however, the authors concluded that the only consistent association was with PM_{10} (30 $\mu g/m^3$ RR=1.09; 95% CI=1.04-1.15). Moreover, across all of the various age, cause, and season categories considered in this research, PM_{10} was the pollutant most coherent in giving positive pollutant RR estimates for both asthma and other LRD (11 of 12 categories positive) in the single pollutant models considered.

Of these new severe morbidity studies, the two studies of doctors' visits are most informative. As the authors of the London study note: "There is less information about the effects of air pollution in general practice consultations but, if they do exist, the public health

impact could be considerable because of their large numbers." Indeed, the Paris doctors' house calls and the London doctors' GP office visits studies both indicate that the effects of air pollution, including PM, can affect many more people than indicated by hospital admissions alone. In the London case, comparing the number of admissions from the authors' earlier study (Anderson et al., 1996) with those for GP visits in the 1999 study (Hajat et al., 1999) indicates that there are approximately 24 asthma GP visits for every asthma admission in that city. In addition, a comparison of the PM_{10} coefficients indicates that the all ages asthma effect size for the GP visits (although not statistically different) was approximately thirty percent larger than that for hospital admissions. Similarly, the number of doctors' house calls for asthma approximated 45/day in Paris (based on an average 9 asthma house calls in the SOS-Medocina data base, representing 20% of the total; Medina et al., [1997]), versus an average 14 asthma admissions/day (Dab et al., 1996), or a factor of 3 more doctors' house calls than hospital admissions. Moreover, the RR for Paris asthma doctors' house calls was substantially higher than asthma admissions (RR=1.32 for 43 $\mu g/m^3$ BS for house calls vs. RR=1.04 per 100 $\mu g/m^3$ BS for hospital admissions). Thus, these two new studies are coherent in supporting the hypothesis that looking at only hospital admissions and emergency hospital visit effects can greatly underestimate the numbers of severe respiratory morbidity events in a population due to acute ambient PM exposure.

6.2.3.4 Key New Hospital Admissions Studies

PM Mass and Composition Studies*:* Several new studies have evaluated PM associations with respiratory hospital admissions. These studies have examined various outcomes, including: total respiratory admissions for all ages; asthma for all ages; total respiratory admissions by age; Chronic Obstructive Pulmonary Disease (COPD) admissions (usually for patients > 64 yrs.), and; Pneumonia admissions (for patients > 64 yrs.). While particle mass is the metric most often employed as the particle pollution index in the U.S. and Canada, some of these new studies have begun to examine the relative roles of various PM constituents, such as $SO_4^=$, in the PM-respiratory hospital admissions association.

Burnett et al. (1997) evaluated the role that the ambient air pollution mix, comprised of gaseous pollutants and various physical and chemical measures of particulate matter, plays in exacerbating daily admissions to hospitals for cardiac diseases and for respiratory diseases

(tracheobronchitis, chronic obstructive long disease, asthma, and pneumonia). They employed daily measures of fine and coarse particulate mass, aerosol chemistry (sulfates and acidity), and gaseous pollution (ozone, nitrogen dioxide, sulfur dioxide, and carbon monoxide) collected in Toronto, Ontario, Canada, in the summers of 1992, 1993, and 1994. After adjusting the admission time series for long-term temporal trends, seasonal variations, the effects of short-term epidemics, day-of-week effects, and ambient temperature and dew point temperature, positive associations were observed for all ambient air pollutants for both respiratory and cardiac diseases. Ozone was the most consistently significant pollutant, and least sensitive to adjustment for other gaseous and particulate measures. The PM associations with the respiratory hospital admissions were significant for PM_{10} (RR=1.11for Δ=50 $\mu g/m^3$; CI=1.05-1.18), $PM_{2.5}$ (RR=1.09 for Δ=25 $\mu g/m^3$; CI=1.03-1.14), $PM_{10-2.5}$ (coarse) mass (RR=1.13 for Δ=25 $\mu g/m^3$; CI=1.05-1.21), sulfate levels (RR=1.11 for Δ=155 nmoles/m^3=15 $\mu g/m^3$; CI=1.06-1.17), and aerosol acidity (RR=1.40 for Δ=75 nmoles/m^3 = 3.6 $\mu g/m^3$, if as H_2SO_4; CI=1.15-1.70).

The study's authors dismissed these various PM associations with adverse health effects based on subsequent regression models that included all recorded pollutants simultaneously, but those simultaneous coefficients and confidence intervals may be somewhat suspect, given high intercorrelations that can exist across the various pollutant coefficients in such a many-pollutant model. The two-pollutant model results are probably more useful in assessing pollutant interactions. The authors also concluded that the individual particle mass and chemistry could not be separated as independent risk factors in the exacerbation of cardio-respiratory diseases in this study. However, even after the simultaneous inclusion of ozone in the model, the associations with the respiratory hospital admissions were still significant for PM_{10} (RR=1.10; CI=1.04-1.16) fine mass (RR=1.06; CI=1.01-1.12), coarse mass (RR=1.11; CI=1.04-1.19), sulfate levels (RR=1.06; CI=1.0-1.12), and aerosol acidity (RR=1.25; CI=1.03-1.53), using the same increments. Of the PM metrics considered here, aerosol acidity yields the highest RR estimate, despite having the lowest mass concentration increment.

Schwartz (1996) sought to replicate previous PM_{10} health effects findings in a location where SO_2 concentrations were relatively low, and the correlation between both airborne particles and ozone with temperature was considerably less than in previous studies. Daily counts of admissions to all hospitals in Spokane, WA for respiratory disease (ICD9 codes 460-519) for persons age 65 years and older were studied. Daily concentrations of PM_{10} and O_3

were each averaged across all monitors in the city. SO_2 concentrations in Spokane were so low that monitoring had been discontinued. Daily respiratory admission counts were regressed on daily average temperature and humidity, day of the week indicators, and air pollution. Long wavelength patterns were addressed using a nonparametric smooth function of day of study. The U-shaped dependence of admissions on temperature and/or humidity was addressed using nonparametric smooth functions of weather variables. Both same-day PM_{10} and two-day lagged O_3 were associated with increased risk of respiratory hospital admissions (RR = 1.085; 95% CI = 1.036-1.136 for a 50-$\mu g/m^3$ increase in PM_{10}, and RR = 1.244; 95% CI = 1.002-1.544 for a 50-$\mu g/m^3$ increase in peak-hour ozone). The PM_{10} association was insensitive to alternative methods of control for weather, including exclusion of extreme temperature days and control for temperature on multiple days. The O_3 results were more sensitive to the approach for weather control. The author noted that the magnitude of these PM_{10} effects, in a location where SO_2 was low and where the correlation between PM_{10} and temperature was close to zero, was similar to that reported in other locations in the eastern United States and Europe, where confounding by weather and SO_2 might be a more substantial concern.

Dab et al. (1996) considered daily hospital admissions to public hospitals due to respiratory causes in Paris, France during 1987-92. Air pollution was monitored by measurement of black smoke (BS) (15 monitoring stations), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), particulate matter less than 13 micrometers in diameter (PM_{13}), and ozone (O_3). The statistical analysis was based on a time series procedure using linear regression modeling followed by a Poisson regression. Meteorological variables, epidemics of influenza, and strikes of medical staff were included in the models. An increase in the mean daily concentration of PM_{13} of 100 $\mu g/m^3$ increased the risk of hospital admissions due to all respiratory diseases by 4.5% (CI = 1.004-1.087), and the BS association was similar (4.1% per 100 $\mu g/m^3$; CI = 1.007-1.075). SO_2 levels consistently influenced hospital admissions for all respiratory diseases, chronic obstructive pulmonary disease, and asthma, but no multiple pollutant models were presented. Asthma was significantly correlated with NO_2 levels, but not PM_{13}. For the all respiratory causes category, the authors found "the strongest association was observed with PM_{13}" for both hospital admissions and mortality, indicating a coherence of association.

Moolgavkar et al. (1997) investigated the association between air pollution and hospital admissions for chronic obstructive pulmonary disease and pneumonia among the elderly in

Minneapolis-St. Paul, MN, and Birmingham, AL, during January 1, 1986 to December 31, 1991. Pollutants included were PM_{10}, SO_2, NO_2, O_3, and CO in Minneapolis-St. Paul, and PM_{10}, O_3, and CO in Birmingham. After adjusting for temperature, day of week, season, and temporal trends, a positive but non-significant association between air pollution and hospital admissions for respiratory causes in Birmingham was found. In contrast, air pollution was significantly associated with hospital admissions for respiratory causes in Minneapolis-St. Paul. Among the individual pollutants, O_3 was most strongly associated with admissions ($t \approx 4.4$), and this association was robust in the sense that it was little affected by the simultaneous consideration of other pollutants. PM_{10}, SO_2, and NO_2 were also associated with hospital admissions (but not CO), although none were singled out by the authors as being more important than the others. In the Minneapolis-St. Paul analysis, PM_{10} was significantly and positively associated with total daily COPD and Pneumonia admissions among the elderly, even after the simultaneous inclusion of O_3. When four pollutants were included in the model (PM_{10}, SO_2, O_3,and NO_2), all pollutants remained positively associated with hospital admissions, but only O_3 remained statistically significant. However, the usefulness of significance tests in such many-pollutant models is suspect, given the intercollinearities of the various pollutants over time.

Asthma hospital admission studies conducted in various communities provide additional new data. A unique study by Sheppard et al. (1999) evaluated relationships between measured ambient pollutants (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, SO_2, O_3 and CO) in Seattle Washington and non elderly (<65 years of age) hospital admission, with a principal diagnoses of asthma. Daily hospital admission to local hospitals for area residents for 1987-94 were regressed on the pollutants in a poisson regression model with control for time trends, seasonal variations, and temperature related weather effects. They report an estimated 4-5% increase in the rate of asthma hospital admission associated with an interquarterly range change in PM (19 $\mu g/m^3$ PM_{10},11.8 $\mu g/m^3$ $PM_{2.5}$, and 9.3 $\mu g/m^3$ $PM_{10-2.5}$) lagged 1 day with relative rates as follows: for PM_{10}, 1.05 (95% CI = 1.02 - 1.08) for $PM_{2.5}$, 1.04 (95% CI = 1.02 - 1.07) and for $PM_{10-2.5}$ 1.04 (95% CI = 1.01 - 1.07). The highest increase in risk was in the spring and fall season. PM and CO were found to be jointly associated with asthma admission. Course particle mass, $PM_{10-2.5}$ was calculated as the difference between weighed PM_{10} and $PM_{2.5}$ values. Daily admission for asthma averaged 2.7.

Lumley and Heagerty (1999) illustrate the effect of reliable variance estimation on data from hospital admissions for respiratory disease on King County, WA for eight years (1987-94), together with air pollution and weather information. However, their weather controls were relatively crude (i.e. seasonal dummy variables and linear temperature terms). They concluded that valid inference is possible in regression models for correlated data when the true dependence structure is unknown. This study is notable for having compared sub-micron PM ($PM_{1.0}$) versus coarse $PM_{10-1.0}$, finding significant hospital admission associations only with $PM_{1.0}$.

Jamason et al. (1997) study weather/asthma relationships in the New York Standard Metropolitan Statistical Area (SMSA) using a synoptic climatological methodology. This procedure relate homogenous air masses to daily counts of overnight asthma hospital admission. Air pollution is reported as having, little impact on asthma during fall and winter. During spring and summer the high risk categories are association with high concentration of various pollutant (i.e., PM_{10}, SO_2, NO_2). In a London study, airborne pollen did not confound the analysis of air pollution to (including black smoke) and daily admissions for asthma during the time period 1987-1992. (Anderson et al., 1998).

Rosas et al. (1998) report a statistical analysis of the relationships between emergency admissions for asthma to a hospital in Mexico City and daily average airborne concentrations of pollen, fungal spores, air pollutants (O_3, NO_2, SO_2, and PM_{10}) and weather factors. The analysis used environmental data averaged over the day of admission and the 2 previous days. However, long-wave influences were not addressed, except for the division of the data by season, which likely resulted in uncontrolled confounding. Perhaps as a result, there were few statistical associations between asthma admissions and air pollutants for the three age groups studied (children under 15 years, adults, and seniors [adults over 59 years]) in either season.

Morgan et al. (1998a) studied air pollution and hospital admissions in Sydney, Australia, from 1990 to 1994, using Poisson regression that allows for overdispersion and autocorrelation. A light scattering index was used as the PM metric. An increase in daily maximum 1-hour particulate concentration (lag 0) from the 10th to the 90th percentile was associated with an increase of 3.0% ($P = 0.08$) in COPD admissions. Daily new particulate concentration (lag 0) from the 10th to the 90th percentile were associated with a significant increase (2.8%) in heart disease admissions in the elderly (65+ years). The estimates of the effects of particulate or COPD and heart disease admissions were reduced in the multiple pollutant models.

Gwynn et al. (1998) considered a two-and-a-half year period (May 1988-Oct. 1990) in the Buffalo, NY region in a time-series analysis of daily mortality and hospital admissions for the total, respiratory, and circulatory categories. Pollutants considered included: PM_{10}, H^+, $SO_4^=$ CoH, O_3, CO, SO_2, and NO_2. The $H^+$and $SO_4^=$ concentrations were determined from daily $PM_{2.5}$ samples that were, unfortunately, not analyzed for mass (in order to avoid possible acid neutralization). Various modeling techniques were applied to control for confounding of effect estimates due to seasonality, weather and day-of-week effects. They found multiple significant pollutant-health effect associations, the most significant being between $SO_4^=$ and respiratory hospital admissions. When calculated in terms of the increments employed across studies in this report, the various PM RR's were: H^+ RR=1.06, 95% C.I.=1.03-1.09 (for Δ=75 nmoles/m^3 = 3.6 μg/m^3, if as H_2SO_4); $SO_4^=$ RR=1.06, 95% C.I.=1.03-1.09 (for Δ=155 nmoles/m^3=15 μg/m^3); and, PM_{10} RR=1.11, 95% C.I.=1.05-1.18(for Δ=50 μg/m^3). These associations were not significantly affected by the inclusion of gaseous co-pollutants into the regression model. Thus, all PM components considered except CoH were found to be associated with increased hospital admissions, but H^+, $SO_4^=$ and O_3 had the most coherent associations with respiratory admissions.

Braga et al. (1999) studied hospital admission for children under 13 years of age in Säo Paula, Brazil in 112 hospitals from October 1992 to October 1993 in relation to daily levels of PM_{10}, O_3, SO_2, CO, and NO_2. The mean levels of PM10 observed of 70 μg/m^3 were associated with an increase of 12% in respiratory admissions. High degrees of interdependence among co-pollutants (independent variables) were observed (PM_{10}-SO_2: 0.73; PM_{10}-CO: 0.6; PM_{10}-NO_2: 0.53). A three pollutant model (PM_{10}, O_3, CO) yielded coefficients that decreased in magnitude and loss of statistical significance. The number of hospital admissions in this study do not reflect the actual health demand observed in the study period, but the number of procedures paid by the state. Thus, the total number of people who could be affected by pollutants remain unknown.

Wordley et al. (1997) examined the presence and magnitude of any relation between short-term variations in ambient concentrations of PM_{10} and hospital admissions and mortality in Birmingham, UK. Air pollution data were taken from a national network monitoring station between 1 April 1992 and 31 March 1994. Daily total hospital admissions for the same period for asthma, bronchitis, pneumonia, chronic obstructive pulmonary disease (COPD), acute ischaemic heart disease, acute cerebro-vascular disease, all respiratory conditions, and all

circulatory conditions were obtained from the West Midlands Regional Health Authority. Multiple linear regression models were constructed after adjusting for confounding factors (day of week, month, linear trend, relative humidity, and temperature). Relative risks of admission at various thresholds of PM_{10} were calculated with the model by comparing the risk of admission over the threshold with the mean risk of admission over the whole period. Potential public health benefits at various thresholds were also calculated with the model to predict the number of admissions that could be avoided if, on each day that PM_{10} had exceeded that threshold, it had instead been kept at the threshold level. Significant associations were found between all respiratory admissions, cerebro-vascular admissions, and bronchitis admissions and PM_{10} on the same day. Pneumonia, all respiratory admissions, and asthma admissions were significantly associated with the mean PM_{10} values for the past three days. The effect of a 10 $\mu g/m^3$ rise in PM_{10} was estimated to represent a 2.4% increase in respiratory admissions, a 2.1% increase in cerebro-vascular admissions, and a 1.1% increase in all causes mortality. Neither regression results for other pollutants, nor multiple pollutant models, were presented. Other air pollutants were reportedly examined, but, according to the authors, "these did not have a significant association with health outcomes independent from that of PM_{10}.

Jacobs et al. (1997) report that increases in rice straw burn acreage were shown to be associated with hospital admissions for asthma in Butte County, CA during a decade of observation. However, rice burning was not correlated with criteria pollutants (i.e., PM_{10} did not show a statistically significant elevation for risk to admissions with asthma).

The results of these new PM mass studies are generally consistent with and supportive of the studies presented in the last PM AQCD (U.S. Environmental Protection Agency, 1996) showing significant associations between increased risk of hospital admissions and ambient PM exposure, indexed by various PM metrics.

The APHEA Black Smoke Studies

There have been a large number of new time-series studies examining the air pollution-hospital admissions association in Europe, but many of these studies have relied primarily on Black Smoke (BS) as their PM metric. BS is mainly an indicator of particulate carbon concentration in the atmosphere, but the relationship between airborne carbon and total mass of PM overall aerosol composition varies from locality to locality, and is likely very different

between Europe and the U.S., due largely to differences in local PM source characteristics (e.g., between gas and diesel powered automobiles). Therefore, while these European BS-health effects studies are of qualitative use in evaluating the PM-health effects association, they are not as useful for quantitative assessment of the health effects of PM in North America.

The most recent European air pollution health effects studies have been conducted as part of the "Air Pollution and Health, a European Approach" (APHEA) study which considers 15 European cities from 10 different countries with a total population of over 25 million. All studies used a standardized data collection and analysis approach which included: consideration of the same suite of air pollutants (BS, SO_2, NO_2, SO_2, and O_3) and the use of time-series regression addressing: seasonal and other long-term patterns; influenza epidemics; day of the week; holidays; weather; and, autocorrelation (Katsouyanni et al., 1996).

Anderson et. al (1997) investigated the short-term effects of air pollution on hospital admissions for chronic obstructive pulmonary disease (COPD) in the APHEA cities. For all ages, the relative risks and 95% confidence limits (95% CL) for a 50 $\mu g/m^3$ increase in daily mean level of pollutant (lagged 1-3 days) were: SO_2 RR=1.02 (0.98, 1.06); BS RR=1.04 (1.01, 1.06); TSP RR=1.02 (1.00, 1.05), NO_2 RR=1.02 (1.00, 1.05); and, O_3 (8 h) 1.04 (1.02, 1.07). Models estimating effects of multiple pollutants simultaneously were not considered. The results for particles and ozone are broadly consistent with those from North America, though the coefficients for BS and TSP are substantially smaller.

Schouten et al. (1996) examined short-term effects of air pollution on emergency hospital admissions for respiratory disease in two APHEA cities in the Netherlands during the period 1977-89. Black smoke did not show any clear associations with admissions in Amsterdam, while in Rotterdam it was positively but not significantly related to the number of admissions. The authors concluded that the results show that the relation between short-term air pollution and emergency hospital admissions is not always consistent at these rather low levels of air pollution (BS-24 h values averaged 14 $\mu g/m^3$; range 1-84 $\mu g/m^3$).

Spix et al. (1998) considered several years of hospital admissions data for all respiratory causes (ICD 460-519) from five West European APHEA cities (i.e., London, Amsterdam, Rotterdam, Paris, Milan). The age groups studied were 15-64 yr (i.e., younger adults) and 65 + yr (older adults). The air pollutants studied were SO_2, particles (i.e., BS or total suspended particles), O_3, and NO_2. The most consistent and strongest finding was a significant increase in

daily admissions for respiratory diseases (adults and elderly) with elevated levels of O_3. This finding was stronger in the elderly, had a rather immediate effect (same or next day), and was homogeneous over cities. For PM, a meta-analysis of the various cities' results for TSP found no overall significant associations in these groups for this outcome, while the daily mean of BS was significant for young adults (50 $\mu g/m^3$ RR=1.028; CI 1.006-1.051), but not for the elderly (50 $\mu g/m^3$ RR=1.020; CI 0.996-1.046). In by-season analyses, it was found that the BS association in younger adults was significant in the cold season only (50 $\mu g/m^3$ RR=1.04; CI 1.02-1.07), while the PM-admissions association was significant for older adults in the warm season (50 $\mu g/m^3$ RR=1.07; CI 1.00-1.15). The authors found that the ozone results were in good agreement with the results of U.S. studies, but no conclusion related to an overall particle effect could be drawn based on these BS and TSP results.

Sunyer and colleagues (1997) analyzed urban air pollution and emergency admissions for asthma during 1986-92 in the APHEA cities of Barcelona, Helsinki, Paris and London. Daily counts of asthma admissions in adults (aged 15-64 years) and children (< 15 years) were considered. Daily admissions for asthma increased significantly with increasing ambient levels of NO_2 in adults, and with NO_2 and SO_2 in children. For a 50 $\mu g/m^3$ increase in BS, a consistently positive (i.e., RR>1.0) but overall non-significant association was observed in all cities for both children (RR=1.03, 95% CI 0.99-1.08) and adults (RR=1.02, 95% CI 0.99-1.06). The authors indicated that their findings of less significant PM-health effects associations than found elsewhere could be explained by the use of black smoke as the indicator, since presumably the proportion of unmeasured biologically active non-black particles varies on a day-to-day basis.

The general coherence of the above-described APHEA results with other results gained under different conditions strengthens the argument for causality in the air pollution-health effects association. Unfortunately, the general use of the less comparable TSP and BS as PM indicators in these studies diminishes the quantitative usefulness of these analyses in evaluating the associations between PM and health effects elsewhere, such as in the U.S.

Low Birth Weight Studies

Several studies examine low birth rate and related endpoints. Bobak and Leon (1998) conducted an ecological study of TSP levels and stillbirth and low birth weight (<2,500 g) in the Czech Republic for 1986-88. The stillbirth rate was not associated with any air pollutants. In a

model with all pollutants, only SO_2 was significantly related to low birth weights. The author notes the biological mechanisms for such an effect are not clear. Ritz and Yu (1999) report that the relation between CO and low birth rate appeared more pronounced after adjustment for concurrent exposure to NO_2, PM_{10}, and ozone. Between 1986 and 1991, Wang et al. (1997) studied in Beijing, China, low birth weight due to pollutants (TSP, SO_2) exposure during the third trimester of pregnancy. The adjusted odds ratio for low birth rate (<2,500 g) was 1.10 (95% CI; 1.05-1.14) for every 100 $\mu g/m^3$ increase in TSP. Biological mechanisms whereby air pollution may be associated with low birth weights remain to be elucidated. Xu et al. (1995) studied the effects of TSP and SO_2 levels on preterm delivery in Beijing, China, from early pregnancy until delivery in 1988. The analyses yielded a significant dose-dependant association between gestational age and SO_2 and TSP levels. The adjusted odds for preterm delivery for each 100 $\mu g/m^3$ increase in TSP was 1.10 (95% CI = 1.01-1.20). The authors concluded that high levels of TSP and SO_2 or a more complex pollution mixture appear to contribute to excess risk of preterm delivery in this population.

6.2.3.5 Syntheses of Comparable Hospital Admissions PM_{10} and $SO_4^=$ Studies

Among the studies discussed above and those summarized in the previous PM AQCD (U.S. Environmental Protection Agency, 1996), those judged most useful for the quantitative evaluation of the size and significance of the PM_{10} association with emergency hospital admissions (i.e., studies that considered comparable age and cause categories) are listed in Table 6-20. The available studies for $SO_4^=$ are similarly listed in Table 6-21. Too few $PM_{2.5}$ studies were available to develop such a table for $PM_{2.5}$, but $SO_4^=$ is a strong indicator of $PM_{2.5}$ concentrations in many locales. Also noted in each table for each study listed are the reported RR estimates (and their respective 95% confidence intervals) for the various health outcome categories most commonly considered by the various studies (e.g., all age total respiratory admissions).

Tables 6-22 and 6-23 present the results of a mathematical synthesis of the various studies listed in Tables 6-20 and 6-21 for hospital admissions and PM_{10} and $SO_4^=$, respectively. These are selected because there are three or more studies with results for these outcomes and pollutants, warranting an overall synthesis of results. In these syntheses, a single overall combined estimate is calculated from a weighted aggregation of the available studies for each

TABLE 6-20. COMPARABLE RESPIRATORY HOSPITAL ADMISSIONS PM_{10} STUDIES

			Single Pollutant Models			Two Pollutant Models (with O_3)		
			50 $\mu g/m^3$			50 $\mu g/m^3$		
Study	Area/Period	Outcome	RR	195	u95	RR	195	u95
Thurston et al. (1994)	Toronto, Ontario summers (86-88)	Respiratory (all ages)	1.23	1.02	1.44	1.22	0.99	1.37
Dab et al. (1996)	Paris, France (1987-92)	Respiratory (all ages)	1.04	1.00	1.08			
Burnett et al. (1997a)	Toronto, Ontario (1992-94)	Respiratory (all ages)	1.11	1.05	1.18	1.10	1.04	1.16
Wordley et al. (1997)	Birmingham, England (92-94)	Respiratory (all ages)	1.12	1.06	1.19			
Gwynn et al. (1998)	Buffalo, NY (1988-90)	Respiratory (all ages)	1.11	1.04	1.190	1.14	1.04	1.24
Thurston et al. (1994)	Toronto, Ontario summers (86-88)	Asthma (all ages)	1.14	0.94	1.34	1.02	0.96	1.26
Dab et al. (1996)	Paris, France (1987-92)	Asthma (all ages)	0.99	0.95	1.03			
Wordley et al. (1997)	Birmingham, England (1992-1994)	Asthma (all ages)	1.17	1.04	1.36			
Schwartz (1995)	Spokane, WA (1988-90)	Respiratory >65yrs	1.08	1.04	1.14			
Schwartz (1995)	New Haven, CT (1988-90)	Respiratory >65yrs	1.06	1.00	1.13	1.07	1.01	1.14
Schwartz (1995)	Tacoma, WA (1988-90)	Respiratory >65yrs	1.10	1.03	1.17	1.11	1.02	1.20
Moolgavkar et al. (1997)	Minneapolis,MN (1986-91)	Respiratory >65yrs	1.09	1.05	1.13	1.07	1.03	1.11
Moolgavkar et al. (1997)	Birmingham, AL (1986-91)	Respiratory >65yrs				1.03	0.99	1.07
Schwartz (1996)	Spokane, WA 1988-90	Pneumonia >65yrs	1.05	0.99	1.13			
Schwartz (1993)	Birmingham, AL (1986-89)	Pneumonia >65yrs	1.09	1.03	1.15			
Schwartz (1994a)	Minneapolis-St. Paul, MN (1986-89)	Pneumonia >65yrs	1.08	1.015	1.15	1.08	1.01	1.15
Schwartz (1994b)	Detroit, MI (1986-89)	Pneumonia >65yrs				1.06	1.02	1.10
Schwartz (1995)	Spokane, WA (1988-90)	COPD >65yrs	1.17	1.08	1.27			
Schwartz (1993)	Birmingham, AL (1986-89)	COPD >65yrs	1.13	1.04	1.22			
Schwartz (1994a)	Minn.-St. Paul, MN (1986-89)	COPD >65yrs	1.10	0.99	1.23	1.25	1.10	1.43
Schwartz (1994b)	Detroit, MI (1986-89)	COPD >65yrs				1.10	1.05	1.17

TABLE 6-21. COMPARABLE RESPIRATORY HOSPITAL ADMISSIONS SO_4 STUDIES

			Single Pollutant Models			Two Pollutant Models (with O_3)		
			15 $\mu g/m^3$			15 $\mu g/m^3$		
Study	Area/Period	Outcome	RR	195	u95	RR	195	u95
Burnett et al. (1995)	Ontario, Canada (83-88)	Respiratory (all ages)	1.04	1.03	1.06	1.03	1.02	1.05
Thurston et al. (1992)	Buffalo, NY Summers (88-89)	Respiratory (all ages)	1.07	1.02	1.11			
Thurston et al. (1992)	New York, NY Summers (88-89)	Respiratory (all ages)	1.01	1.00	1.02			
Thurston et al. (1994)	Toronto, Canada Summers (86-88)	Respiratory (all ages)	1.11	1.00	1.23	1.07	0.99	1.15
Gwynn et al. (1998)	Buffalo, NY (1988-90)	Respiratory (all ages)	1.06	1.03	1.09	1.14	1.08	1.21
Burnett et al. (1997)	Toronto, Canada (1992-94)	Respiratory (all ages)	1.11	1.06	1.17	1.06	1.00	1.12
Thurston et al. (1992)	New York, NY Summers (88-89)	Asthma (all ages)	1.02	1.00	1.03			
Thurston et al. (1992)	Buffalo, NY Summers (88-89)	Asthma (all ages)	1.02	0.98	1.15			
Thurston et al. (1994)	Toronto, Canada Summers (92-94)	Asthma (all ages)	1.11	0.99	1.23	1.04	0.91	1.18
Burnett et al. (1995)	Ontario, Canada (1983-88)	Asthma (all ages)	1.04	1.02	1.07			
Bates and Sizto (1987)	Ontario, Canada (1983-88)	Respiratory <15yrs	1.03	0.99	1.05			
Burnett et al. (1995)	Ontario, Canada (1983-88)	Respiratory 15-64yrs	1.04	1.02	1.06			
Burnett et al. (1995)	Ontario, Canada (1983-88)	Respiratory >64yrs	1.04	1.02	1.07			
Burnett et al. (1995)	Ontario, Canada (1983-88)	COPD (all ages)	1.06	1.02	1.08			

* Pollutant increment (in $\mu g/m^3$) used to calculate the presented RR.

TABLE 6-22. SYNTHESIS OF COMPARABLE TIME-SERIES HOSPITAL ADMISSIONS STUDIES' ESTIMATES OF RELATIVE RISK DUE TO PM_{10} EXPOSURE (per 50 $\mu g/m^3$)

		Single Pollutant Model			Two Pollutant Model (with O_3)		
Hospital Admissions Category	Number of Studies	Pooled RR	Pooled L95%	Pooled U95%RR	Pooled RR	Pooled L95%	Pooled U95% RR
Respiratory (all ages)	5	1.10	1.05	1.15	1.12	1.07	1.17
Asthma (all ages)	3	1.07	0.95	1.21	1.02	0.96	1.25
Respiratory (>64yrs.)	4	1.08	1.06	1.11	1.07	1.04	1.10
Pneumonia (>65 yrs.)	4	1.08	1.04	1.12	1.07	1.03	1.10
COPD (>65yrs.)	4	1.14	1.08	1.19	1.15	1.03	1.31

TABLE 6-23. SYNTHESIS OF COMPARABLE TIME-SERIES HOSPITAL ADMISSIONS STUDIES' ESTIMATES OF RELATIVE RISK DUE TO $SO_4^=$ EXPOSURE (per 15 $\mu g/m^3$)

		Single Pollutant Model			Two Pollutant Model (with O_3)		
Hospital Admissions Category	Number of Studies	Pooled RR	Pooled L95%	Pooled U95%RR	Pooled RR	Pooled L95%	Pooled U95% RR
Respiratory (all ages)	6	1.06	1.03	10.9	1.05	1.03	1.07
Asthma (all ages)	4	1.03	1.01	1.05	N/A	N/A	N/A

N/A = No studies available that provide results for this category.

pollutant and health outcome. To obtain these combined estimates, we used a two-stage random effects model approach, as suggested by DerSimonian and Laird (1986) to take into account the among-studies variance.

The syntheses in Tables 6-22 and 6-23 indicate reasonably consistent RR effect sizes for PM_{10} and $SO_4^=$ (i.e., within their respective confidence intervals) across admissions categories. However, the aggregate PM_{10} RR's are not significant for the asthma category, while there is a suggestion that the PM_{10} RR may be larger for the elderly with COPD than for other respiratory admissions categories. For $SO_4^=$, both asthma and total respiratory admissions have aggregate RR estimates that are significant. Comparing the aggregate PM_{10} and $SO_4^=$ results in Tables 6-22 and 6-23 collectively suggests that, although the differences between these two components' RR's are not statistically significant, the aggregate PM_{10} respiratory admissions RR effect sizes in these tables are approximately double those for $SO_4^=$. However, the concentration increment employed for PM_{10} in these calculations (50 $\mu g/m^3$) is more than three times the $SO_4^=$ concentration increment employed (15 $\mu g/m^3$), which suggests that the $SO_4^=$ effect size may be larger than for PM_{10} overall, when viewed on an equal weight basis.

6.2.3.6 Overall Conclusions

The results of these new PM mass studies are generally consistent with and supportive of the studies presented in the previous PM AQCD (U.S. Environmental Protection Agency, 1996). Moreover, mathematical syntheses of multiple hospital admissions studies for the various age and disease categories (including relevant studies from the previous CD) were conducted as part of this new review. Overall, it was found that significant and reasonably consistent RR effect sizes (i.e., within their respective confidence intervals) were generally found across admissions categories for both PM_{10} and $SO_4^=$. As discussed by Hill (1965), such coherence across outcomes and among multiple studies conducted in different places by different investigators are supportive of the conclusion that these associations are caused by PM mass or a closely related pollutant correlate.

Hospital admissions studies considering multiple PM components were also evaluated in order to try to assess the relative roles of the various components in the reported PM-health effects associations (in those studies where multiple PM components were considered). These results indicated that sulfates and acidic aerosols were often among the PM metrics most strongly associated with respiratory morbidity.

The doctors' visits studies in Paris (Medina et al., 1997) and London (Hajat et al., 1999) indicate that the use of hospital admissions alone can understate the total severe morbidity effects

of air pollution. In both Paris and London, the number of doctors' visits amount to many times the number of hospital admissions. Moreover, the Paris Black Smoke RR for asthma doctors visits was actually much higher than that for asthma hospital admissions (doctors' visits RR=1.74 for 100 $\mu g/m^3$, versus hospital admissions RR=1.04). Thus, these results support the hypothesis that considering only hospital admissions and emergency hospital visit effects may greatly underestimate the numbers of medical visits occurring in a population as a result of acute ambient PM exposure.

6.2.4 Cardiovascular Effects Associated with Acute Ambient PM Exposure

6.2.4.1 Introduction

Very little information specifically addressing acute cardiovascular morbidity effects of PM existed at the time of the 1996 PM AQCD. While the literature still remains relatively sparse, an important new body of data now exists that both extends the available quantitative information on the ecologic relationship between ambient pollution and hospital admissions and which, more intriguingly, illuminates some of the physiological changes that may occur on the mechanistic pathway leading from PM exposure to adverse cardiac outcomes.

This section begins with a brief summary of the conclusions that were reached in the 1996 PM AQCD regarding acute cardiovascular impacts of PM. Next, new studies falling into two general classes are reviewed: ecologic time series studies of daily hospitalizations in relation to ambient PM and other pollutants; and individual-level studies of temporal changes in physiological measures of cardiac function as they relate to ambient pollution. This review is followed by a discussion of several issues that are important in interpreting the available data, including the identification of potentially susceptible sub-populations, the roles of environmental co-factors such as weather and other air pollutants, temporal lags in the relationship between exposure and outcome, and the relative importance of various size-classified PM sub-components (e.g., $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$). In each case the extent of the available research data base bearing on the issue is noted, and the current state of knowledge summarized.

6.2.4.2 Summary of Conclusions from 1996 PM AQCD

Just two studies were available for review in the 1996 PM AQCD that provided data on acute cardiovascular morbidity outcomes (Schwartz and Morris, 1995; Burnett et al., 1995).

Both studies were of ecologic time series design using standard statistical methods. Analyzing four years of data on the ≥ 65 year old Medicare population in Detroit, MI, Schwartz and Morris (1995) reported significant associations between ischemic heart disease admissions and PM_{10}, controlling for environmental covariates. Based on an analysis of admissions data from 168 hospitals throughout Ontario, Canada, Burnett and colleagues (1995) reported significant associations between particle sulfate concentrations, as well as other air pollutants, and daily cardiovascular admissions. The relative risk due to sulfate particles was slightly larger for respiratory than for cardiovascular hospital admissions. The AQCD concluded on the basis of these studies that "There is a suggestion of a relationship to heart disease, but the results are based on only two studies and the estimated effects are smaller than those for other endpoints." (U.S. Environmental Protection Agency, 1996, p. 12-100). The AQCD went on to state that acute impacts on CVD admissions had been demonstrated for elderly populations (i.e., ≥ 65), but that insufficient data existed to assess relative impacts on younger populations.

Also relevant to an evaluation of the acute impacts of particles on cardiovascular endpoints are insights gained from time series studies of daily mortality, which, aside from the outcome studied, are nearly identical in design and analysis to time series studies of hospitalizations. It is also probable that acute effects of air pollution on cardiovascular hospitalizations and mortality follow qualitatively similar etiologic mechanisms.

Several acute mortality studies reviewed in the 1996 AQCD analyzed cause-specific deaths (usually total cardiovascular and total respiratory) in relation to ambient particle concentrations. The AQCD noted that, in general, cause-specific analyses "reported higher estimated relative risks for respiratory and cardiovascular categories than for total or other categories" (U.S. Environmental Protection Agency, 1996, p. 12-349). It was noted that these findings were consistent with analyses of case reports from historic air pollution episodes, like the December, 1952 London episode, in which the mortality impacts were greatest among the elderly and those with pre-existing respiratory and/or cardiovascular disease. A comparative analysis of age- and cause-specific mortality effects of particles in modern-day Philadelphia with those observed in the 1952 London episode concluded that the patterns of mortality were largely consistent, once the order of magnitude difference in exposure levels was taken into account (Schwartz, 1994c,d).

Viewed as a group, the acute morbidity and mortality studies reviewed in the 1996 AQCD were thus consistent with the notion that acute health risks of PM are larger for cardiovascular

and respiratory causes than for other causes. Given the tendency for end-stage disease states to include both respiratory and cardiovascular impairment, and the associated diagnostic overlap that often exists, it was not possible on the basis of these studies alone to determine which organ system, if any, was most critically impacted.

6.2.4.3 Review of New Studies

Acute Hospitalization Studies

Four separate analyses of hospitalization data in Canada have been reported since 1995 (Burnett et al., 1995; 1997a,b; 1999). A variety of locations, outcomes, PM exposure metrics, and analytical approaches were utilized in these four studies, which hinders somewhat our ability to draw broad, cross-cutting conclusions from the full group of studies.

The first study, reviewed briefly in the 1996 AQCD, analyzed six years of data from 168 hospitals in Ontario, CN. Cardiovascular and respiratory hospital admissions were analyzed in relation to sulfate and ozone concentrations. Sulfate lagged one day was associated with cardiovascular admissions, with a percent effect of 2.8 (CI 1.8-3.8) per 13 $\mu g/m^3$ without ozone in the model and 3.3 (CI 1.7-4.8) with ozone included. When cardiovascular admissions were split out into sub-categories, larger associations were observed between sulfates and coronary artery disease and heart failure than for cardiac dysrhythmias. Sulfate associations with total admissions were larger for the sub-population $\geq$ 65 (3.5% per 13 $\mu g/m^3$) than for those < 65 years old (2.5% per 13 $\mu g/m^3$). There was little evidence for seasonal differences in sulfate associations.

Burnett et al. (1997a) analyzed daily congestive heart failure hospitalizations in relation to carbon monoxide and other air pollutants (ozone, NO_2, SO_2, COH) in ten large Canadian cities as a replication of an earlier U.S. study by Morris et al. (1995). The Canadian study expanded upon the previous work both by its size (11 years data in each of 10 large cities) and also by including a measure of particulate matter air pollution (coefficient of haze); no particle data were included in the Morris et al. study. The study was restricted to the population $\geq$ 65 years old. The authors noted that all pollutants except ozone were correlated, making it difficult to statistically separate them. COH, CO, and NO_2 measured on the same day as admission (i.e., lag 0) were all strongly associated with congestive heart failure admissions in univariate models. However, in

multi-pollutant models, CO remained a strong predictor whereas COH did not. No gravimetric particle data were included in this analysis.

The roles played by size-selected gravimetric and chemically speciated particle metrics as predictors of cardiovascular hospitalizations were explored in an analysis of data from metropolitan Toronto for the summers of 1992-1994 (Burnett et al., 1997b). The analysis utilized dichotomous sampler ($PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$) and hydrogen ion and sulfate data collected at a central site as well as ozone, NO_2, SO_2, CO, and COH data collected at multiple sites in Toronto. Hospital admissions categories included total cardiovascular (i.e., the sum of ischemic heart disease, cardiac dysrhythmias, and heart failure) and total respiratory. Model specification with respect to pollution lags was completely data-driven, with all lags and averaging times out to 4 days prior to admission evaluated in exploratory analyses, and "best" metrics chosen on the basis of maximal t-statistics.

The relative risks of cardiovascular admissions were positive and generally statistically significant for all pollutants analyzed in univariate regressions, but were especially significant for ozone, NO_2, COH, and $PM_{10-2.5}$ (i.e., regression t-statistics > 3). Associations involving gaseous pollutants were generally robust to inclusion of PM covariates, whereas the PM covariates, aside from COH, were not robust to inclusion of multiple gaseous pollutants. In particular, $PM_{2.5}$ was not a robust predictor of cardiovascular admissions in multi-pollutant models. Whereas an 11 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 3.1 percent increase (t=1.8) in cardiovascular admissions in a univariate model, the percent effect was reduced to -0.7 (t=0.3) in a model that included ozone, NO_2, and SO_2. COH, like CO and NO_2, is generally thought of as a measure of primary motor-vehicle emissions during the non-heating season. The authors concluded that "particle mass and chemistry could not be identified as an independent risk factor for exacerbation of cardiorespiratory diseases in this study beyond that attributable to climate and gaseous air pollution."

Burnett et al. (1999) reported results of an ambitious attempt to explore cause-specific hospitalizations for persons of all ages in relation to a large suite of gaseous and particulate air pollutants using 15 years of data from Toronto. Cardiovascular admissions were split out into separate categories for analysis, including dysrhythmias, heart failure, and ischemic heart disease. The analysis also examined several respiratory causes, as well as cerebral vascular diseases and diseases of the peripheral circulation; the latter categories were included because they should

show associations with PM if the mechanism of action is related to increases in plasma viscosity, as suggested by Peters et al. (1997d) (see study review below). The PM metrics analyzed were $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$ that had been estimated from daily TSP and TSP sulfate data based on a regression analysis on dichotomous sampling data that were available every sixth day during an eight-year subset of the full study period. This use of estimated rather than measured PM components limits the interpretation of the PM results reported here. Model specification for lags was again data-driven based on maximal t-statistics.

In multi-pollutant models, there were no significant PM associations with any of the three cardiovascular hospitalization outcomes. For example, while an 18 $\mu g/m^3$ increase in estimated $PM_{2.5}$ was associated with a 5.7 percent increase (t-statistic = 6.08) in ischemic heart disease admissions in a univariate analysis, the $PM_{2.5}$ association was reduced to 1.6 percent (n.s.) when NO_2 and SO_2 were included in the model. The gaseous pollutants generally dominated most regressions. There also were no associations between PM and cerebral or peripheral vascular disease admissions. While these PM findings do not speak to the issue of the relative roles of various size-classified PM components (because all the PM data were estimated from TSP and sulfates in ways that were not made explicit), they do suggest that a linear combination of TSP and sulfate concentrations does not have a strong independent association with cardiovascular admissions when a full range of gaseous pollutants are also modeled. In this sense, these results are generally consistent with those obtained from the summer Toronto analysis reviewed above (Burnett et al., 1997b).

The Burnett et al. studies represent the most extensive body of results for PM in conjunction with multiple gaseous pollutants. While the inconsistent use of alternative PM metrics in the various analyses confuses the picture somewhat, a general finding is of lack of robustness of associations between cardiovascular outcomes and PM. This was seen for COH in the analysis of 10 Canadian cities (Burnett et al., 1997a), for $PM_{2.5}$ and PM_{10} in the analysis of summer data in Toronto (Burnett et al., 1997b), and for linear combinations of TSP and sulfates (i.e., estimated $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$) in the analysis of 15 years of data in Toronto (Burnett et al., 1999). One exception was the associations reported between cardiovascular admissions to 168 Ontario hospitals and sulfate concentrations (Burnett et al., 1995), where the sulfate association was robust to the inclusion of ozone. However, that study did not include CO in the regressions, a gaseous pollutant often associated with cardiovascular outcomes in several studies.

Thus, it is possible that the sulfate results of Burnett et al. (1995) represent confounding by omitted pollutants. Also, although gravimetric PM variables were not robust predictors in the Toronto summer analysis, CoH was a robust predictor (Burnett et al., 1997b), perhaps representing the role of primary motor vehicle emissions. This contrasts however with CoH's lack of robustness in the 10-city analysis (Burnett et al., 1997a).

No associations between PM_{10} and daily ischemic heart disease admissions were observed by Wordley and colleagues (1997) in an analysis of two years of daily data from Birmingham, UK. On the other hand, PM_{10} was associated with respiratory admissions and cardiovascular mortality during the study period. The inconsistency of results across causes and outcomes is difficult to interpret, but may relate in part to the relatively short time series analyzed. The authors stated that gaseous pollutants did not have significant associations with health outcomes independent of PM; however, no results were presented from models involving gaseous pollutants.

Associations with PM_{10} were reported by Morris and Naumova (1998) in their analysis of four years of congestive heart failure data among people $\geq$ 65 years old in Chicago, IL. While the analysis was directed primarily at evaluating modification by temperature of CO effects on congestive heart failure admissions (building on previous results of Morris et al., 1995), results were also presented for PM_{10}, as well as for ozone, NO_2, and SO_2. As many as eight monitoring sites were available for calculating daily gaseous pollutant concentrations; however only one site in Chicago monitored daily PM_{10}. Only same-day results were presented based on an initial exploratory analysis showing strongest effects at for same-day pollution exposure (i.e., lag 0). Strong and robust associations were reported between congestive heart failure admissions and CO. Associations between hospitalizations and PM_{10} were observed in univariate regressions (RR = 1.04; C.I. 1.01-1.07), but these diminished somewhat in a multi-pollutant model (RR = 1.02; C.I. 0.99-1.06). Although these results suggest a more robust association with CO than with PM_{10}, the observed differences may be explained by differential exposure misclassification for PM_{10} (monitored at one site) as compared with CO (eight sites). Thus, no firm conclusions regarding PM/gaseous confounding are warranted on the basis of this study alone.

PM_{10} associations with cardiovascular hospitalizations were also examined in two studies by Schwartz (1997, 1999a). The 1997 study analyzed three years of daily data for Tucson, AZ

linking total cardiovascular hospital admissions for persons ≥ 65 years old with PM_{10}, CO, ozone, and NO_2. As was the case in Chicago, only one site was monitored daily PM_{10} while multiple sites were available for gaseous pollutants. Both PM_{10} and CO were independently (i.e., robustly) associated with admissions while ozone and NO_2 were not. The percent effect of a 23 $\mu g/m^3$ increase in PM_{10} changed only slightly from 2.75 (CI 0.52-4.04) to 2.37 (CI 0.08-4.72) when CO was included in the model along with PM_{10}.

Schwartz (1999a) extended the analytical approach used in Tucson to an additional eight U.S. metropolitan areas, limiting the analysis to a single county in each location to enhance the representativeness of the air pollution data. The locations analyzed were: Chicago, IL, Colorado Springs, CO, Minneapolis, MN, New Haven, CT, St. Paul, MN, Seattle, WA, Spokane, WA, and Tacoma, WA. Again, the analysis focused on total cardiovascular hospital admissions among persons ≥65 yr old. In univariate regressions, remarkably consistent PM_{10} associations with cardiovascular admissions were observed across the eight locations, with a 25 $\mu g/m^3$ increase in PM_{10} associated with between 1.8 and 4.2 percent increases in admissions. The univariate eight-county pooled PM_{10} effect was 2.48 percent (CI 1.81-3.14), similar to the 2.99 percent effect per 25 $\mu g/m^3$ observed in the previous Tucson analysis. In a bivariate model that included CO, the pooled PM_{10} effect size diminished somewhat to 1.86 percent (CI 1.01-2.71). As was the case in previous studies (Morris and Naumova, 1998; Schwartz, 1997), the association between cardiovascular admissions and CO was robust to the inclusion of PM_{10} in the model.

The PM_{10} effects were positive in all locations, and statistically significant in New Haven, Chicago, St. Paul, Spokane, Tacoma, and Tucson, but not in Colorado Springs, Minneapolis, and Seattle. CO effects were also positive in all locations, and significant in 7 of 9. The PM_{10} effect in Minneapolis (2.03%, CI -1.87% to 6.09%) was much smaller than in the immediately adjacent city of St. Paul (4.19%, CI 1.44% to 7.00%) although not significantly different. The CO effects show the opposite relationship, larger in Minneapolis (4.09%, CI 1.59% to 6.65%) than in St. Paul (0.74%, CI -1.84% to 3.39%). CO and PM_{10} are not strongly correlated in these 'Twin Cities', however, 0.244 in Minneapolis and 0.113 in St. Paul, so that it is unlikely that collinearity between PM_{10} and CO accounted for the differences. The PM_{10} effects in Seattle and Tacoma are more similar (1.77% vs. 2.63%), but the CO effects are different (4.22%, CI 2.44% to 6.02% in Seattle, vs. 1.84%, CI 0.24 to 3.46% in Tacoma), even though the correlation between PM_{10} and CO is high in both cities (0.642 in Seattle, 0.676 in Tacoma).

Schwartz (1999a) argues that the low correlation between the effect size estimates and the PM_{10}-vs.-CO or PM_{10}-versus-co-pollutant correlation coefficients is evidence that there is little confounding across pollutants. However, since the health effects of air pollution may have different seasonal dependence and may involve complex multivariate relationships among weather and pollution in the different cities, further examination of this hypothesis may be required.

Also relevant to the present review of associations between acute cardiovascular morbidity and PM are nine recent studies of acute cardiovascular mortality (Borja-Aburto et al., 1997, 1998; Michelozzi et al., 1998; Morgan et al., 1998b; Pönkä et al., 1998; Schwartz et al., 1996; Simpson et al., 1997; Wordley et al., 1997; Zmirou et al., 1998). Acute mortality can be viewed as a more severe manifestation of the same pathophysiologic mechanism, if any, that is responsible for acute hospital admissions following PM exposure. All nine studies reported significant associations between acute cardiovascular mortality and measures of ambient PM, though the PM metrics utilized and the relative risk estimates varied across studies. PM measurement methods included gravimetrically analyzed filter samples (TSP, PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$), beta gauge (particle attenuation of beta radiation), nephelometry (light scattering), and black smoke (filter reflectance). Where tested, PM associations appeared to be generally more robust to inclusion of gaseous covariates than was the case for acute hospitalization studies (Borja-Aburto et al., 1997, 1998; Morgan et al., 1998b; Wordley et al., 1997; Zmirou et al., 1998). One study which examined multiple alternative PM metrics reported strongest associations with $PM_{2.5}$ and no associations for $PM_{10-2.5}$ and hydrogen ion. These results for acute cardiovascular mortality are qualitatively consistent with those reviewed above for hospital admissions.

6.2.4.4 Individual-Level Studies of Cardiovascular Physiology

Several very recent studies carried out by a variety of groups have reported longitudinal associations between physiologic measures of cardiovascular function and ambient PM concentrations. These studies possess several important advantages over the ecologic time-series studies discussed above, including the measurement of physiologic outcomes on an individual basis that potentially may yield profound insights into mechanisms, as well as improved assessment of individual exposures and covariates. Such studies have the capability to assess

heterogeneity of responses across individuals and to investigate variations in susceptibility as a function of individual factors such as age and pre-existing health status. Though the populations studied to date have for the most part been relatively small, the effects that have observed in association with PM exposures, especially those related to alterations in the balance of sympathetic and parasympathetic control of the heart, offer the first compelling insights into possible pathophysiologic mechanisms for PM effects on cardiovascular ill-health in humans.

Three independent studies have recently reported associations between repeated measures of PM and changes in heart-rate variability in small panels of elderly subjects (Pope et al., 1999a; Liao et al., 1999; Gold et al., 1998, 1999). Liao and colleagues (1999) studied 26 elderly subjects (age range: 65-89 years) over three consecutive weeks at a retirement center in metropolitan Baltimore. 18 subjects were classified as "compromised" on the basis of previous cardiovascular conditions including hypertension. Daily six-minute resting heart rate data were collected during which the time between sequential R-R intervals were recorded. A Fourier transform was applied to the R-R interval data to enable separation of variability (i.e., variance) into two major components: low frequency and high frequency for separate analysis. $PM_{2.5}$ was monitored daily both indoors and outdoors using standard methods. Regression analyses controlled for inter-subject differences in average variability, in effect allowing each subject to serve as his/her own control. Statistically significant associations were observed between decreases in both high and low frequency heart rate variations and $PM_{2.5}$ concentrations measured indoors or outdoors. Associations were stronger for the 18 subjects with compromised cardiovascular health.

Pope and colleagues (1999a) reported similar findings in a panel of six elderly subjects (plus one younger subject suffering from Crohn's disease) selected from a larger group of 90 subjects who participated in a study of heart rate and oxygen saturation in the Utah Valley (Pope et al., 1999b). The six elderly subjects ranged in age from 69 to 89 years and had histories of cardiopulmonary disease. Subjects carried Holter monitors for up to 48 hours during different weeks that varied in ambient PM_{10} concentrations. N-N heartbeat intervals were recorded and used to calculate several measures of heart rate variability in the time domain. PM_{10} data were obtained from three sites in the study area. Regression analysis with subject-specific intercepts was performed, controlling for daily barometric pressure. Two HR measures related primarily to long-term HR variability were negatively associated with same-day ambient PM_{10}. Heart rate, as

well as a measure related primarily to short-term HR variability, were both positively, but less strongly, associated with PM_{10}. An effect on HR was also observed in the larger cohort of 90 subjects (Pope et al., 1999b).

Gold and colleagues (1998, 1999) reported decreases in HRV among 21 active elderly subjects aged 53-87 years in association with $PM_{2.5}$ measured in the two hours prior to physical exam.

Although differences in the processing and analysis of HR data (e.g., frequency- vs. time-domain analyses) make it difficult to quantitatively compare results of the above studies, they imply that PM, or some associated co-pollutant, is associated with alterations in the normal balance of sympathetic and parasympathetic control of HR variability in susceptible populations - i.e., the elderly and infirm. Depressions of HR variability have been associated with adverse cardiac outcomes in prospective studies (Neas, 1999).

6.3 MORTALITY EFFECTS OF PARTICULATE MATTER EXPOSURE

6.3.1 Introduction

The relationship of PM and other air pollutants to excess mortality has been intensively studied and has played an important role in previous health risk assessments (U.S. Environmental Protection Agency, 1986, 1996). Mortality is the most severe adverse health endpoint, and in some ways the easiest to study. Excellent death records are maintained at every level of government in almost all nations, and records are made available to academic investigators. Furthermore, from a narrowly technical point of view, individual deaths are more amenable to statistical analyses, since individual deaths from natural causes (typically respiratory and cardiovascular diagnoses) are statistically independent except in rare extremely infectious instances. Individual deaths are also non-recurring events, unlike hospital admissions or respiratory symptoms.

In this section recent findings are evaluated for the two most important epidemiology designs by which mortality is studied. Time series mortality studies are discussed in Section 6.3.2, and prospective cohort studies in Section 6.3.3. The time series studies are most appropriate to assessing acute responses to short-term PM exposure, although some recent work

(not yet published) suggests that the time series data sets can be used to examine responses to exposures over a longer time scale. Time series studies use a community-level response, the total number of deaths each day, by age or by cause of death. The prospective cohort studies provide a useful complement to the time series studies. These studies use individual health records, with adjustments of survival lifetimes or hazard rates adjusted for individual risk factors, but so far have provided less information about the role of exposures of extended duration.

6.3.2 Mortality Effects of Short-Term Particulate Matter Exposure

6.3.2.1 Summary of 1996 PM Criteria Document Findings on Unresolved Issues

The time-series mortality studies reviewed in the 1996 and past criteria documents provided strong evidence that ambient air pollution was associated with increases in daily mortality. The 1996 AQCD summarized 37 PM-mortality time-series studies (of which 13 were PM_{10} studies) published between 1988 and 1996. The available information from these studies were consistent with the hypothesis that PM is a causal agent in the mortality impacts of air pollution. The PM_{10} relative risk estimates derived from the PM_{10} studies reviewed in the 1996 AQCD suggested that an increase of 50 $\mu g/m^3$ in the 24-hr average of PM_{10} is associated with an increased risk of premature mortality of the order of RR = 1.025 to 1.05 in the general population (total deaths minus accident/injury). Higher relative risks are indicated for the elderly and for those with pre-existing respiratory conditions.

While a large number of studies reported PM-mortality associations, there were several important issues that needed to be addressed in interpreting those relative risks. The 1996 AQCD extensively discussed most critical issues including: (1) seasonal confounding and effect modification; (2) confounding by weather; (3) confounding by co-pollutants; (4) measurement error; (5) functional form and threshold; (6) harvesting and life shortening. As the issues related to model specification became further clarified, increasing numbers of recent studies have addressed most of the critical issues, and some of the issues were at least partially resolved, while others required further investigations and additional data. The following paragraphs briefly summarize the status of these issues at the time of the 1996 AQCD publication.

One of the most important components in time-series model specification was the adjustment for seasonal cycles and other longer-term temporal trends. Not adequately adjusting for these temporal trends could result in biased RRs. Residual over-dispersion and

autocorrelation also result from inadequate control for these temporal trends. Modern smoothing methods allow efficient fits of these temporal trends, and minimize the statistical problems although some issues of statistical methodology may require additional research. Most recent studies have controlled for these seasonal and other temporal trends, and it was unlikely that inadequate control for these trends seriously biased the estimated PM coefficients. The effect modification by season has been examined in several studies. Season specific analyses are often not feasible in small sizes (due to marginally significant PM effect size), but some studies (e.g., Samet et al., 1996; Moolgavkar and Luebeck, 1996) suggested that estimated PM coefficients varied from season to season. However, it is not certain whether these results are real seasonal effect modification, or due to the varying extent of correlation between PM and co-pollutants or weather variables in each season.

While most available studies included some function of weather variables and some reported sensitivity of PM coefficients to weather model specification, some speculated that inadequate weather model specifications may still have ascribed the residual weather effects to PM. Two PM studies (for Philadelphia, Samet et al. [1996, 1998]; for Utah Valley, Pope and Kalkstein [1996]) included collaboration with a meteorologist who modeled weather effects using synoptic weather categories. These studies reported that estimated PM effects were similar if weather effects on mortality were fitted by synoptic weather variables or by other models. The results also indicated that the synoptic weather model did not provide better model fits in predicting mortality when than other weather model specifications used in past PM-mortality studies. Thus, these results suggested that the reported PM effects were not explained by inadequate modeling of weather effects.

Many PM studies have considered at least one co-pollutant in the mortality regression, but increasing number of studies examined several multiple pollutants. In most cases, when PM indices were significant in single pollutant models, an addition of a co-pollutant diminished the PM effect size somewhat, but did not eliminate the associations. When multiple pollutant models were analyzed by season, the PM coefficients were less stable, again, possibly due to PM's varying correlation with co-pollutants among season, or due to smaller sample sizes in seasonal subsets. In many studies, PM indices were more significant than other pollutants in single and multiple pollutant models. Thus, it was concluded that PM-mortality associations were not seriously distorted by co-pollutants. However, interpretation of relative significance of

each pollutant in mortality regression as relative causal strength was difficult because of lack of quantitative information on relative exposure measurement/characterization errors among air pollutants, as discussed below.

Measurement errors can influence the size and significance of air pollution coefficients in time-series regression analyses. This issue is also important in assessing confounding among the multiple pollutants, as varying extent of such error among the pollutants would also influence corresponding relative significance. The 1996 AQCD discussed several types of such exposure measurement/characterization error including site-to-site variability and site-to-person variability. These errors are thought to bias the estimated PM coefficients downward in most cases. However, there was not sufficient quantitative information available at the time to allow an estimation of such bias.

The 1996 AQCD also reviewed evidence for threshold and functional form of short-term PM mortality associations. Several studies indicated that montonic associations were seen below the PM standards. It was considered difficult, however, to statistically identify a threshold from available data because of low data density at lower concentrations, potential influence of measurement error and adjustments for other covariates. Thus, the use of relative risk (rate ratio) derived from the log-linear Poisson models was considered adequate.

The extent of prematurity of death (i.e., mortality displacement, or harvesting) in PM-mortality association has important public health policy implications. At the time of the 1996 criteria review, only a few studies had investigated this issue. While one of the studies suggested that the extent of such prematurity may be only a few days, this finding may not be generalizable because the RR estimate was obtained only for identifiable PM episodes. There was not sufficient evidence to suggest the extent of prematurity for non-episodic periods, from which most of the recent PM relative risks were derived.

Only a limited number of PM-mortality studies analyzed fine particles and chemically specific components of PM. The Harvard Six-Cities Study (Schwartz et al., 1996) analyzed size-fractionated PM ($PM_{2.5}$, $PM_{10/15}$, and $PM_{10/15-2.5}$) and PM chemical components (sulfates and H^+). The results suggested that $PM_{2.5}$ was most significantly associated with mortality among the components of PM. While H^+ was not significantly associated with mortality in this and earlier analyses (Dockery et al., 1992), the smaller sample size for H^+ than for other PM components made a direct comparison difficult. The 1996 AQCD also discussed that the mortality

associations with BS or COH reported in earlier studies in Europe and the U.S. during the 1950s to 1970s most likely reflected contributions from fine particles, as those PM indices had low 50% cut-off diameters (≈ 4.5μm). Furthermore, there are respiratory morbidity studies that showed associations between hospital admissions/visits with components of PM in the fine particle range. Thus, the U.S. EPA concluded that there was adequate evidence to suggest that fine particles play especially important roles in observed PM mortality effects.

Summarizing status of the issues raised in the 1996 AQCD: (1) The observed PM effects are unlikely to be seriously biased by inadequate statistical modeling (e.g., control for seasonality); (2) The observed PM effects are unlikely to be significantly confounded by weather; (3) The observed PM effects may be to some extent confounded or modified by co-pollutants, and such extent may vary from season to season; (3) Determining the extent of confounding and effect modification by co-pollutants requires knowledge of relative exposure measurement characterization error among pollutants; there was insufficient information on this; (4) No evidence for a threshold for PM-mortality associations was reported. Statistically identifying a threshold from existing data was also considered difficult, if not impossible; (5) Some limited evidence for harvesting, a few days of life-shortening, was reported for episodic periods. No study was conducted to investigate harvesting in non-episodic US data; (6) A limited number of studies suggested a causal role of fine particles in PM-mortality associations, but in the light of historical data, biological plausibility, and the results from morbidity studies, a greater role of fine particles than coarse particles was suggested.

The following sections assess results from the studies that have been published since the 1996 AQCD. Because a large number of PM-health effects studies are currently being conducted and numerous PM-related publications are expected after this draft is completed (but before review of the final draft), the current assessment of the evidence here is incomplete. First, the results from several studies that analyzed data from multiple cities are reviewed. Then, rather than simply documenting the synopses of individual studies, the newly available results are discussed with regard to the previously unresolved issues noted above.

6.3.2.2 New Multi-City Studies

Several studies conducted time-series analyses in multiple cities. The major advantage of these studies over the meta-analyses of multiple "independent" studies is the consistency in data

handling and model specifications, thus eliminating variation due to study design. Also, many of the cities included in these studies were the ones for which no time-series analyses had been conducted. Therefore, unlike regular meta-analysis, they likely do not suffer from omission of negative studies caused by publication bias. Furthermore, any heterogeneity of air pollution effects can be systematically evaluated in multiple-city analyses. Thus, the results from multi-city studies can provide most valuable evidence regarding the consistency and heterogeneity, if any, of PM health effects.

APHEA Studies

The Air Pollution and Health: a European Approach (APHEA) project is a coordinated multi-center study of the short-term effects of air pollution on mortality and hospital admissions using data from 15 European cities, with a wide range of geographic, sociodemographic, climatic, and air quality patterns. The obvious strength of this approach is to be able to evaluate potential effect modifiers in a consistent manner. It should be noted that PM indices measured in those cities were mostly British Smoke, with exception of Paris, Lyon (PM_{13}), Barcelona (BS and TSP), Bratislava, Cologne, and Milan (TSP). There have been three papers published that presented either a meta-analysis or a pooled summary estimates of these multi-city mortality results: (1) Katsouyanni et al. (1997) SO_2 and PM results from 12 cities; (2) Touloumi et al. (1997) ambient oxidants (O_3 and NO_2) results from six cities; (3) Zmirou et al. (1998) cause-specific mortality results from 10 cities. The following briefly discuss each paper's findings.

Katsouyanni et al. (1997) SO_2 and PM results from 12 cities. The cities included were: Athens, Barcelona, Bratislava, Cracow, Cologne, Lodz, London, Lyons, Milan, Paris, Poznan, and Wroclaw. In western European cities it was found that an increase of 50 $\mu g/m^3$ in SO_2 or BS was associated with a 3% (95% confidence interval 2% to 4%) increase in daily mortality and the corresponding figure for PM_{10} (they used conversion: PM_{10} = TSP*0.55) was 2% (1% to 3%). In central eastern European cities the increase in mortality associated with a 50 $\mu g/m^3$ change in SO_2 was 0.8% (-0.1% to 2.4%) and in BS (per a 50 $\mu g/m^3$ change) 0.6% (0.1% to 1.1%). Cumulative effects of prolonged (two to four days) exposure to air pollutants resulted in estimates comparable with the one-day effects. The effects of both SO_2 and BS were stronger during the summer and were mutually independent. Regarding the contrast between the western and central eastern Europe results, the authors speculated that this could be due to: difference in

exposure representativeness, difference in pollution toxicity or mix, difference in proportion of sensitive sub-population, and model fit for seasonal control. Bobak and Roberts (1997) commented that the heterogeneity between eastern and western Europe could be explained by the difference in mean temperature. They plotted the estimated RR for SO_2 versus mean temperature (Figure 6-1), and showed that Spearman correlation for SO_2 was 0.85 (0.72 for BS). However, in response to this explanation, Katsouyanni and Touloumi (1998) mentioned that they had examined the source of heterogeneity, and found that other factors could apparently explain the difference in estimates as well as or even better than temperature (e.g., the correlation between age standardized mortality and the effect estimates was -0.92), and in light of other potential explanations, they considered it premature to ascribe the difference in effect estimates to temperature. They are conducting additional analyses to fully investigate the effect modifiers in APHEA 2.

Touloumi et al. (1997) ambient oxidants results from six cities. Touloumi et al. summarized the results of the short-term effects of ambient oxidants (O_3 and NO_2) on daily deaths from all causes (excluding accidents). These studies are discussed here to provide a basis of comparison with estimated SO_2 or BS effects in the APHEA cities. Six cities in Central and Western Europe provided data on daily deaths and NO_2 and/or O_3 levels. Poisson autoregressive models allowing for overdispersion were fitted. Fixed effects models were used to pool the individual regression coefficients when there was no evidence of heterogeneity among the cities and random effects models otherwise. Significant positive associations were found between daily deaths and both NO_2 and O_3. Increases of 50 $\mu g/m^3$ in NO_2 (1-hour maximum) or O_3 (1-hour maximum) were associated with a 1.3% (95% CI 0.9-1.8) and 2.9% (95% CI 1.0-4.9) increase in the daily mortality, respectively. There was a tendency for larger effects of NO_2 in cities with higher levels of BS. The pooled estimate for the O_3 effect was only slightly reduced, but the coefficient for NO_2 was reduced by half (but remained significant) when BS was included in the model. The authors speculated that the short-term effects of NO_2 on mortality may be confounded by other vehicle-derived pollutants.

Zmirou et al. (1998) cause-specific mortality results from 10 cities. This analysis presented cause-specific mortality results for APHEA cities. Again, using Poisson autoregressive models adjusting for trend, season, influenza epidemics, and weather, each pollutant's relative risk was estimated in each city, and "meta-analyses" of city specific estimates

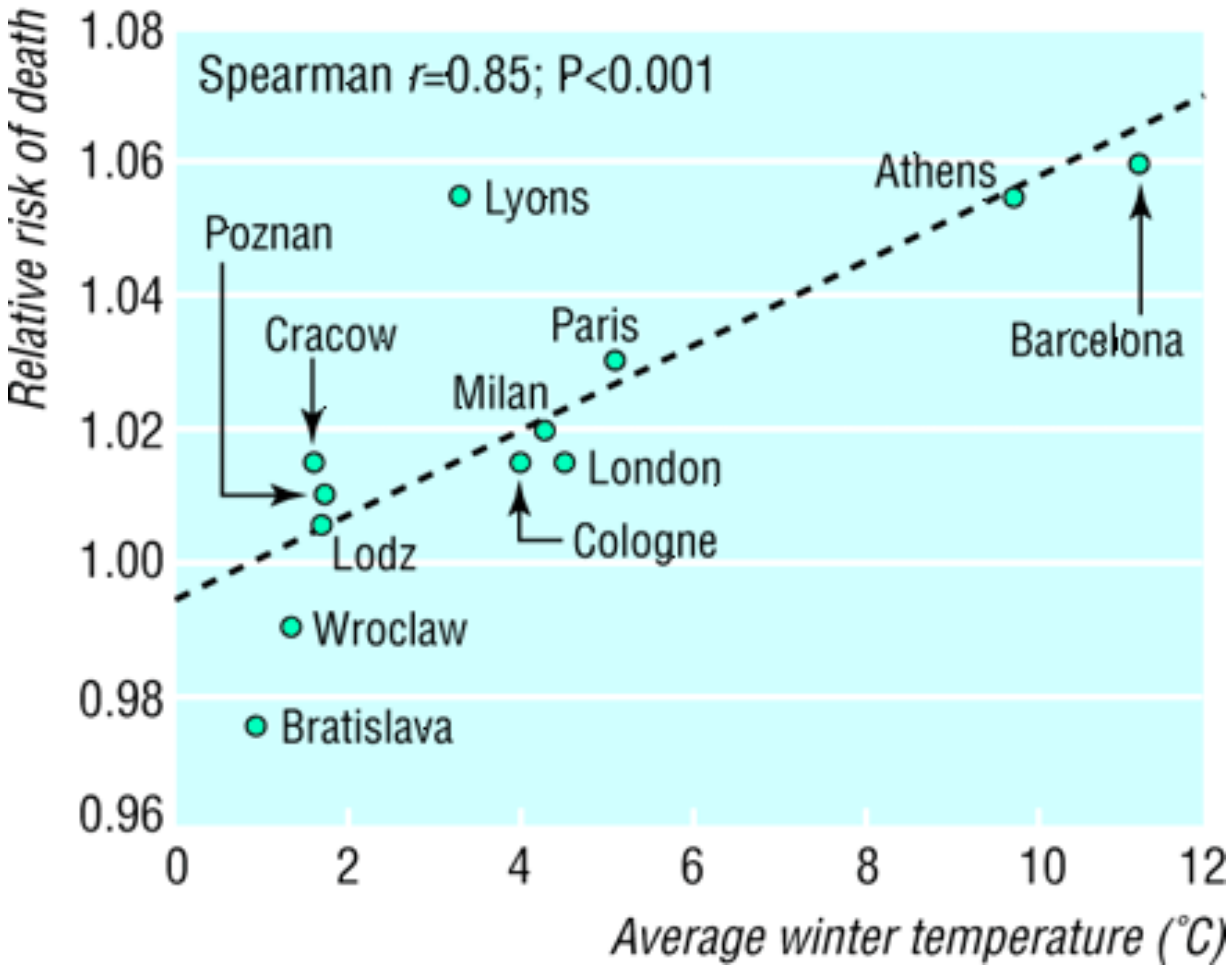

Figure 6-1. Relationship between the effect estimates from Katsouyanni et al. (1997) and average temperature. Source: Bobak and Roberts (1997).

1 were conducted. The pooled RRs for cardiovascular mortality were 1.02 (95% CI: 1.01-1.04) per
2 50 $\mu g/m^3$ increase in BS and 1.04 (95% CI: 1.01-1.06) per 50 $\mu g/m^3$ increase in SO_2 in western
3 European cities. The pooled RRs for respiratory mortality in western European cities were
4 1.04 (95% CI: 1.02-1.07) and 1.05 (95% CI: 1.03-1.07) for BS and SO_2, respectively. However,
5 these associations were not found in the central European cities. Again, the investigators point
6 out the potential explanation for the difference between the western and central European cities:
7 smaller fraction of elderly population and likely larger exposure representativeness error in the

central European cities. The lack of consistency in NO_2 - mortality associations was also mentioned.

Urban Air Pollution Mix and Daily Mortality in 11 Canadian Cities (Burnett et al., 1998). The number of daily deaths for non-accidental causes were obtained in 11 cities from 1980 to 1991 and linked to concentrations of ambient gaseous air pollutants using relative risk regression models for longitudinal count data. No PM index was included in their analyses because daily PM measurements were not available. NO_2 had the largest effect on mortality with a 4.1% increased risk ($p < 0.01$), followed by O_3 at 1.8% ($p < 0.01$), SO_2 at 1.4% ($p < 0.01$), and CO at 0.9% ($p = 0.04$) in multiple pollutant regression models. A 0.4% reduction in excess mortality was attributed to achieving a sulfur content of gasoline of 30 ppm in five Canadian cities. They compared the previously estimated percentage reduction in deaths due to $PM_{2.5}$ and sulfates (computed by the Canadian Health and Economics Assessment Panel based on results from Harvard 6-city time-series analysis), and noted that the reductions in risk due to reduction in concentrations of the mix of CO, SO_2, and NO_2 averaged among the five cities were 12 times greater than that for sulfate and 19 times greater than for $PM_{2.5}$. However, because the estimates from PM were not based on the Canadian data, and model specification could have made difference in risk estimates, a direct comparison between the risk reduction estimates for PM and the gaseous pollutants may not be adequate.

6.3.2.3 New Results from Individual City Studies

Studies in individual cities can provide more detailed information on specific PM components or source types. Identification of the chemical properties or size range of PM components that are responsible for the reported PM effects would be very valuable for understanding the biological mechanism of PM effects. Multiple PM components are rarely measured simultaneously, but several new studies investigated this issue. Also, several studies examined size specific component of PM.

Table 6-24 summarizes newly available individual studies (excludes studies that were discussed in the 1996 PM CD) and lists name of the city, study period, the type of PM indices used and their mean level, basic study description (mortality categories, covariates included, type of regression, etc.), main results, the "representative" RR for the PM index used, the lag reported, and the reference. While our main interest in this document is the PM effects observed in U.S.

TABLE 6-24. SUMMARIES OF RECENTLY PUBLISHED SINGLE-CITY PM TIME-SERIES STUDIES

City/Year/PM (mean)	Study Description	Results and Comments	PM RR for total deaths	PM Lags	Reference
U.S. Cities					
Philadelphia, PA 1973-1988 TSP (68)	A critical review paper, with an analysis of total daily mortality for its association with TSP, SO_2, NO_2, and O_3, adjusting for temporal trends, temperature, and also conducting analysis by season, using GAM models.	RR results presented as figures, and seasonal difference noted. TSP, SO_2, O_3 - mortality associations varied across season. TSP associations were stronger in summer and fall. NO_2 was the most significant predictor.	Ranged from ~ 0 % (winter) to ~ 4% (summer)	1 day lag	Moolgavkar and Leubeck (1996)
Philadelphia, PA 1974-1988 TSP (67)	Total, cardiovascular, respiratory, and by-age mortality regressed on TSP, SO_2, NO_2, O_3, and CO, adjusting for temporal trends and weather, using GAM.	TSP, SO_2, O_3, and 1-day lagged CO individually showed statistically significant associations with total mortality. No NO_2 associations unless SO_2 or TSP was also considered. The effects of TSP and SO_2 were diminished when both pollutants were included.	1.1 % (0, 2.1) per 35$\mu g/m^3$ increase in TSP	0 day lag	Kelsall et al. (1997)
Spokane, WA 1989-1995 PM_{10}: (dust-storm days:263; "control" days: 42)	Effects of high concentration of coarse crustal particles was investigated by comparing the death counts on 17 dust storm episodes to those on non-episode days on the same day of the years in other years, adjusting for temperature, dewpoint, and day-of-week, using Poisson regression.	No association was found between the mortality and dust storm days on the same day or the following day.	0% (-19, 22) for dust storm days.	0 day lag (lagged days also reported to have no associations)	Schwartz et al. (1999)
Ogden, Salt Lake City, and Provo/Orem, UT 1985-1995 PM_{10} (32 for Ogden; 41 for SLC; 38 for P/O)	Associations between PM_{10} and total, cardiovascular, and respiratory deaths were investigated in three metropolitan areas in Utah's Wasatch Front using GAM Poisson model and adjusting for seasonality, temperature, humidity, and barometric pressure. The analysis was conducted with or without dust (crustal coarse particles) storm episodes, as identified on the high "clearing index" days, an index of air stagnation.	Salt Lake City, where past studies reported little PM_{10}-mortality associations, had substantially more dust storm episodes. When the dust storm days were screened out from analysis and PM_{10} data from multiple monitors were used, comparable RRs were estimated for Salt Lake City and Provo/Orem.	12% (4.5, 20); 2.3% (0, 4.7); 1.9% (-2.1, 6.0) per 50$\mu g/m^3$ PM_{10} for 0 day lag	0 day lag, but the RRs for longer averaging days increased for Salt Lake City and Provo/Orem	Pope et al. (1999b)

TABLE 6-24 (cont'd). SUMMARIES OF RECENTLY PUBLISHED SINGLE-CITY PM TIME-SERIES STUDIES

City/Year/PM (mean)	Study Description	Results and Comments	PM RR for total deaths	PM Lags	Reference
Dallas, TX 1990-1994 PM_{10} (25)	Total, respiratory, cardiovascular, cancer, and remaining non-accidental deaths were related to PM_{10}, O_3, NO_2, SO_2, and CO, adjusting for temperature, dewpoint, day-of-week, and seasonal cycles (trigonometric terms) using Poisson regression.	O_3 (avg. of 1-2 day lags), NO_2 (avg.. 4 -5 day lags), and CO (avg. of lags 5- 6 days) were significantly positively associated with total mortality. PM_{10} and SO_2 were not significantly associated with any deaths.	-0.6% (-2.2, 1.1) per 8.3 $\mu g/m^3$ PM_{10}	0 day lag (other lags also reported to have no associations)	Gamble (1998)
King County, WA 1990-1994 PM_{10} (30); nephelometer (0.59 bsp unit)	Out-of-hospital deaths (total, respiratory, COPD, ischemic heart disease, heart failure, sudden cardiac death screening codes, and stroke) were related to PM_{10}, nephelometer (0.2 - 1.0 μm fine particles), SO_2, and CO, adjusting for day-of-week, month of the year, temperature and dewpoint, using Poisson regression.	Nephelometer data were not associated with mortality. Cause-specific death analyses suggest PM associations with ischemic heart disease deaths. Mortality associations with SO_2 and CO were not mentioned. The mean daily death counts were small (e.g., 7.7 for total ; 1.6 for ischemic heart disease). This is an apparently preliminary analysis.	1.4% (-1.3, 4.2) per 10$\mu g/m^3$ PM_{10}	avg. of 2 to 4 day lag	Levy (1998)
Santa Clara County, CA 1989-1996 $PM_{2.5}$ (13); PM_{10} (34); $PM_{10-2.5}$ (11); CoH (0.5 unit) ; NO_3 (3.0); SO_4 (1.8)	Total, cardiovascular, and respiratory deaths were regressed on PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, CoH, nitrate, sulfate, O_3, CO, NO_2, adjusting for trend, season, and min and max temperature, using Poisson GAM model. Season-specific analysis was also conducted. The same approach was also used to re-analyze 1980-1986 data (previously analyzed by Fairley [1990]).	$PM_{2.5}$ and nitrate were most significantly associated with mortality, but all the pollutants (except $PM_{10-2.5}$) were significantly associated in single poll. models. In 2 and 4 poll. models with $PM_{2.5}$ or nitrate, other pollutants were not significant. The RRs for respiratory deaths were always larger than those for total or cardiovascular deaths. The difference in risk between season was not significant for $PM_{2.5}$. The 1980-1986 results were similar, except that CoH was very significantly associated with mortality.	9% in one poll. model; 10-13% in 2 poll. model; 13% in 4-poll. model, per 28 $\mu g/m^3$ increase in $PM_{2.5}$	0 day lag	Fairley (1999)
Buffalo, NY 1988-1990 PM_{10} (24); CoH (0.2 /1000ft); $SO_4^=$ (62 nmoles/m^3)	Total, circulatory, and respiratory mortality and unscheduled hospital admissions were analyzed for their associations with H^+, $SO_4^=$, PM_{10}, CoH, O_3, CO, SO_2, and NO_2, adjusting for seasonal cycles, day-of-week, temperature, humidity, using Poisson and negative binomial GAM models.	For total mortality, all the PM components were significantly associated, with H^+ being the most significant, and CoH the least significant predictors. The gaseous pollutants were mostly weakly associated with total mortality.	2.2% (0.5, 4.0) per 9.6 g/m^3 PM_{10}	2 day lag	Gwynn et al. (1999)

TABLE 6-24 (cont'd). SUMMARIES OF RECENTLY PUBLISHED SINGLE-CITY PM TIME-SERIES STUDIES

City/Year/PM (mean)	Study Description	Results and Comments	PM RR for total deaths	PM Lags	Reference
Canada					
Toronto 1970-1991 TSP (80); CoH (0.42 /1000ft)	Total, cardiovascular, COPD, pneumonia, respiratory, cancer, and the remaining mortality series were related to TSP, SO_2, CoH, NO_2, O_3, and CO, adjusting for seasonal cycles (by high-pass filtering each series) temperature, humidity, day-of-week, using OLS regression. Factor analysis of multiple pollutants was also conducted to extract automobile related pollution, and mortality series were regressed on the resulting automobile factor scores.	TSP (0 day lag) was significantly associated with total and cardiovascular deaths. NO_2 0 day lag) was a significant predictor for respiratory and COPD deaths. 2-day lagged O_3 was associated with total, respiratory, and pneumonia deaths. Factor analysis showed a factor with high loadings for NO_2, CoH, and CO, apparently representing automobile factor. This factor was a significant predictor for total, cancer, cardiovascular, respiratory, and pneumonia deaths.	2.8% per 100$\mu g/m^3$ TSP	0 day lag	Özkaynak et al. (1996)
Toronto 1980-1994 TSP (60); CoH (0.42); $SO_4^=$ (9.2 $\mu g/m^3$); PM_{10} (30, estimated); $PM_{2.5}$ (18, estimated)	Total, cardiac, and other nonaccidental deaths (and by age groups) were regressed on TSP, CoH, $SO_4^=$, CO, NO_2, SO_2, O_3, estimated PM_{10} and $PM_{2.5}$ (based on the relationship between the existing every-6th-day data and $SO_4^=$, TSP and CoH), adjusting for seasonal cycles, day-of-week, temperature, and dewpoint using GAM Poisson model.	Essentially all the pollutants were significant predictors of total deaths in single pollutant models, but in two pollutant models with CO, most pollutants' estimated RRs were reduced (all the PM indices remained significant). Based on the results from the co-pollutant models and various stepwise regressions, the authors noted that the effects of the complex mixture of air pollutants could be "almost completely explained by the levels of CO and TSP".	2.0% (0.7, 3.3) per 88 $\mu g/m^3$ TSP; 2.9% (1.5, 4.4) per 42 $\mu g/m^3$ PM_{10}; 4.2% (2.9, 5.6) per 22 $\mu g/m^3$ $PM_{2.5}$	0 day lag for TSP and PM_{10}; Avg. of 0 and 1 day for CoH and $PM_{2.5}$	Burnett et al. (1998)
Mexico City					
Mexico-City 1990-1992 TSP (median: 204)	Total, respiratory, cardiovascular, and age-specific (age >= 65) deaths were related to O_3, TSP, and CO, adjusting for minimum temperature (temperature also fitted seasonal cycles) using Poisson models.	O_3, SO_2, and TSP were all associated with total mortality in separate models, but in multiple pollutant model, only TSP remained associated with mortality. CO association weak.	6% (3.3, 8.3) per 100 $\mu g/m^3$ for total deaths	0 day lag	Borja-Aburto et al. (1997)

TABLE 6-24 (cont'd). SUMMARIES OF RECENTLY PUBLISHED SINGLE-CITY PM TIME-SERIES STUDIES

City/Year/PM (mean)	Study Description	Results and Comments	PM RR for total deaths	PM Lags	Reference
Mexico-City 1993-1995 $PM_{2.5}$ (mean:27)	Total, respiratory, cardiovascular, other deaths, and age-specific (age >= 65) deaths were related to $PM_{2.5}$, O_3, and NO_2, adjusting for 3-day lagged temperature and periodic cycles, using Poisson GAM model.	$PM_{2.5}$, O_3, and NO_2 were associated with mortality with different lag/averaging periods (1 and 4 day lags; 1-2 avg.; 1-5 avg., respectively). $PM_{2.5}$ associations were most consistently significant. SO_2 was available, but not analyzed because of its "low" levels.	1.3% and 1.4% (0.2, 2.5) per 100 $\mu g/m^3$ for total deaths for 0 and 4 day, respectively	0 day and 4 day lag	Borja-Aburto et al. (1998)
Mexico-City 1993-1995 $PM_{2.5}$ (mean: 27.4 μg/m3)	Infant mortality (avg. ~ 3/day) related to $PM_{2.5}$, O_3, and NO_2, adjusting for temperature and smoothed time, using Poisson GAM models.	Excess infant mortality was associated with $PM_{2.5}$, but also with NO_2, and O_3 in the same average/lags. NO_2, and O_3 associations were less consistent in multi-pollutant models.	6.9% (2.5, 11.3) per 10 $\mu g/m^3$	Avg. 3-5 lag days	Loomis et al. (1999)
Europe					
London, UK 1987-1992 BS (15)	Total, cardiovascular, and respiratory mortality series were regressed on BS, O_3, NO_2, and SO_2, adjusting for seasonal cycles, day-of-week, influenza, holidays, temperature, humidity, and autocorrelation using Poisson model.	Both O_3 (0 day lag) and BS (1 day lag) were significant predictors of total deaths. O_3 was also positively significantly associated with respiratory and cardiovascular deaths. The effect size estimates per the same distributional increment (10% to 90%) were larger for O_3 than for BS. These effects were larger in warm season. SO_2 and NO_2 were not consistently associated with mortality.	1.7% (0.8, 2.6) per 14 $\mu g/m^3$ increase (10% to 90%) in BS	1 day lag	Anderson et al. (1996)
London, UK 1992-1994 BS (13) PM_{10} (29)	Total, cardiovascular, and respiratory (by age) mortality series were regressed on PM_{10}, BS, O_3, NO_2, CO, and SO_2, adjusting for seasonal cycles, day-of-week, influenza, holidays, temperature, humidity, and autocorrelation using Poisson model.	All effect size estimates (except O_3) were positive for total deaths (though not significant for single lag models). The effects of O_3 found in 1987-1992 were not replicated, except in cardiovascular deaths. Multiple day averaging (e.g., 0-1, 0-2 days) tend to give more significant effect size estimates. The effect size for PM_{10} and BS were similar for the same distributional increment.	1.2% (0.0, 2.4) per 16 $\mu g/m^3$ increase (10% to 90%) in BS 0.8% (-0.6, 2.2) per 31 $\mu g/m^3$ increase (10% to 90%) in BS	1 day lag for BS	Bremner et al. (1999)

TABLE 6-24 (cont'd). SUMMARIES OF RECENTLY PUBLISHED SINGLE-CITY PM TIME-SERIES STUDIES

City/Year/PM (mean)	Study Description	Results and Comments	PM RR for total deaths	PM Lags	Reference
England and Wales, and Greater London, UK PM_{10} (56, during the worst heat wave; 39, July-August mean)	Excess deaths, by age, sex , and cause, during the 1995 heat wave were estimated by taking the difference between the deaths during heat wave and the 31-day moving averages (for 1995 and 1993-94 separately). The pollution effects, additively for O_3, PM_{10}, and NO_2, were estimated based on the published season-specific coefficients from the 1987-1992 study (Anderson et al., 1996).	Air pollution levels at all the locations rose during the heat wave. 8.9% and 16.1% excess deaths were estimated for England and Wales, and Greater London, respectively. Of these excess deaths, up to 62% and 38%, respectively for these locations, may be attributable to combined pollution effects.	2.6% increase for PM_{10} in Greater London during heat wave	NA	Rooney et al. (1998)
Edinburgh, UK 1981-1995 PM_{10} (21, by TEOM only for 1992-1995) BS (8.7)	Both mortality (total, cardiovascular, and respiratory) and emergency hospital admissions (cardiovascular and respiratory), in two age groups (<65 and >= 65), were analyzed for their associations with PM_{10}, BS, SO_2, NO_2, O_3, and CO, using Poisson regression adjusting for seasonal cycles, day-of-week, temperature, and wind speed.	Among all the pollutants, BS was most significantly associated with all cause, cardiovascular, and respiratory mortality series. In the subset in which PM_{10} data were available, the RR estimates for BS and PM_{10} for all cause elderly mortality were comparable. Other pollutants' mortality associations were generally inconsistent.	1.5% (0.5, 2.5) per 10 $\mu g/m^3$ increase in BS for all cause mortality in age 65+ group	Avg. of 1-3 day lags	Prescott et al. (1998)
Birmingham, UK 1992-1994 PM_{10} (apparently beta-attenuation, 26)	Mortality data were analyzed for COPD, pneumonia, all respiratory diseases, all circulatory diseases, and all causes. Mortality associations with PM_{10}, NO_2, SO_2, and O_3 were examined using OLS (with some health outcomes log- or square-root transformed), adjusting for day-of-week, month, linear trend, temperature and relative humidity. The study also analyzed hospital admission data.	Total, circulatory, and COPD deaths were significantly associated with 1-day lag PM_{10} . The gaseous pollutants "did not have significant associations independent from that of PM_{10}", and the results for gaseous pollutants were not presented. The impact of reducing PM_{10} to below 70 $\mu g/m^3$ was estimated to be "small" (0.2% for total deaths), but the PM_{10} level above 70$\mu g/m^3$ occurred only once during the study period.	1.1% (-0.1, 2.1) per 10 $\mu g/m^3$ PM_{10}	1 day lag	Wordley et al. (1997)

TABLE 6-24 (cont'd). SUMMARIES OF RECENTLY PUBLISHED SINGLE-CITY PM TIME-SERIES STUDIES

City/Year/PM (mean)	Study Description	Results and Comments	PM RR for total deaths	PM Lags	Reference
Rotterdam, the Netherlands 1983-1991 TSP (median 42); BS (median 13)	Total mortality (also by age group) was regressed on TSP, Fe (from TSP filter), BS, O_3, SO_2, CO, adjusting for seasonal cycles, day-of-week, influenza, temperature, and humidity using Poisson GAM model.	Daily deaths were most consistently associated with TSP. TSP and O_3 effects were "independent" of SO_2 and CO. Total iron (from TSP filter) was associated "less consistently" with mortality than TSP was. The estimated RRs for PM indices were higher in warm season than in cold season.	5% (1, 9) per 91 $\mu g/m^3$ TSP	1 day lag	Hoek et al. (1997)
East Berlin 1981-1989 "SP" (beta attenuation, 97)	Total mortality (as well as deviations from long-wave cycles) was regressed on SP and SO_2, adjusting for day-of-week, month, year, temperature, and relative humidity, using OLS, with options to log-transform pollution, and w/ and w/o days with pollution above 150 $\mu g/m^3$.	Both SP and SO_2 were significantly associated with total mortality with 2 day lag in single pollutant model. When both pollutants were included, their coefficients were reduced by 33% and 46% for SP and SO_2, respectively.	6.1% per 100 $\mu g/m^3$ "SP"	2 day lag	Rahlenbeck and Kahl (1996)
Helsinki, Finland 1987-1993 TSP (median 64); PM_{10} (median 28)	Total and cardiovascular deaths, for age groups < 65 and 65 +, were related to PM_{10}, TSP, SO_2, NO_2, and O_3, using Poisson model adjusting for temperature, relative humidity, day-of-week, temporal patterns, holiday and influenza epidemics.	No pollutant was significantly associated with mortality from all causes or from cardiovascular in age group (65+). Only in age less than 65 group, PM_{10} was associated with total and cardiovascular deaths with 4 and 5 day lags, respectively. The "significant" lags were rather "spiky". O_3 was also associated with cardiovascular mortality in age under 65 group with inconsistent signs and late and spiky lags (negative on day 5 and positive on day 6).	3.5% (1.1, 5.9) per 10 $\mu g/m^3$ PM_{10}	4 day lag (other lags negative or zero)	Pönkä et al. (1998)
Madrid, Spain 1986-1992 "TSP" (beta attenuation, 47 for average of 2 stations)	Total, respiratory, and cardiovascular deaths were related to TSP and SO_2. Multivariate autoregressive integrated moving average models used to adjust for season, temperature, relative humidity, and influenza epidemics.	TSP (1-day lag) and SO_2 (3-day lagged) were independently associated with mortality.	4.8% (1.8, 7.7) per 100 $\mu g/m^3$ TSP	1 day lag	Alberdi Odriozola et al. (1998)

TABLE 6-24 (cont'd). SUMMARIES OF RECENTLY PUBLISHED SINGLE-CITY PM TIME-SERIES STUDIES

City/Year/PM (mean)	Study Description	Results and Comments	PM RR for total deaths	PM Lags	Reference
Rome, Italy 1992-1995 TSP ("PM_{13}" beta attenuation, 84)	Total mortality was related to PM_{13}, SO_2, NO_2, CO, and O_3, using Poisson GAM model , adjusting for seasonal cycles, temperature, humidity, day-of-week, and holiday. Analysis of mortality by place of residence, by season, age, place of death (in or out of hospital), and cause was also conducted.	PM_{13} and NO_2 were most consistently associated with mortality. CO and O_3 coefficients were positive, SO_2 coefficients negative. RR estimates higher in the warmer season. RRs similar for in- and out-of hospital deaths.	0.38% (0.09, 0.68) per 10 $\mu g/m^3$ PM_{13}	0 day lag	Michelozzi, et al. (1998)
Milan, Italy 1980-1989 TSP ("PM_{13}" beta attenuation, 142)	Specific causes of death (respiratory, respiratory infections, COPD, circulatory, cardiac, heart failure, and myocardial infarction) were related to TSP, SO_2, and NO_2, adjusting for seasonal cycles, temperature, and humidity, using GAM Poisson model.	All three pollutants were associated with all cause mortality. Cause-specific analysis was conducted for TSP only. Respiratory infection and heart failure deaths were both associated with TSP on the concurrent day, whereas the associations for myocardial infarction and COPD deaths were found for the average of 3 to 4 day prior TSP.	3.3% (2.4, 4.3) per 100 $\mu g/m^3$ TSP	0 day lag	Rossi et al. (1999)
South America					
São Paulo, Brazil 1991-1992 PM_{10} (beta-attenuation, 65)	Associations between intrauterine mortality and PM_{10}, NO_2, SO_2, CO, and O_3 were investigated using Poisson regression adjusting for season and weather. Association between ambient CO and carboxyhemoglobin of blood sampled from the umbilical cord of non-smoking pregnant mothers were investigated in separate time period.	NO_2, SO_2, and CO were individually significant predictor of the intrauterine mortality. NO_2 was most significant in multi-pollutant model. PM_{10} and O_3 were not significantly associated with the mortality. There was an association between the ambient CO levels and carboxyhemoglobin of blood sampled from the umbilical cords.	4.1% (-1.8, 10.4) per 50 $\mu g/m^3$ PM_{10} for intrauterine mortality	0 day lag (?)	Pereira et al. (1998)

TABLE 6-24 (cont'd). SUMMARIES OF RECENTLY PUBLISHED SINGLE-CITY PM TIME-SERIES STUDIES

City/Year/PM (mean)	Study Description	Results and Comments	PM RR for total deaths	PM Lags	Reference
Australia					
Brisbane 1987-1993 PM_{10} (27, not used in analysis) Nephelometer (0.26 bscat/10^4m, size range: 0.01-2 μm).	Total, cardiovascular, and respiratory deaths (also by age group) were related to PM (nephelometer), O_3, SO_2, and NO_2, adjusting for seasonal cycles, day-of-week, temperature, dewpoint, holidays, and influenza, using Poisson GEE to adjust for autocorrelation. Season-specific (warm and cold) analyses were also conducted.	Same-day PM and O_3 were associated most significantly with total deaths. The O_3 effect size estimates for cardiovascular and respiratory deaths were consistently positive (though not significant), and larger in summer. PM's effect size estimates were comparable for warm and cold season for cardiovascular deaths, but larger in warm season for respiratory deaths. NO_2 and SO_2 were not associated with mortality.	0.9% (0.3, 1.5) per 0.1 bscat/10^4m nephelometer increment	0 day lag	Simpson et al. (1997)
Sydney 1989-1993 Nephelometer (0.30 bscat/10^4m). Site-specific conversion: $PM_{2.5}$ ~ 9; PM_{10} ~ 18	Total, cardiovascular, and respiratory deaths were related to PM (nephelometer), O_3, and NO_2, adjusting for seasonal cycles, day-of-week, temperature, dewpoint, holidays, and influenza, using Poisson GEE to adjust for autocorrelation.	PM, O_3, and NO_2 all showed significant associations with total mortality in single pollutant models. In multiple pollutant models, the PM and O_3 effect estimates for total and cardiovascular deaths were marginally reduced, but the PM effect estimate for respiratory deaths was substantially reduced.	2.6% (0.9, 4.2) per 14 μg/m^3 $PM_{2.5}$ or 28 μg/m^3 PM_{10} (10 % to 90%)	Avg. of 0 and 1 day lags	Morgan et al. (1998b)
Asia					
Delhi, India 1991-1994 TSP (375)	Total (by age group), respiratory, cardiovascular deaths were related to TSP, SO_2, and NO_x, using GEE Poisson model (to control for autocorrelation), adjusting for seasonal cycles (trigonometric terms), temperature, and humidity. 70% of all deaths occur before age 65 (in US, 70% of deaths occur after age 65).	TSP was significantly associated with all mortality series except with the very young (age 0-4) and the "very old" (age >=65). The results were reported to be unaffected by addition of SO_2 to the model. The authors note that, because those who are affected are younger (than Western cities), more life-years are likely to be lost per person from air pollution impacts.	2.3% (significant at 0.05, but SE of estimate not reported) per 100μg/m^3	2 day lag	Cropper et al. (1997)

TABLE 6-24 (cont'd). SUMMARIES OF RECENTLY PUBLISHED SINGLE-CITY PM TIME-SERIES STUDIES

City/Year/PM (mean)	Study Description	Results and Comments	PM RR for total deaths	PM Lags	Reference
Bangkok, Thailand 1992-1995 PM_{10} (beta attenuation, 65)	Total, cardiovascular, respiratory deaths were examined for their associations with PM_{10} (separate measurements showed that ~50% of PM_{10} was $PM_{2.5}$),using Poisson GAM model adjusting for seasonal cycles, day-of-week, temperature, humidity.	All the mortality series were associated with PM_{10} at various lags. The effects appear across all age groups. No other pollutants were examined.	1% (0.5, 1.6) per 10 $\mu g/m^3$ PM_{10}	3 day lag (0 and 2 day lags also significant)	Ostro et al. (1998)
Seoul and Ulsan, Korea 1991-1995 TSP (beta attenuation, 93 for Seoul and 72 for Ulsan)	Total mortality series was examined for its association with TSP, SO_2, and O_3, in Poisson GEE (exchangeable correlation for days in the same year), adjusting for season, temperature, and humidity.	All the pollutants were significant predictors of mortality in single pollutant models. TSP was not significant in multiple pollutant models, but SO_2 and O_3 remained significant.	5.1% (3.1, 7.2) for Seoul , and -0.1% (-3.9, 3.9) for Ulsan, per 100$\mu g/m^3$ TSP	Avg. of 0, 1, and 2 day lags	Lee et al. (1999)

cities, the results from other countries are certainly useful in evaluating the consistency and source-type specificity, if any, of PM effects. Not all of the studies listed in Table 6-24 will be discussed in detail here, but instead, the studies will be discussed in the context of issues.

6.3.2.4 New Studies on the Temporal Structure of Short-Term Effects

Consistency of Lags for Short-Term PM Exposure

Table 6-24 lists the lags for which the PM-mortality associations were reported. In most studies, after the basic model (the best model with weather and seasonal cycles as covariates) is developed, several pollution lags (usually 0 to 3 or 4 days) are individually introduced, and most significant lag(s) is chosen for the RR calculation. While this practice may bias the chance of finding a significant association, without a firm biological reason to establish a fixed pre-determined lag, it appears reasonable. Due to likely individual variability in response to air pollution, the apparent lags of effects observed for aggregated population counts are expected to be "distributed" (i.e., symmetric or skewed bell-shape). The "most significant lag" in such distributed lags is also expected to statistically fluctuate. It should also be noted that if one chooses the most significant single lag day only, and if more than one lag day show positive (significant or otherwise) associations with mortality, then reporting a RR for only one lag would also underestimate the pollution effects. Some studies did consider several multiple-day averaging of exposure variables to capture such multi-day effects, but this practice is not a prevailing one.

An additional complication in assessing the shape of distributed lag is that the apparent spread of the distributed lag may depend on the pattern of the persistence of air pollution (i.e., episodes may persist for a few days), which may vary from city to city. Also, it is possible that the extent of lag and its spread may vary depending on the cause of death. For example, Rossi et al. (1999) report that, in their analysis of TSP-cause specific mortality in Milan, Italy, the lags varied for different cause of death (i.e., same day for respiratory infections and heart failure, 3-4 days for myocardial infarction and COPD). Thus, the lag for the total mortality may exhibit mixed lags (weighted by the frequency of deaths in each cause). A somewhat unusual example, from this perspective was reported from a recent Mexico City study (Borja-Aburto et al., 1998) in which they found significant $PM_{2.5}$-total mortality associations for same day and 4-day lag, but not in the intervening 2 to 3 days (percent increase per 10 $\mu g/m^3$ were 1.34, -0.16, 0.41, 0.43,

1.36, 0.99, for 0 through 5 day lags, respectively). The authors hypothesize that, "This phenomenon is consistent with both a harvesting of highly susceptible persons on the day of exposure to high pollution levels and a lagged increase in mortality due to delayed effects of reduction of pulmonary defenses, cardiovascular complications, or other homeostatic changes among less-compromised individuals". However, the 4-day lagged effects are certainly not the most frequently reported lag.

Figure 6-2 shows the distribution of the reported lags from Table 6-24 as well as from Table 12-25 in the 1996 AQCD. It can be seen that the same day and 1-day lag are the most frequently reported lags. This is also consistent with the immediate effects observed in the 1952 London Smog episode.

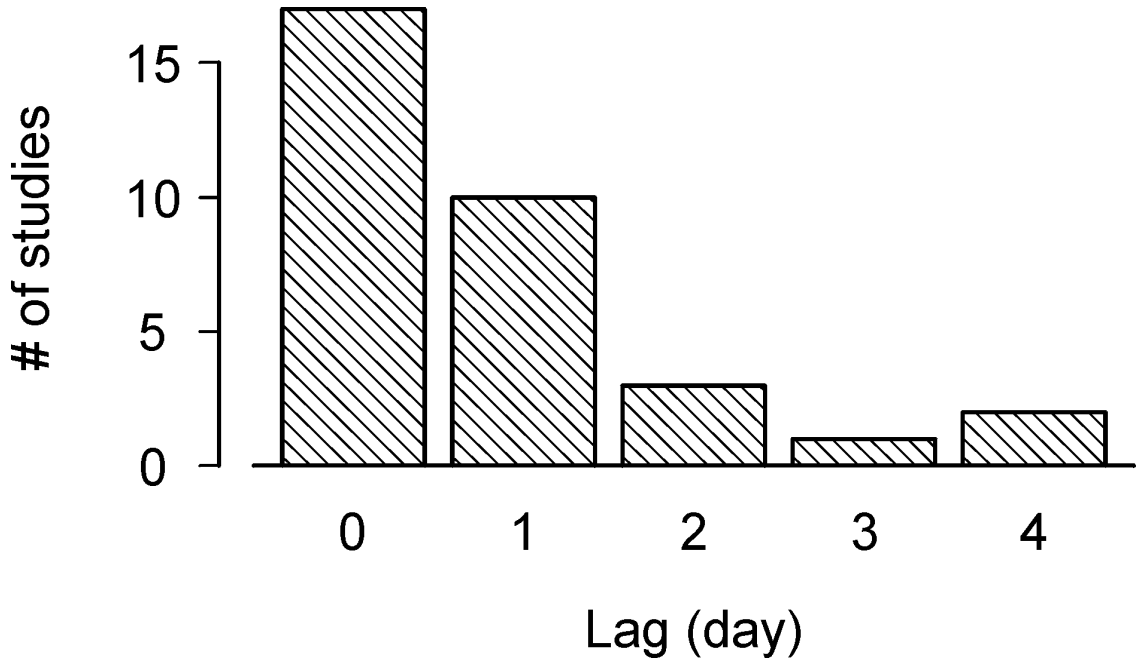

Figure 6-2. Frequency distribution of the lag day for which PM RRs were computed in 33 studies (from Table 6-24 and Table 12-25 in the 1996 PM CD). Multiple-day averaged lags were omitted.

New Assessments of Mortality Displacement

There have been a few studies that investigated the question of "harvesting", a phenomenon in which a deficit in mortality results following the days with (pollution-caused) elevated mortality, due to the depletion of susceptible population pool. The issue is important in interpreting the public health implication of the reported short-term PM mortality effects. In the 1996 AQCD, suggestive evidence was observed (Spix et al., 1993) during a period when the air pollution levels were relatively high. Recent studies generally used data from areas with lower, non-episodic pollution levels.

Schwartz (1999b) separated time-series air pollution, weather, and mortality data from Boston, MA, into three components: (1) seasonal and longer fluctuations; (2) "intermediate" fluctuations; (3) "short-term" fluctuations. By varying the cut-off between the intermediate and short term, he sought the evidence of harvesting. The idea is, for example, if the extent of harvesting were a matter of a few days, then associations between weekly average values of mortality and air pollution (controlling for seasonal cycles) would not be seen. He reported that, for COPD, there was evidence that most of the mortality was only displaced by a few months; for pneumonia, heart attacks, and all cause mortality, the effect size increased as the longer time scales were included. The percent increase in deaths associated with a 10 $\mu g/m^3$ increase in $PM_{2.5}$ increased from 2.1% (95%CI: 1.5, 4.3) to 3.75% (95%CI: 3.2, 4.3).

Zeger et al. (1999) first illustrated, through simulation, the implication of harvesting for PM regression coefficients (i.e., mortality relative risk) as observed in frequency domain. Three levels of harvesting, 3 days, 30 days, and 300 days, were simulated. As expected, the shorter the harvesting, the larger the PM coefficient in the higher frequency range. However, in the real data from Philadelphia, the regression coefficients increased toward the lower frequency range, suggesting that the extent of harvesting, if it exists, is not in the short-term range. Zeger et al. suggested that "harvesting-resistant" regression coefficients can be obtained by excluding the coefficients in the very high frequency range (to eliminate short-term harvesting) and in the very low frequency range (to eliminate seasonal confounding). Since the observed frequency domain coefficients in the very high frequency range were smaller than those in the mid frequency range, eliminating the "short-term harvesting" effects would only increase the average of the coefficients in the rest of the frequency range.

Frequency domain analyses are rarely performed in air pollution health effects studies, perhaps except the spectra analysis (variance decomposition by frequency) to identify seasonal cycles. Examinations of the correlation by frequency (*coherence*) and the regression coefficients by frequency (*gain*) may be useful in evaluating the potentially frequency-dependent relationships among multiple time series. A few past examples in air pollution health effects studies include: (1) Shumway et al. (1983) analysis of London mortality analysis in which they observed that significant coherence occurred beyond two week periodicity (they interpreted this as "pollution has to persist to affect mortality); (2) Shumway et al. (1988) analysis of Los Angels mortality data in which they also found larger coherence in the lower frequency; (3) Ito (1990) analysis of London mortality data in which he observed relatively constant gain (regression coefficient) for pollutants across the frequency range, except the annual cycle. These results also suggest that associations and effect size are, at least, not concentrated in the very high frequency range.

Both Schwartz (1999b) and Zeger et al. (1999) analyses suggest that the extent of harvesting, if any, is not a matter of few days. Other past frequency domain studies are also at least qualitatively in agreement with the evidence against the short-term only harvesting. Since very long wave cycles (> 6 months) need to be controlled in time-series analyses, it is not possible to estimate the extent of harvesting beyond 6 months periodicity in a time-series study design. While these studies suggest that observed short-term associations are not simply due to short-term harvesting, more data are needed to quantify prematurity of deaths.

Santa Clara County, CA. Fairley (1999) conducted a time-series analysis of mortality-air pollution relationship in Santa Clara County, CA for years 1989-1996. His previous analysis of this locale (Fairley, 1990) showed an association between Coefficient of Haze (CoH) and mortality in the same County for 1980-1986 period. Fairley provides useful information regarding the type of air pollution in the study area. In contrast to Eastern or Midwestern cities, SO_2 levels are so low (<10 ppb) that it is no longer measured. Consequently, sulfate is low, and it represents only 5% of $PM_{2.5}$ (in contrast to up to 45% in Eastern U.S.). Also, unlike Eastern cities where fine particles are high during summer due to sulfate levels, in Santa Clara County, fine particles are much higher in winter (25 $\mu g/m^3$ in winter vs. 10 $\mu g/m^3$ during the rest of the year) due to contributions from wood burning and ammonium nitrate.

Total, cardiovascular, and respiratory deaths were regressed on PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, CoH, nitrate, sulfate, O_3, CO, NO_2, adjusting for trend, season, and min and max temperature, using GAM Poisson models. Season-specific analysis was also conducted. The same approach was also used to re-analyze 1980-1986 data (previously analyzed by Fairley, 1990). $PM_{2.5}$ and nitrate were most significantly associated with mortality, but all the pollutants (except $PM_{10-2.5}$) were significantly associated in single pollutant models. In multiple pollutant models with $PM_{2.5}$ or nitrate, other pollutants were not significantly associated with mortality. The RRs for respiratory deaths were always larger than those for total or cardiovascular deaths. The difference in risk between season was not significant for $PM_{2.5}$. The 1980-1986 results were similar, except that CoH was a very significantly associated with mortality, consistent with the results from the author's 1990 analysis.

This study presents the first evidence of the mortality effects of directly measured $PM_{2.5}$ in the West Coast. While other studies of PM in the West Coast (PM_{10} in Los Angeles [Kinney et al., 1995]; visibility-derived $PM_{2.5}$ in San Bernardino and Riverside Counties [Ostro, 1996]) indicated larger effect estimates in summer, Fairley's result indicates that the estimated $PM_{2.5}$ coefficients were relatively constant across season. This may be in part due to the difference in air pollution mix between the Los Angeles Metropolitan area and Santa Clara County (i.e., San Francisco Bay area). Fairley's results also indicated that the coarse fraction of PM_{10} ($PM_{10-2.5}$) was not a significant predictor of mortality, consistent with Schwartz et al. (1999) findings from six-cities study.

Mexico City Studies. There have been three time-series mortality studies in Mexico that examined PM indices: (1) TSP-mortality study for years 1990-1993 (Loomis et al., 1996; Borja-Aburto et al., 1997); (2) $PM_{2.5}$-mortality (total, cardiovascular, and respiratory) for years 1993-1995 (Borja-Aburto et al., 1999a); and (3) $PM_{2.5}$-infant (children less than 1 year of age) mortality study 1993-1995 (Borja-Aburto et al., 1999b). The TSP study (the study focus was on O_3) considered O_3, SO_2, and CO as co-pollutants, and the $PM_{2.5}$ studies considered O_3 and NO_2. In the $PM_{2.5}$ studies, SO_2 was available, but not analyzed because the concentration was "comparable to the those in the cities wit lowest levels". These studies employed Poisson models with adjustment for temperature and long-term trends, but the TSP study employed the iteratively weighted and filtered least-square method to control for autocorrelation and

over-dispersion, while the $PM_{2.5}$ studies used generalized additive models to model mortality as a smooth function of time, which should also remove autocorrelation and over-dispersion.

In the TSP results (Loomis et al., 1996), the RRs for total mortality using single pollutant models were: 1.049 (95% CI 1.030, 1.067) per 100 $\mu g/m^3$ increase in TSP; 1.029 (95% CI 1.015, 1.044) per an increase of 100 ppb in one-hour maximum O_3; and, 1.075 (95% CI 0.984, 1.062) per 100-ppb increase for SO_2. CO was only weakly associated with mortality, and was not considered further in multiple pollutant models. When all three pollutants were considered simultaneously, only TSP remained associated with mortality, indicating excess mortality of 5% per 100 $\mu g/m^3$ increase [RR = 1.052, 95% CI 1.034, 1.072]. Excess mortality was larger and more significant for persons over 65 years of age. Addition of SO_2 to the TSP model did not change the TSP coefficient. Air pollution levels in Mexico City were much higher than U.S. levels. For example, the 25th percentile of daily 1-hr maximum ozone was 122 ppb; the median for TSP, SO_2, CO, and O_3 (all daily mean) were 204 ($\mu g/m^3$), 53 (ppb), 5.8 (ppm), and 54 (ppb), respectively. The authors concluded: ".... it is difficult to attribute the observed effects to a single pollutant. The technical feasibility and scientific validity of isolating the effect of single pollutants in such complex mixtures requires further research and careful consideration".

In the $PM_{2.5}$- mortality (total, cardiovascular, and respiratory) analysis, $PM_{2.5}$, O_3, and NO_2 were associated with mortality with different lag/averaging periods (1 and 4 day lags; 1-2 d avg.; 1-5 d avg., respectively). $PM_{2.5}$ associations were most consistently significant. As mentioned previously, the authors interpret this pattern of 1 and 4 day lag associations as the immediate harvesting of highly susceptible people and delayed effects on less compromised individuals (2 and 3 day lags were not significant). EPA estimates, based on this result, in a single pollutant model, a 25 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 3.5 percent increase in total mortality both on the current day and four days after exposure (95% CI=0.5-6.3 percent). Inclusion of O_3 and NO_2 in a three-pollutant model somewhat increased the estimated $PM_{2.5}$ effect: 4.2 percent (95% CI= 0.6-7.9). A 10 ppb increase in the mean of 1 and 2 day lagged O_3 was associated with a 1.8 percent increase in cardiovascular disease.

In the $PM_{2.5}$ - infant mortality analysis, excess infant mortality was associated with $PM_{2.5}$, but also with NO_2, and O_3 in the same lag pattern (3 to 5 day lag). NO_2, and O_3 associations were less consistent in multi-pollutant models. The RR calculated for infant mortality per 10 $\mu g/m^3$

increase in $PM_{2.5}$ (average of 3 to 5 day lags) was 6.9% (2.5, 11.3). In three pollutant models, it was 6.3% (-0.5, 13.2).

These Mexico City studies collectively suggest significant mortality associations with PM indices, but there are some notable differences. In the TSP analyses, the authors found "no independent effect of O_3", while in the $PM_{2.5}$ study, the O_3-cardiovascular mortality association remained significant in two and three pollutant models. This may be, in part, due to the smaller number of sample days available for multi-pollutant models in the TSP analysis (n=211 days, compared to n>800 days for $PM_{2.5}$ analysis). The weaker associations for gaseous pollutants in these studies may also be partly explained by poorer spatial uniformity for gaseous pollutants, as the spatial correlation reported in the TSP analysis indicate better site-to-site correlation for TSP ($r \sim 0.85$) than for gaseous pollutants ($r \sim 0.5$).

Northeastern United States/Eastern Canada: Summer Haze and Automobile

Toronto, Ontario and Buffalo, NY are relatively close in distance and both experience the same regional summer haze pollution, which contains O_3 and acid aerosols/sulfate. The studies from these two locales will be discussed and contrasted in the following paragraphs.

Toronto, Ontario. The main focus of the Burnett et al. (1998) study was on CO effects on mortality in metropolitan Toronto during 1980-1994, but their analysis also considered NO_2, O_3, SO_2, TSP, CoH, $SO_4^=$, and estimated PM_{10} and $PM_{2.5.}$ After adjusting for day-of-week, nonparametric smooth function of day of study, and weather variables, all of these pollutants, except O_3, were significantly positively associated with nonaccidental mortality in one pollutant models. In two pollutant models with CO as co-pollutant, these pollutants' coefficients, as well as CO's, were reduced, although all PM indices' coefficients remained significant. The correlation between CO and other pollutants ranged from -0.23 (O_3) to 0.56 (CoH), but the smallest positive correlation was with TSP (0.19). CO and TSP were selected for inclusion in the final model using the stepwise procedures. In the two pollutant model with TSP and CO, the excess risk for TSP was 1.5% (0.2, 2.8) per 88$\mu g/m^3$ increase (5^{th} to 95^{th} percentile range). The authors mention that the vast majority (86%) of emissions for CO in Toronto are from vehicular sources, while only a small fraction of TSP (21%) was attributed to vehicles. Thus, air pollution from vehicular sources, CO in particular, was suggested as a cause of increased mortality in this

locale. This is consistent with the results from earlier Özkaynak et al. (1996) analysis of Toronto data 1970-1991 (discussed in Section 6.3.2.9).

While various PM indices were considered in this analysis, PM_{10} and $PM_{2.5}$ were available only every-6th-day during 1984-1990 (total of 272 days during the 15 year study period). Since the missing PM_{10} and $PM_{2.5}$ values were imputed using daily values of TSP sulfates (which may suffer from artifact due to the TSP glass fiber filter), TSP, and CoH, it is difficult to compare the estimated PM_{10} and $PM_{2.5}$ effects with those of other PM components. However, in the unimputed data, sulfates were strong predictors of $PM_{2.5}$ (R^2=0.77), and TSP was a weak predictor of $PM_{2.5}$ (R^2=0.22), a moderate predictor of PM_{10} (R^2=0.50), and a stronger predictor of $PM_{10-2.5}$ (R^2=0.63). Thus, the estimated PM_{10} and $PM_{2.5}$ may have adequately represented daily fluctuations of the thoracic and fine components. The RRs for these estimated PM_{10} and $PM_{2.5}$ were significant in single pollutant models and with CO in the model.

Buffalo, NY. Gwynn et al. (1998) analyzed a two and a half year record of daily H^+ and $SO_4^=$ measurements collected in the Buffalo, NY region. Their analysis of respiratory, circulatory, and total daily mortality and hospital admissions also considered PM_{10}, CoH, O_3, CO, SO_2, and NO_2. Poisson and negative binomial regression models were employed, adjusting for seasonality, weather, and day-of-week. For total mortality, all the PM components were significantly associated, with H^+ being the most significant and CoH the least significant predictors. The gaseous pollutants were mostly weakly associated with total mortality. The effect size estimated for respiratory mortality with inter-quartile-ranges of these PM components were 2 to 3 times larger than those for total mortality (except CoH), but were less significant due to the large standard error of coefficients (from the small daily counts). Parallel analyses of hospital admission and mortality data in this study allowed an examination of "coherence", or the consistency check for causality suggested by Bates (1992). Gwynn et al. noted that H^+, $SO_4^=$, and O_3 showed the most coherent associations with respiratory hospital admissions and respiratory mortality (RRs for respiratory mortality, H^+: RR=1.55 per 346 nanomole/m^3, 95% CI=1.16-2.07; $SO_4^=$: RR=1.24 per 329 nanomoles/m^3, 95% CI=1.05-1.47; O_3: RR=1.16 per 61 ppb daily average, 95% CI=1.02-1.33, calculated for maximum - mean increment), lending support to the theory of a "summer haze effect" (Bates and Sizto, 1987).

The Toronto results (Burnett et al., 1998) suggest the importance of motor vehicle related primary pollutants, although all the PM components were significant predictors of mortality in both single and two pollutant models. The secondary regional pollutant, O_3 (which was the only pollutant that was negatively correlated with CO), was not associated with mortality in Toronto. In contrast, in Buffalo, it was secondary "summer haze mix", O_3, $SO_4^{=}$, and H^+, that showed the most "coherent" effects in mortality and morbidity. Automobile related primary pollutants, CO, CoH, and NO_2 were not as strongly associated with mortality as the "summer haze mix" in Buffalo. Since Buffalo and Toronto are geographically close, the levels of "summer haze mix" were relatively comparable. One possible reason for the apparent discrepancy between the results from these two cities may be explained by the relative contributions of the primary (automobile) pollution and the regional summer haze mix. In fact, the daily average CO level in Toronto (1.2 ppm) was 70% higher than that in Buffalo (0.7 ppm). Also, another primary vehicle-related pollutant, CoH, was twice as high in Toronto as in Buffalo (0.42 vs. 0.2, respectively, 1,000 linear feet). It is also possible that the relative spatial representativeness of sites for primary pollutants used in these cities may have been different. Measurements of primary pollutants are likely more influenced by strong local source impact than the regional secondary pollutants, and therefore, the location of monitor is more crucial.

In studies where multiple PM components were examined, in most cases, all the PM components were significantly associated with mortality. Unless mutually exclusive size fractionated PM components (i.e., $PM_{2.5}$ vs. $PM_{10-2.5}$) are examined, as in Schwartz et al. (1996) 6 city time-series analysis, establishing size dependency of PM effects remains difficult.

Examination of the role of acid aerosols on mortality in the U.S. has been difficult partly because the number of days available for acid aerosol measurements were smaller than that for other PM components, as was the case for the six city time-series data. Gwynn et al. (1999) analysis of Buffalo data used comparable sample sizes for all PM components, and their results are suggestive of the role of acidic particles, but distinguishing the individual pollutant effects of the "summer haze mix" was not possible. These results suggest that, while it is difficult to identify "responsible" PM components, identification of a group of pollutants that represents a certain source type or pollution mix is useful.

New Studies on Crustal Particle Effects

In the 1996 AQCD, the only study that analyzed both fine and coarse particles (Schwartz et al., 1996) at that time suggested that fine particles ($PM_{2.5}$), but not coarse particles ($PM_{10-2.5}$) were associated with daily mortality. Since then, a few studies investigated the effects of coarse particles, as identified as crustal wind-blown particles, or crustal particles within fine particles.

Schwartz et al. (1999) investigated the association of coarse particle concentrations with non-accidental deaths in Spokane, Washington, where dust storms elevate coarse particle concentration. During the 1990-1997 period, 17 dust storm days were identified. The average PM_{10} levels during those storms were 263 $\mu g/m^3$, compared to 39 $\mu g/m^3$ for the entire period. The coarse particle domination of PM_{10} data on those dust storm days was confirmed by a separate measurement of PM_{10} and PM_1 during a dust storm in August, 1996: the PM_{10} level was 187 $\mu g/m^3$, while PM_1 level was only 9.5 $\mu g/m^3$. The deaths on the day of a dust storm were contrasted with deaths on control days (n=95 days in the main analysis and 171 days in the sensitivity analysis), which are defined as the same day of the year in other years when dust storms did not occur. The relative risk for dust storm exposure was estimated using Poisson regressions, adjusting for temperature, dewpoint, and day of the week. Various sensitivity analyses considering different seasonal adjustment, year effects, and lags, were conducted. The expected relative risk for these storm days with an increment of 221 $\mu g/m^3$ would be about 1.20, based on PM_{10} relative risk from past studies, but the estimated RR for high PM_{10} days was 1.00 (95% CI=0.81-1.22). Schwartz et al. concluded that there was no evidence to suggest that coarse particles in the Spokane summer dust storms were associated with daily mortality.

Pope et al. (1999b) investigated PM_{10}-mortality associations in three metropolitan areas (Ogden, Salt Lake City, and Provo/Orem) in Utah's Wasatch Front mountain region during 1985-1995 period. While the three metropolitan areas shared common weather pattern, pollution levels and patterns among the three areas were different due to different emission sources. They ingeniously utilized the index of air stagnation, a clearing index (the National Weather Service computes this index from temperature, moisture and wind), to identify and screen obvious windblown dust days, as clearly identified as high PM_{10} days on the days with low air stagnation index. They found that Salt Lake City experienced substantially more episodes of wind-blown dusts. They therefore conducted Poisson regression of mortality series using both unscreened and screened PM_{10} data. The effects of screening was most apparent in Salt Lake City results.

After screening, the RRs per 10 $\mu g/m^3$ increase in PM_{10} for mortality in three metropolitan areas were 1.6% (0.3 - 2.9), 0.8% (0.3 - 1.3), and 1.0% (0.2 - 1.8) for Ogden, Salt Lake City, and Provo/Orem, respectively. These results suggest that the pollution episodes of wind-blown (crustal-derived) dusts were less associated with mortality than were the episodes of (presumably) combustion-related particles.

Laden et al. (1999) analyzed the Harvard Six-Cities data to investigate the role of crustal particles in fine particles on daily mortality. The elemental abundance data (from X-ray fluorescence spectroscopy analysis of daily filters) were analyzed to estimate the concentration of crustal particles using factor analysis. Then, they estimated city-specific association of mortality with fine crustal mass using Poisson regression (regressing mortality on factor scores for "crustal factor"), adjusting for time trends and weather. They found no associations between fine crustal mass factor and mortality. Details could not be reviewed because this was an abstract.

These results suggest that crustal particles (coarse or fine) are not associated with daily mortality in these cities.

6.3.2.5 New Assessments of Confounding

Assessment of Co-Pollutant Confounding

As discussed above, the issue of potential confounding by weather was extensively examined in two studies as reviewed in the 1996 AQCD, and was considered essentially resolved. Therefore, discussion of confounding in this section is focused on potential confounding among pollutants. Evaluating the extent of confounding of multiple pollution effects in time-series studies can be complicated by differences in model specification (e.g., choice of lags). The following example of Philadelphia analyses conducted by two groups illustrates the complexity of this issue.

Moolgavkar and Luebeck (1996) speculated that many of the past PM-mortality studies suffered from "serious" deficiencies in their control of the confounding effects of other pollutants. As a consequence, they argued, the small risks reported to be associated with the particulate component of air pollution could be attributed to residual confounding by co-pollutants. They conducted a new analysis of mortality in Philadelphia (1973-1988) that considered four pollutants simultaneously, as well as seasonal effects, to illustrate this point. Their findings are qualitatively similar to Samet et al. (1996) (or Kelsall et al. [1997], which

presented essentially the same results) in which the Philadelphia data for the study period 1974-1988 were analyzed also by season and with simultaneous inclusion of multiple pollutants. The Samet et al. (1996) study (Kelsall et al., 1997) was extensively discussed in the 1996 PM CD (Section 12.6), and therefore will be discussed only in comparison to Moolgavkar-Luebeck results here. Both studies reported that pollution effects varied by season, and TSP coefficients diminished when other pollutants were simultaneously included.

The notable differences in findings between Samet's group and Moolgavkar-Luebeck included: (1) NO_2 in Samet et al.'s study was mostly negatively associated (except summer) with mortality, while in Moolgavkar-Luebeck study, NO_2 was mostly positively associated (except winter); (2) O_3 in Samet et al.'s study was positively associated with mortality across seasons (weakest in the summer), while in Moolgavkar-Luebeck study, O_3 was positively associated with mortality only in the summer. The difference may have been due to the absence of CO in Moolgavkar-Luebeck analysis, or the difference in the optimum lags chosen for pollutants (in Samet et al. study, concurrent day levels were used for all the pollutants except CO; in Moolgavkar-Luebeck study, one-day lag was used for all pollutants except NO_2). Thus, there are some differences between the two groups of investigator's results from essentially the same data. Moolgavkar-Luebeck concluded that "..it is not possible with the present evidence to show a convincing correlation between particulate air pollution and mortality", while Samet's group concluded "...These analyses confirm the association between TSP and mortality found in previous studies in Philadelphia and the association is robust to consideration of other pollutants".

Analyses of one city's data by different researchers may produce conflicting results, but these discrepancies can in part result from instability of regression coefficients due to collinearity of co-pollutants, as well as model specification choice. The collinearity problem may be further complicated by different seasonal patterns of concentrations for each pollutant, including differential changes in distribution shape for each pollution, changes in temporal correlations for each pollutant, and changes in the matrix of correlations of pollutants with each other (and with weather variables) across season. PM indices can contain both primary and secondary particles, whose seasonal patterns may vary from city to city. There may be regional, local city-to-city, or even within city difference in the relative impact of source types. The issue of relative exposure

error among co-pollutants, which further complicates the confounding problem, is discussed in the measurement error section.

Thus, an evaluation of apparently inconsistent results from a city or a few cities analyzed using different model specifications, without quantitative information on city specific characteristics, is unlikely to yield useful information to resolve the issue of confounding. By analyzing multiple cities' data, a more consistent pattern may emerge, although difference in approach may still result in inconsistent multi-city results by different researchers. Thus, a more definitive discussion of confounding by co-pollutants awaits a large multi-city studies (e.g., Samet's 100 city study) that are underway and expected to produce results soon.

Simulation Analysis of Confounding. Since no single model specification can be "correct" in addressing confounding effects of co-pollutants, discrepancies in results among studies, even for the same data set, are expected. While any assessment of relative "adequateness" of these alternative model specifications is difficult with observational data, the implication of "inadequate" model specifications may be studied through simulations using synthetic data in which the "correct" model is known. Chen et al. (1999) conducted such simulations using synthetic data set in which the causal variables are known, and the effects of model misspecifcation were studied in the presence of two variables (x_1 and x_2), with varying level of correlation, in a Poisson model. They considered three situations: (1) *model underfit,* in which mortality was generated with both x_1 and x_2, but regressed only on x_1; (2) *model overfit*, in which mortality was generated with only x_1, but regressed on both x_1 and $x_{2;}$ (3) *model misfit*, in which mortality was generated with either x_1 or x_2 but regressed on the other variable. They observed that the confounding of covariates in an overfitted model does not bias the estimated coefficients but reduces their significance; and that the effect of model underfit or misfit leads to not only erroneous estimated coefficients but also erroneous significance. Chen et al. (1999), based on these observations, suggested that "models which use only one or two air quality variables, such as PM_{10} and SO_2, are probably unreliable, and that model containing several correlated and toxic or potentially toxic air quality variables should also be investigated...". While conceptually useful, this simulation study ignored one factor that is crucial in evaluating the implication of confounding, the relative error. For example, including several correlated pollutants in regression model may lead to erroneous inference unless one considers the relative

error associated with each of the pollutants. Several simulation studies that considered such relative errors are discussed in Section 6.4.6.4.

Alternative Approaches to Deal with Confounding and Address Source-Type Specific Effects: Use of Factor Analysis

In time-series analyses of the acute effects of PM, the usual approach to deal with gaseous co-pollutantss is to treat them as confounders and to simply include them simultaneously in regression models. There has even been a suggestion, as mentioned above, based on a simulation analysis of synthetic data, that "several" correlated pollutants should be included in regression models (Chen et al., 1999). This prevailing approach can not only lead to misleading conclusions in "identifying" a specific : "causal" pollutant (e.g., when pollutants have a varying extent of exposure error), but also ignores the potential combined effects of PM and gaseous co-pollutants (e.g., when PM adsorbs SO_2 and carries it deeper in the airways, as shown by Amdur and Chen, 1989).

Another potential problem of the simultaneous inclusion of PM and gaseous pollutants is that the gaseous pollutant in question may be coming from the same source, or the PM constituent may be derived from the gaseous pollutants. For example, SO_2 can be converted to sulfate, which is a PM constituent. Since a *confounder* cannot be an intermediate step in the causal pathway (Rothman and Greenland, 1998), strictly speaking, SO_2 does not qualify as a confounder of PM, except in a situation where the PM is known to be solely of secondary origin (transported aerosols), and SO_2 is solely from local origin. Furthermore, any reduction in emission of a gaseous pollutant may also result in reducing the level of PM. In such a case, the inference drawn from the results of simultaneous regression may be misleading, because the relative risk for PM is based on the assumption that the covariates could be kept unchanged while the PM level changes.

Alternative approaches are needed to address the above noted weakness in the general practice of effect estimation using simple simultaneous regressions. There have been a few alternative approaches tried in recent years to estimate the effects of air pollution. For example, Özkaynak et al. (1996) analyzed 21 years of mortality and air pollution data in Toronto, Canada. In addition to the usual simultaneous inclusion of multiple pollutants in mortality regression, they also conducted a factor analysis of all the air pollution and weather variables including TSP, SO_2,

Coefficient-of-Haze (CoH), NO_2, O_3, CO, relative humidity and temperature. The factor with the largest variance contribution (~50%) had the highest factor loadings for CO, CoH, and NO_2, which they considered as representative of motor vehicle emissions, since this pollution grouping was also consistent with the emission inventory information for that city. They then regressed mortality on the factor scores (a linear combination of standardized scores for the covariates), after filtering out seasonal cycles and adjusting for temperature and day-of-week effects. The estimated excess mortality from motor vehicle pollution ranged from 1 to 6%, depending on the outcomes.

Another recent example of the application of factor analysis is an analysis of the Harvard Six-Cities data to investigate the role of crustal particles in fine particles on daily mortality (Laden et al., 1999). They used elemental abundance data (obtained from X-ray fluorescence spectroscopy analysis of daily filters) to estimate the concentration of crustal particles using factor analysis. Then, they estimated city-specific association of mortality with fine crustal mass by Poisson regression, adjusting for time trends and weather. They found no associations between fine crustal mass factor and mortality.

Daisey et al. (1999) conducted an exploratory analysis of mortality in relation to specific PM source types for three New Jersey cities (Camden, Newark, and Elizabeth) using factor analysis - Poisson regression technique. During the three year study period (1981-1983), extensive chemical speciation data were available including nine trace elements, sulfate, particulate organic matter. Total (excluding accidents and homicides), cardiovascular and respiratory mortality were analyzed. Daisey et al. first conducted a factor analysis of trace elements and sulfate, identifying major source types: automobile (Pb, CO); geological (Mn, Fe); oil burning (V, Ni); industrial (Zn, Cu); and sulfate/secondary aerosols (sulfate). In addition to Poisson regression of mortality on these factors, they also used an alternative approach in which the inhalable particle mass (IPM, $D_{50} < 15\ \mu m$) was first regressed on the factor scores of each of the source types to apportion the PM mass, then the estimated daily PM mass for each source type was included in Poisson regression, so that RR could be calculated per mass concentration basis for each PM source types. They found that oil burning (V, Ni), various industrial sources (Zn, Cd), motor vehicle (Pb, CO), and the secondary aerosols as well as individual PM indices IPM, FPM ($D_{50} < 3.5\ \mu m$), and sulfates were associated with total and/or cardio-respiratory

mortality in Newark and Camden, but not in Elizabeth. In Camden, the RRs for the source-oriented PM were higher (~ 1.10) than those for individual PM indices (~1.02).

Factor analyses have been routinely used in air pollution source apportionment field, but its application to short-term health effects analyses is relatively new. It may be a useful alternative approach for a source-oriented evaluation of the combined effects of fine particles and gaseous co-pollutants. The advantages of the use of factor analysis approach include: (1) it allows an examination of association between a health outcome and a group(s) of pollutants that vary together (due to the same source type); (2) use of independent or orthogonal factors or components in a regression model may allow much more stable estimates of the effects of groups of pollutants that occur together; (3) it may reduce inflated uncertainty on effect size estimates associated with including individual highly correlated pollution variables. The potential drawback of the factor analysis approach is that the resulting factor that may represent a source-type well may not necessarily have the variation that is relevant for the health outcome. There are also additional issues in interpreting the results from the analyses that utilize factor analysis, including the "interpretability" of resulting factors as derived from a common source, and technical issues such as the choice of rotation of factors. While potentially useful, some issues still need to be investigated.

6.3.2.6 New Assessments of Cause-Specific Mortality

In most of the new studies that examined nonaccidental total, circulatory, and respiratory mortality categories (Borja-Aburto et al., 1997; Wordley et al., 1997; Borja-Aburto et al., 1998; Gwynn et al., 1998; Ostro et al., 1998; Prescott et al., 1998), estimated PM effects were generally higher for respiratory deaths than for circulatory or total deaths, consistent with the same findings in the 1996 PM CD.

Evaluation of the cause-specificity of various pollution and weather variables' mortality associations may be helpful in checking consistency with criteria for causality. A review of the newly available studies and previous studies do not necessarily provide consistent patterns of cause specificity that can distinguish one pollutant from others. For example, in Toronto analysis by Burnett et al. (1998), they reported that, although the estimated CO RR was higher for cardiac death category, "a clear positive association" was also observed for non-cardiac categories. However, since the presumed mechanism for CO (i.e., binding to carboxyhemoglobin) may result

in impaired oxygen delivery to the peripheral tissues, leading to other complications that may not be necessarily cardiac, the apparent lack of cause-specificity for CO in this case may not be easily interpreted as confounded associations.

Seeking unique cause-specificity of various pollutants has been also difficult because the "cause specific" categories examined are rather broad (usually cardiovascular and respiratory), and overlap or co-existence of cardiovascular and respiratory conditions is expected. Examinations of more specific cardiovascular and respiratory sub-categories may be necessary to test hypotheses on any specific mechanism, but smaller sample sizes for more specific sub-categories may make a meaningful analysis difficult. The study by Rossi et al. (1999), however, examined associations between TSP and detailed cardio-vascular and respiratory cause-specific mortality in Milan, Italy for years 1980-1989. They found a significant association for respiratory infections (11% increase per 100 $\mu g/m^3$ increase in TSP; 95%CI: 5, 17) and for heart failure (7%; 95%CI: 3, 11), both on the same day TSP. The associations with myocardial infarction (10%; 95%CI: 3, 18) and COPD (12%; 95%CI: 6, 17) were found for the average of 3 and 4 day TSP levels. They noted the difference in lags between temperature effects (i.e., cold temperature at lag 1 day for respiratory infections; hot temperature at lag 0 for heart failure and myocardial infarction) and air pollution (TSP) effects. The immediate hot temperature effects and the lagged cold temperature effects for total and cardiovascular mortality have been reported in many of the past studies (e.g., Philadelphia, Chicago), but investigations of the differences in lags of PM effects for specific cardiovascular or respiratory categories have rarely been conducted in time-series mortality studies.

Some of recent PM studies did examine more specific type of deaths, such as intrauterine mortality (Pereira et al., 1998) and post neonatal mortality (Woodruff et al., 1997; Bobak and Leon, 1998). In the case of intrauterine mortality, PM_{10} was not a significant predictor, but CO's association was supported by the association between increased carboxyhemoglobin in fetal blood and ambient CO levels on the day of delivery measured in a separate study. The Woodruff et al. study used logistic regressions (adjusting for demographic and environmental factors) to examine relationship between exposure to PM_{10} in the first two month of life and the chance of dying from specific causes of death between 1 month and 1 year of age using cohort data of about 4 million infants. They found associations between PM_{10} and deaths from respiratory causes, as well as sudden infant death syndrome. Bobak and Leon (1998) also reported associations

between air pollution (TSP, NO_2, SO_2) and respiratory causes for post neonatal period using a matched case-control study design. While these are not time-series studies, the presumed exposure-effect period is not "long-term". These and other study design may be potentially useful to investigate more specific cause or type of deaths that are difficult to analyze in time-series study design.

6.3.2.7 New Assessment of Methodological Issues

Methodological issues in time-series analyses of air pollution-mortality association were discussed extensively in the 1996 AQCD. Since then, increasing numbers of researchers have been utilizing essentially the same Poisson regression approach: (1) model seasonal cycles and other temporal trends using smoothing functions of time; (2) model weather effects using smoothing functions of temperature, humidity, and/or their interaction at various lags; (3) after adjustment for these confounding factors, enter various lags (and averaging periods) of air pollutant, and report results for all the lags, and/or report results for the lags that resulted in the highest significance; (4) repeat (3) with other pollutants in the model; (5) conduct sensitivity analyses using alternative weather model specifications. Seasonal cycles and weather effects are often modeled using Generalized Additive Models (GAM). As the modeling temporal trends became more efficient using the GAM models, it became clearer that the residual over-dispersion and autocorrelation can be essentially eliminated. Also, more researchers appear to rely on Akaike's Information Criteria (AIC) or on the more conservative Bayes (Schwarz) Information Criterion (BIC) to choose between models when epidemiological reasoning does not favor one over the other. Similar estimates may be obtained by other techniques, such as the Liang-Zeger Generalized estimating Equation (GEE) method described in (Samet et al., 1995) that deals with autocorrelated time series. While these techniques do not necessarily eliminate inadequate model specifications, they do help "standardize" the approaches that researchers can take, reducing the inconsistency in model specification among studies.

Differences in results among investigators using the same or similar data sets are more likely to be associated with other differences in model-building strategy, not with statistical methodology. These often include: (1) choice of the range of lags and averaging periods of pollution included; (2) smoothing spans used for modeling temporal trends and weather effects; (3) the increment used to calculate relative risks; and, (4) choice to detrend pollution variables.

The choice of lag can lead to inconsistent results even for the same data. The choice of the combination of lags multiply as the number of co-pollutants in the model increases. In the case of temperature effects, it has been repeatedly observed that the heat effects tend to be immediate (0 or 1 day lag), while cold effects tend to lag longer (2 to 4 days). For air pollutants, however, reported lags are less consistent.

The smoothing span for temporal trends can be determined based on epidemiological reasons (for example, to eliminate influenza epidemics) or to optimize goodness of fit using AIC or BIC criteria. The effects of temporal smoothing choices on the estimated effect size of pollution variables may be substantial, but is not reported by many investigators. The span for weather effects is usually determined through data exploration. Characterizing PM and co-pollutant effect size by RR across the inter-quartile range for all the co-pollutants may be problematic when co-pollutants have inconsistent distributional properties, such as different within-season ranges and between-season ranges. While these issues may appear rather minor, in practice, they appear to make substantial differences in reported effects and interpretations.

6.3.2.8 Summary of Newly Available Information

- Since the 1996 PM AQCD, thus far, there have been more than 30 new time-series PM-mortality analyses, several of which investigated multiple cities using consistent data analytical approaches. PM relative risks estimated for daily mortality in these studies are generally positive, statistically significant, and consistent with the previously reported PM-mortality associations. However, several studies also showed significant associations between mortality and gaseous pollutants, such as CO and O_3. Since a large number of studies, including U.S. multi-city studies, are expected to be published in the next several months, a quantitative summary of PM and other pollutants' effects will not be attempted at this time.
- The multi-city study conducted in European cities showed generally consistent associations between mortality and both SO_2 and PM indices in western European cities, but not in central and eastern European cities. The pooled estimate of PM_{10} - mortality relative risks calculated for western European cities were roughly comparable to the estimates from US data. The contrast between western and central eastern Europe results was speculated to be due to:

difference in exposure representativeness, difference in pollution toxicity or mix, difference in proportion of sensitive sub-population, or climate.

- Several new studies are available regarding the role of size and chemistry in PM-mortality associations. In Santa Clara County, CA, $PM_{2.5}$, as well as nitrate, were significantly associated with mortality. The studies conducted in US and Canadian cities also showed mortality associations with specific fine particle components of PM including H^+, $SO_4^=$, as well as $PM_{2.5}$. CoH, which likely reflects motor vehicle related carbon particles, was significantly associated with mortality in Toronto, Canada, where its level is relatively high, but not in Buffalo, NY, where its level was lower (50% of that in Toronto). Seeking the effects of a group of source types, rather than any individual component, may be useful for inferring causes of adverse health effects. An association between $PM_{2.5}$ and mortality was also reported in Mexico City. Several studies that investigated the role of crustal and coarse particles suggest that crustal particles, coarse or fine, are unlikely to be associated with mortality.
- A few studies conducted simulation analyses of effects of measurement errors on the estimated PM mortality effects. These studies suggest that PM effects are more likely underestimated than overestimated, and that spurious PM effects (i.e., qualitative bias such as change in the sign of the coefficient) due to transferring of effects from other covariates require extreme conditions, and are therefore unlikely. The error due to the difference between the average personal exposure and the ambient level are likely the major source of bias in estimated relative risk. One study also suggested that apparent linear exposure-response curves are unlikely to be artifacts of measurement error.
- Newly available simulation and empirical analyses suggest that the extent of harvesting, if it exists, is not in the short-term (i.e., ~ 3 days) range. These new results, combined with the results from a few past studies, suggest that the PM-mortality risk estimates are not heavily influenced by displacement of mortality in the very short-term period. More analyses are needed to replicate these findings in order to evaluate whether they apply to other cities than Philadelphia and Boston.
- An increasing number of studies have considered co-pollutants in their analyses. While PM indices remained significant in most of these multi-pollutant analyses, the relative significance of mortality associations among co-pollutants varied from study to study. Several studies

suggested that the relative significance of mortality associations may be partly explained by differences in the spatial representativeness of the monitors from which the exposure-related data were derived. The apparent difference among cities may also be explained by the difference in relative impact of source types (e.g., regional pollutants vs more local automobile related pollution). More systematic and quantitative evaluation of these factors using multi-city data could explain the apparent discrepancy in individual study results.

6.3.3 Human Mortality and Long-Term Exposure to PM of Ambient Origin

6.3.3.1 Studies Published Prior to the 1996 Particulate Matter Criteria Document

Aggregate Population Cross-Sectional Chronic Exposure Studies

Mortality effects associated with chronic, long-term exposure to particulate matter (PM) air pollution of outdoor origins have been assessed in cross-sectional studies and, more recently, in prospective cohort studies. A number of older cross-sectional studies from the 1970s provided indications of increased mortality associated with chronic (annual average) exposures to ambient PM, especially with respect to fine mass or sulfate ($SO_4^{=}$) concentrations. However, questions unresolved at that time regarding the adequacy of statistical adjustments for other potentially important covariates (e.g., cigarette smoking, economic status, etc.) across cities tended to limit the degree of confidence that was placed by the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996) on such purely "ecological" studies or on quantitative estimates of PM effects derived from these studies. Evidence comparing the toxicities of specific PM components was relatively limited. The sulfate and acid components had already been discussed in detail in the previous PM AQCD (U.S. Environmental Protection Agency, 1986).

Lippmann (1989) hypothesized that the acidic portion of the fine particle aerosol (i.e., H^+) was an important contributor to the adverse health effects of PM. Özkaynak and Thurston (1987) applied source apportionment methods to the IP Network data, finding that fine particles from coal combustion and from the metals industry were more important contributors to the PM-mortality association than other PM mass contributors (e.g., soil particles). Lipfert (1984) examined the 1980 U.S. mortality-PM data set using much more heavily specified models, finding that $PM_{2.5}$ was the strongest particulate variable in linear models (with Mn, a possible tracer for metals industry emissions, also approaching significance).

Semi-Individual (Prospective Cohort) Chronic Exposure Studies

Semi-individual cohort studies have used subject-specific information about relevant covariates (such as cigarette smoking, occupation, etc.), providing more certain findings of long-term PM exposure effects than past purely "ecological studies" (Künzli and Tager, 1997). At the same time, these better designed cohort studies have largely confirmed the magnitude of the effect estimates from past cross-sectional study results, renewing interest and confidence in their findings.

Prospective cohort semi-individual studies of mortality associated with chronic exposures to air pollution of outdoor origins have yielded especially valuable insights into the adverse health effects of long-term PM exposures. The extensive Harvard 6-Cities Study (Dockery et al., 1993) and the American Cancer Society (ACS) Study (Pope et al., 1995) agreed in their findings of statistically significant positive associations between fine particles and excess mortality, although the ACS study did not evaluate the possible contributions of other air pollutants. Neither study considered multi-pollutant models, although the 6-City study did examine various gaseous and particulate matter pollutants (including total particles, $PM_{2.5}$, $SO_4^=$ H^+ SO_2, and ozone), finding that sulfate and $PM_{2.5}$ fine particles were best associated with mortality. The RR estimates for total mortality in the 6-Cities study (and 95 percent confidence intervals, CI) per increments in PM indicator levels were: RR=1.42 (CI=1.16-2.01) for 50 $\mu g/m^3$ PM_{10}, RR=1.31 (CI=1.11-1.68) for 25 $\mu g/m^3$ $PM_{2.5}$, and RR=1.46 (CI=1.16-2.16) for 15 $\mu g/m^3$ $SO_4^=$. The estimates for total mortality derived from the ACS study were RR=1.17 (CI=1.09-1.26) for 25 $\mu g/m^3$ $PM_{2.5}$, and 1.11 (CI=1.06-1.16) for 15 $\mu g/m^3$ $SO_4^=$. The ACS pollutant RR estimates are smaller than those from the 6-Cities study, although their 95% continence intervals overlap. In some cases in these studies, the life-long cumulative exposure of the study cohorts included distinctly higher past PM exposures, especially in the cities with historically higher PM concentrations such as Steubenville, OH; but more current PM measurements were used to estimate the chronic PM exposures. In the ACS study, the pollutant exposure estimates were based upon concentrations at the start of the study (during 1979-1983. Also, the average age of the ACS cohort was 56, which could overestimate the pollutant RR estimates, and might underestimate the life-shortening associated with PM associated mortality. Thus, while caution must be exercised regarding the use of the reported quantitative risk estimates, the 6-Cities and

ACS semi-individual studies provided consistent evidence of a significant mortality association with long-term exposure to PM of ambient origins.

In contrast to the 6-Cities and ACS studies, early results from the Adventist Health Study on Smog (AHSMOG) of California nonsmokers by Abbey et al. (1991) and Abbey et al. (1995) found no significant mortality effects of previous PM exposure in a relatively young cohort. However, these analyses used TSP as the PM exposure metric, rather than more health relevant PM metrics such as PM_{10} or $PM_{2.5}$, included fewer subjects than the ACS study, and considered a shorter follow-up time than the 6-Cities study (ten years vs. 15 years for the 6-Cities study). Moreover, the AHSMOG study included only non-smokers, who the 6-cities studies indicate to have lower pollutant RR's than smokers, suggesting that a longer follow-up time than considered in the past (10 years) might be required to have sufficient power to detect significant pollution effects than is required in studies that include smokers, such as the 6-Cities and ACS studies. Thus, to date, greater emphasis has been placed on the 6-Cities and ACS studies.

Overall, these past chronic exposure studies collectively indicate that there are increases in mortality that are associated with long-term exposure to airborne particles of ambient origins. These estimates of long-term PM exposure effect size for total mortality (e.g., RR=1.17 for 25 $\mu g/m^3$ $PM_{2.5}$ from the ACS study) are much larger than those reported from daily mortality PM studies (e.g., multi-study pooled RR=1.044 per 50 $\mu g/m^3$ PM_{10}, from Schwartz, 1997). Thus, even the upper limit estimate of the long-term implications of the reported daily mortality effects (i.e., assuming that they are fully additive over time) falls well below the chronic exposure study mortality effect estimates. This suggests that a major fraction of the reported mortality relative risk estimates associated with chronic PM exposure reflect cumulative PM impacts above and beyond those that could be exerted by the sum of acute exposure events.

The 1996 PM AQCD reached several conclusions concerning four key questions about the prospective cohort studies. Relevant sections from Ch. 12 (pp. 180-182) of the 1996 document are quoted directly:

1. Have potentially important confounding variables been omitted?

"While it is not likely that the prospective cohort studies have overlooked plausible confounding factors that can account for the large effects attributed to air pollution, there may be some further adjustments in the estimated magnitude of these effects as individual and

community risk factors are included in the analyses." These include individual variables such as education, occupational exposure to dust and fumes, and physical activity, as well as ecological (community) variables such as regional location, migration, and income distribution. Further refinement of the effects of smoking status may also prove useful.

2. Can the most important pollutant species be identified?

"The issue of confounding with co-pollutants has not been resolved for the prospective cohort studies. ... Analytical strategies that could have allowed greater separation of air pollutant effects have not yet been applied to the prospective cohort studies." The ability to separate the effects of different pollutants, each measured as a long-term average on a community basis, was clearly most limited in the Six Cities study. The ACS study offered a much larger number of cities, but did not examine differences attributable to the (spatial and temporal) differences in the mix of particles and gaseous pollutants across the cities. The AHSMOG study constructed time- and location-dependent pollution metrics for most of its subjects that might have allowed such analyses, but no results were reported, then or subsequently.

3. Can the time scales for long-term exposure effects be evaluated?

"Careful review of the published studies indicated a lack of attention to this issue. Long-term mortality studies have the potential to infer temporal relationships based on characterization of changes in pollution levels over time." This potential was greater in the Six Cities and AHSMOG studies because of the greater length of the historical air pollution data for the cohort.

4. Is it possible to identify pollutant thresholds that might be helpful in health assessments?

"Model specification searches for thresholds have not been reported for prospective cohort studies." The time scale of an air pollution exposure metric for which a threshold is being sought is a key element in a model specification search.

"The chronic exposure studies, taken together, suggest that there may be increases in mortality in disease categories that are consistent with long-term exposure to airborne particles, and that at least some fraction of these deaths are likely to occur between acute exposure

episodes. If this interpretation is correct, then at least some individuals may experience some years of reduction of life as a consequence of PM exposure." (P 12-368).

Many of these issues remain unresolved at this time. Extensive reanalyses of the Six Cities and ACS studies are underway to evaluate these questions, under the sponsorship of the Health Effects Institute. Preliminary public presentations (Health Effects Institute, 1999) suggest that the published findings of the original investigators (Dockery et al., 1993; Pope et al., 1995) are based on substantially valid data sets and statistical analyses, and that small corrections in input data have very little effect on the findings. Additional investigations to evaluate the effects of alternative model specifications are in progress, and may be available in time for the final draft of this document.

Recently published analyses of the AHSMOG study (Abbey et al., 1999; Beeson et al., 1998) considerably extend the earlier findings of the investigators, and also show some differences from earlier studies. Of particular interest are their findings in relation to lung cancer. These are discussed below in some detail. Additional studies suggest possible effects of sub-chronic PM exposures on infant mortality (Woodruff et al., 1997; Bobak and Leon, 1998), and these are also included below in this discussion of long-term PM exposure effects on mortality.

6.3.3.2 Prospective Cohort Studies of Chronic Exposure Published Since the Last Particulate Matter Criteria Document

Abbey et al. (1999)

The Adventist Health Study of Smog (AHSMOG) enrolled 6,338 non-smoking non-Hispanic white Seventh Day Adventist residents of California, ages 27 to 95 years, in 1977. The participants had resided for at least 10 years within 5 miles (8 km) of their then-current residence locations. Subjects lived either within the 3 major California air basins (San Diego, Los Angeles, or San Francisco), or else were part of a random 10% sample of Adventist Health Study participants in the rest of California. The study has been extensively described elsewhere (Hodgkin et al., 1984; Abbey et al., 1991; Mills et al., 1991). Mortality status of the subjects after ca. 15-years of follow-up (1977-1992) was determined by a variety of tracing methods, finding 1,628 deaths (989 female, 639 male) in the cohort. There were 1,575 deaths from all natural (non-external) causes, of which 1,029 were cardiopulmonary deaths, 135 were

non-malignant respiratory deaths (ICD9 codes 460-529), and 30 were lung cancer deaths (ICD9 code 162). Abbey et al. also created an additional death category, contributing respiratory causes (CRC). CRC included any mention of nonmalignant respiratory death as either an underlying cause or a contributing cause on the death certificate coded by an exposure-blinded nosologist (the other groups listed only underlying causes), with 410 deaths (246 female and 164 male). A large number of analyses were done for the CRC category, due to the large numbers and relative specificity of respiratory causes as a factor in the deaths.

Education was used as an index of socio-economic status, rather than income. Physical activity and occupational exposure to dust were also used as covariates. Migration is not a major concern in this residentially stable cohort.

A number of exposure indicators were used: mean values of PM_{10} (imputed from TSP in the earlier years of the study), $SO_4^=$, SO_2, O_3, and NO_2; and "threshold" indicators, days per year with $PM_{10} > 100$ $\mu g/m^3$, and hours per year with $O_3 > 100$ ppb. The "standard" increments used for PM_{10} and SO_4 in these tables are the same as described above for the short-term mortality studies, 50 $\mu g/m^3$ for PM_{10} and 15 $\mu g/m^3$ for SO_4, and 30 days per year for exceedances of PM_{10} above 100 $\mu g/m^3$. The mean values for PM_{10} and SO_4 during the study period were 51 and 7.2 $\mu g/m^3$ respectively, and 31 days per year for PM_{10} exceedances over 100 $\mu g/m^3$. The means were much larger than the inter-quartile ranges (IQR) of 24 and 3.0 $\mu g/m^3$. IQR is the increment used for other variables. RR and confidence limits using IQR from (Abbey et al., 1999) are shown to 2 decimal places, those estimated for standard increments are shown to 3 decimal places.

Cox proportional hazard models adjusted for a variety of covariates, or stratified by sex, were used in the models. The "time" variable used in most of the models was survival time from date of enrollment, except that age on study was used for lung cancer effects due to the expected lack of short-term effects. A large number of covariate adjustments were evaluated, as shown in Table 6-25 and described by Abbey et al. (1999).

The CRC estimates of RR from 30 days per year with $PM_{10} > 100$ $\mu g/m^3$ for males and females combined are shown in Table-25. Positive and statistically significant effects are found for almost all models that include age, pack-years of smoking, and body-mass index (BMI) categories as covariates. Subsets of the cohort also often had elevated risks. Former smokers had higher relative risks than never-smokers (RR for PM_{10} exceedances for never-smokers was

TABLE 6-25. RELATIVE RISK OF MORTALITY FROM CONTRIBUTING NON-MALIGNANT RESPIRATORY CAUSES, FOR 30 DAYS PER YEAR WITH $PM_{10} > 100\ \mu g/m^3$

PM Covariate Model	RR	RR LCL	RR UCL
BASE (age, sex)	1.069	0.978	1.168
BASE + pack-years	1.096	1.000	1.201
BASE + pack-years + body-mass-index cats.	1.122	1.022	1.233
BASE + pack-years + body-mass-index cats.+ exercise cats.	1.122	1.017	1.239
STANDARD (age, pack-y., y. lived with smoker, occup., educ., BMI)	1.122	1.017	1.239
STANDARD w. PM_{10} (100) over last 4 years only	1.102	1.001	1.214
STANDARD, subset for former smokers	1.155	0.937	1.424
STANDARD, subset for never smokers	1.116	0.999	1.246
STANDARD, subset for low anti-oxidant vitamin intake	1.175	1.008	1.370
STANDARD, subset for high anti-oxidant vitamin intake	1.055	0.917	1.214
STANDARD, subset for < 4 h/wk outdoors	1.048	0.896	1.227
STANDARD, subset for 4-16 h/wk outdoors	1.122	0.928	1.358
STANDARD, subset for 16+ h/wk outdoors	1.207	1.015	1.436
STANDARD, subset for reported respiratory symptoms	1.321	1.079	1.616

Source: Abbey et al. (1999).

marginally significant by itself, in spite of the reduced sample size). Subjects with low intake of anti-oxidant vitamins A, C, E had significantly elevated risk of response to PM_{10} whereas those with adequate intake did not, suggesting that dietary factors (or possibly other socio-economic or life style factors for which they are a surrogate) may be important covariates in other studies.

There also appears to be a gradient of PM_{10} risk with respect to time spent outdoors, with individuals who had spent at least 16 hours per week outside at distinctly elevated risk from PM_{10} exceedances. The extent to which time spent outdoors is a surrogate for other variables or is a modifying factor reflecting temporal variation in exposure to ambient air pollution is not certain. For example, males spend about twice as much time outdoors as females, so that outdoor exposure time is confounded with gender.

A considerably different picture is shown when the analyses are broken down by gender. Table 6-26 shows much lower RR for female CRC deaths for all co-pollutants, with all female RR positive, but not statistically significant. The CRC for males remains significant only for PM_{10} exceedances, but not for other air pollution metrics. The PM_{10} exceedance effect for CRC for both sexes is roughly the average of that for males and females.

TABLE 6-26. RELATIVE RISK OF MORTALITY FROM CONTRIBUTING NON-MALIGNANT RESPIRATORY CAUSES, BY SEX AND AIR POLLUTANT, WITH ALTERNATIVE COVARIATE MODEL

Pollution Index	Pollution Incr.	Females			Males		
		RR	RR LCL	RR UCL	RR	RR LCL	RR UCL
PM_{10}>100, d/yr	30 days/yr	1.069	0.936	1.220	1.188	1.030	1.370
PM_{10} mean	50 $\mu g/m^3$	1.219	0.739	2.011	1.537	0.879	2.688
SO_4 mean	15 $\mu g/m^3$	1.105	0.396	3.086	1.219	0.411	3.619
O_3>100 ppb, h/yr	551 h/yr (IQR)	1.01	0.77	1.33	1.20	0.88	1.64

Source: Abbey et al. (1999).

Personal monitoring was not conducted on this part of the cohort, and other factors such as occupational exposure for which the questionnaire was not adequate may also account for male vs. female differences, along with gender differences in the amount of time spent outdoors. Finally, it is not surprising that individuals reporting respiratory symptoms in 1977 may be at greater risk to PM_{10} or other environmental insults presumably involved in subsequent CRC deaths, and prior health status may also be gender-related.

Table 6-27 shows much lower RR for female non-external deaths for all co-pollutants, with no female RR positive nor statistically significant. Deaths from non-external causes for males remains statistically significant for PM_{10} exceedances, but not for other air pollution metrics. However, the RR estimates for males for other air pollutant metrics are relatively large.

Table 6-28 shows much lower RR for female cardio-pulmonary deaths for all co-pollutants, with only the female RR for mean SO_2 positive and none statistically significant. Deaths from

TABLE 6-27. RELATIVE RISK OF MORTALITY FROM ALL NON-EXTERNAL CAUSES, BY SEX AND AIR POLLUTANT, FOR AN ALTERNATIVE COVARIATE MODEL

		Females			Males		
Pollution Index	Pollution Incr.	RR	RR LCL	RR UCL	RR	RR LCL	RR UCL
PM_{10}>100, d/yr	30 days/yr	0.958	0.899	1.021	1.082	1.008	1.162
PM_{10} mean	50 $\mu g/m^3$	0.879	0.713	1.085	1.242	0.955	1.616
SO_4 mean	15 $\mu g/m^3$	0.732	0.484	1.105	1.279	0.774	2.116
O_3>100 ppb, h/yr	551 h/yr (IQR)	0.90	0.80	1.02	1.140	0.98	1.32
SO_2 mean	3.72 (IQR)	1.00	0.91	1.10	1.05	0.94	1.18

Source: Abbey et al. (1999).

TABLE 6-28. RELATIVE RISK OF MORTALITY FROM CARDIOPULMONARY CAUSES, BY SEX AND AIR POLLUTANT, FOR AN ALTERNATIVE COVARIATE MODEL

		Females			Males		
Pollution Index	Pollution Incr.	RR	RR LCL	RR UCL	RR	RR LCL	RR UCL
PM_{10}>100, d/yr	30 days/yr	0.929	0.857	1.007	1.062	0.971	1.162
PM_{10} mean	50 $\mu g/m^3$	0.841	0.639	1.107	1.219	0.862	1.616
SO_4 mean	15 $\mu g/m^3$	0.857	0.498	1.475	1.279	0.002	1018
O_3>100 ppb, h/yr	551 h/yr (IQR)	0.88	0.76	1.02	1.06	0.87	1.29
O_3 mean	10 ppb	0.975	0.865	1.099	1.066	0.920	1.236
SO_2 mean	3.72 (IQR)	1.02	0.90	1.15	1.01	0.86	1.18

Source: Abbey et al. (1999).

cardiopulmonary causes for males is no longer statistically significant for PM_{10} exceedances, nor for other air pollution metrics. However, the RR estimates for males for air pollutant metrics are relatively large.

Table 6-29 shows lower RR for female lung cancer deaths for all co-pollutants, but some female RR are positive and statistically significant: mean NO_2, mean SO_2 for all women and for

TABLE 6-29. RELATIVE RISK OF MORTALITY FROM LUNG CANCER, BY SEX AND AIR POLLUTANT, FOR AN ALTERNATIVE COVARIATE MODEL

			Females			Males		
Pollution Index	Pollution Incr.	Smoking Category	RR	RR LCL	RR UCL	RR	RR LCL	RR UCL
PM_{10}>100, d/yr	30 days/yr	All[1]	1.055	0.657	1.695	1.831	1.281	2.617
PM_{10} mean	50 $\mu g/m^3$	All	1.808	0.343	9.519	12.385	2.552	60.107
NO_2 mean	19.78 (IQR)	All	2.81	1.15	6.89	1.82	0.93	3.57
O_3>100 ppb, h/yr	551 h/yr (IQR)	All	1.39	0.53	3.67	4.19	1.81	9.69
		never smoker				6.94	1.12	43.08
		past smoker				4.25	1.50	12.07
O_3 mean	10 ppb	All	0.805	0.436	1.486	1.853	0.994	3.453
SO_2 mean	3.72 (IQR)	All	3.01	1.88	4.84	1.99	1.24	3.20
		never smokers	2.99	1.66	5.40			

Source: Abbey et al. (1999).

Note 1: All = both never smokers and past smokers.

female never-smokers. Deaths from lung cancer for males remains statistically significant for all air pollution metrics except mean NO_2, and is nearly significant for mean O_3. The RR estimates for males for all air pollutant metrics are relatively large. However, the confidence intervals are wide, due to the small numbers of lung cancer deaths (18 for females and 12 for males).

Lung cancer effects are significant for males for PM_{10} and O_3 metrics, but not for females. Lung cancer metrics for mean SO_2 are significant for both males and females. Lung cancer deaths are significant for mean NO_2 for females, but not for males. This pattern is not readily interpretable but may be attributable to the small numbers of deaths.

The CRC effects identified in this study are significant when both females and males are included, but not when female and male subjects are analyzed separately, except for male subjects with PM_{10} exceeding 100 $\mu g/m^3$. The effects of PM_{10} exceeding 100 $\mu g/m^3$ on mortality from all non-external causes are also statistically significant for males, but not for other air pollutants, and not for females. Separate analyses by gender may be more appropriate in order to

maintain the assumption of "proportional hazards" necessary for the validity of Cox method of analysis.

In general, this study suggests a pattern of mortality from diverse causes in males, but provides little evidence for female mortality from these causes. The male causes are primarily associated with exposures to PM_{10}, especially $PM_{10} > 100$ $\mu g/m^3$. Other air pollutants are associated with lung cancer deaths in females as well as males.

The analyses reported here attempted to separate PM_{10} effects from those of the other pollutants by use of two-pollutant models, but none of the quantitative findings from these models were reported. The text mentions that the PM_{10} coefficient for CRC remained stable or increased when other pollutants were added to the model. Lung cancer models for males were evaluated for co-pollutant effects in detail. NO_2 remained nonsignificant in all two-pollutant models, and the other pollutant coefficients were stable in magnitude. The PM_{10} and O_3 effects remained stable when SO_2 was added, suggesting that their effects are independent. However, the effects of PM_{10} and O_3 were hard to separate because these pollutants were highly correlated in this study. When both exceedances $PM_{10} > 100$ $\mu g/m^3$ and $O_3 > 100$ ppb were used in the model, both RR were reduced in magnitude, but the O_3 exceedance RR remained more significant than the RR for the PM_{10} exceedance. The possibility that the finding of a significant PM_{10} effect is partially attributable to correlation with other pollutants such as O_3 cannot be completely precluded. The finding of an O_3 effect on lung cancer is not readily explained, and the finding of a PM_{10} effect on lung cancer (consistent with the ACS and Six Cities studies) is more plausible.

The SO_2 coefficient for lung cancer in females remained stable in two-pollutant models when PM_{10} and O_3 exceedances were included. This suggests that the significance of the SO_2 effect for females may not be an artifact attributable to collinearity with these co-pollutants.

Beeson et al. (1998)

This study uses essentially the same data as in (Abbey et al., 1999), but concentrates on lung cancer incidence (1977-1992) as an endpoint. There were only 20 female cases and 16 male cases of lung cancer among the 6,338 subjects. The exposure metrics were constructed to be specifically relevant to cancer, being the annual average of the monthly exposure indices from January, 1973, through the following months, but ending 3 years before the date of diagnosis of

the case. This allows a 3-year lag between exposure and diagnosis of lung cancer, allowing for a latency period. Therefore, statistical indices for exposure have somewhat different statistics than in (Abbey et al., 1999), such as the IQR and mean. In spite of improved treatment of lung cancer over the last decades, this disease still has a rather pessimistic prognosis compared to other diagnoses of long-term mortality, so is discussed along with the mortality analyses.

The covariates in the Cox proportional hazards model were pack-years of smoking and education, and the time variable was attained age. A number of additional covariates were evaluated for inclusion in the model, but only 'current use of alcohol' met the criteria for inclusion in the final model. Individual pollutants evaluated were PM_{10}, SO_2, NO_2, and O_3. No interaction terms with the pollutants proved to be significant, including outdoor exposure times. Gender-specific relative risk estimates were reported for the various risk factors.

Results are shown in Table 6-30 for males and Table 6-31 for females. Standard increments were used for PM_{10} mean (50 $\mu g/m^3$) and exceedances of PM_{10} > 100 $\mu g/m^3$ (30 d/y). RR and confidence limits using IQR from (Beeson et al., 1998) are shown to 2 decimal places, those estimated for standard increments are shown to 3 decimal places.

The male RR for lung cancer are positive and are statistically significant for all PM_{10} indicators. Male RR reported are positive and predominantly significant for O_3 indicators, except for mean O_3, number of O_3 exceedances > 60 ppb, and in former smokers. Reported RR for mean SO_2 are positive and significant except when restricted to proximate monitors. RR for mean NO_2 is positive but not significant.

The very high RR for mean PM_{10} for males (31.1) may be attributable to the small number of cases (N = 16) and the large standard increment (50 $\mu g/m^3$) used. When data are restricted to subjects with at least 80 percent A/B quality data (within 32 km of the residence), the RR is reduced to 9.26 over 50 $\mu g/m^3$. The RR over the IQR of 24 $\mu g/m^3$ in the full data set is 5.21, so that the use of the IQR may be more appropriate for the exposure in long-term studies. The female RR reported are much smaller, not being statistically significant for any indicator of PM_{10} or O_3, and statistically significant only for mean SO_2.

Extensive multi-pollutant analyses were carried out, but the results are not described in detail. Regression coefficients for PM_{10} and SO_2 were not reduced when O_3 or NO_2 were added to the single-pollutant models for males. The regression coefficients for the two-pollutant model with PM_{10} and SO_2 remained highly positive and significant, which the authors suggest may be

TABLE 6-30. RELATIVE RISK OF LUNG CANCER INCIDENCE IN MALES, BY AIR POLLUTANT, FOR ADVENTIST HEALTH STUDY

Pollution Index	Pollution Incr.	Covariate Model or Sub-Group	RR	RR LCL	RR UCL
PM_{10}>40 $\mu g/m^3$	139 d/y (IQR)	standard	4.50	1.31	15.44
PM_{10}>50 $\mu g/m^3$	149 d/y (IQR)	standard	4.96	1.54	16.00
PM_{10}>60 $\mu g/m^3$	132 d/y (IQR)	standard	4.72	1.69	13.18
PM_{10}>80 $\mu g/m^3$	78 d/y (IQR)	standard	3.43	1.71	6.88
PM_{10}>100 $\mu g/m^3$	30 d/y	standard	2.127	1.454	3.112
PM_{10} mean	50 $\mu g/m^3$	standard	31.147	3.978	243.85
SO_2 mean	3.7 ppb	standard	2.66	1.62	4.39
NO_2 mean	2.0 ppb	standard	1.45	0.67	3.14
O_3>60 ppb	935 h/y	standard	2.14	0.82	5.62
O_3>80 ppb	756 h/y	standard	2.96	1.09	8.04
O_3>100 ppb	556 h/y	standard	3.56	1.35	9.42
O_3>120 ppb	367 h/y	standard	3.75	1.55	9.90
O_3>150 ppb	185 h/y	standard	3.61	1.78	7.35
O_3 mean	2.1 ppb	standard	2.23	0.79	6.34
PM_{10}>100 $\mu g/m^3$	30 d/y	never smokers	2.102	1.325	3.335
O_3>100 ppb	556 h/y	never smokers	4.48	1.25	16.04
O_3>100 ppb	556 h/y	past smokers	2.15	0.42	10.89
PM_{10}>100 $\mu g/m^3$	30 d/y	high population density	2.865	1.794	4.574
O_3>100 ppb	556 h/y	high population density	10.18	2.44	42.45
SO_2 mean	3.7 ppb	high population density	3.22	1.87	5.54
PM_{10} mean	50 $\mu g/m^3$	> 80% data from monitors within 20 miles of residence	9.256	1.135	75.516
SO_2 mean	3.7 ppb	> 80% data from monitors within 20 miles of residence	2.18	0.92	5.20

Source: Beeson et al. (1998).

TABLE 6-31. RELATIVE RISK OF LUNG CANCER INCIDENCE IN FEMALES, BY AIR POLLUTANT, FOR ADVENTIST HEALTH STUDY

Pollution Index	Pollution Incr.	Covariate Model or Sub-Group	RR	RR LCL	RR UCL
PM_{10}>50 $\mu g/m^3$	149 d/y (IQR)	standard	1.21	0.55	2.66
PM_{10}>60 $\mu g/m^3$	132 d/y (IQR)	standard	1.25	0.57	2.71
SO_2 mean	3.7 ppb	standard	2.14	1.36	3.37
O_3>100 ppb	556 h/y	standard	0.94	0.41	2.16
PM_{10}>100 $\mu g/m^3$	30 d/y	high population density	1.089	0.726	1.633
SO_2 mean	3.7 ppb	high population density	2.11	1.32	3.38
PM_{10} mean	50 $\mu g/m^3$	> 80% data from monitors within 20 miles	2.425	0.310	19.004
SO_2 mean	3.7 ppb	> 80% data from monitors within 20 miles	2.52	1.19	5.33

Source: Beeson et al. (1998).

associated with independent effects of PM_{10} and SO_2 on lung cancer incidence. PM_{10} was more strongly correlated with lung cancer in males than the other pollutants. For females, the SO_2 coefficient remained significant when co-pollutants were added one at a time, and was the air pollutant most strongly associated with lung cancer in females.

Relationship to Earlier AHSMOG Studies

The results of the preceding two studies are somewhat different than those of earlier studies using the same cohort. Abbey et al. (1991) reported completely non-significant relationships between total ('all natural causes') mortality and air pollution. The RR for 1000 h/y of TSP > 200 $\mu g/m^3$ was 0.99 (CI 0.87-1.13), and for 500 h/y of O_3 > 100 ppb was 1.00 (CI 0.89-1.12), after 10 years of follow-up.

Abbey et al. (1991) report no statistically significant increases in all malignant neoplasms for males attributable to air pollution. The RR for 1000 h/y of TSP > 200 $\mu g/m^3$ was 0.96 (CI 0.68-1.36), and for 500 h/y of O3 > 100 ppb was 1.09 (CI 0.80-1.47), after 10 years of follow-up. However, there was a statistically significant increase in all malignant neoplasms in females. The RR for females attributed to 1000 h/y of TSP > 200 $\mu g/m^3$ was 1.37 (CI 1.05-1.80).

Neoplasms in females attributed to 500 h/y > 100 ppb were much less significant with RR = 1.03 (CI 0.81-1.32).

There were only 17 cases of respiratory cancer in this study, so while the estimated RR were large (1.72 for TSP and 2.25 for O_3), the confidence intervals were also very wide (CI 0.81-3.65 for TSP and 0.96-5.31 for O_3 effects). Findings of significant effects of TSP on respiratory symptoms but not lung cancer may be attributed to the longer latency time of cancers. Additional results reported by Mills et al. (1991) further elaborated on site-specific cancers among females, but only breast cancers (RR = 1.51) and 'other' cancers (RR = 1.65) showed a marginal relationship (P = 0.10) to TSP exceedances in the 10-year follow-up. These results are also summarized in (Abbey et al., 1995).

6.3.3.3 Relationship of AHSMOG to Six Cities and ACS Study Findings

The results of the recent AHSMOG mortality studies (Abbey et al., 1999) are compared with the earlier Six Cities study (Dockery et al., 1993) and ACS study (Pope et al., 1995) to a greater level of detail than in the 1996 PM AQCD. Tables 6-32, 6-33, and 6-34 compare the estimated RR for total, cardiopulmonary, and lung cancer mortality respectively among the studies. The PM indices used are the mean PM_{10} concentration for the Six Cities and AHSMOG studies (increment 50 $\mu g/m^3$), and the mean $PM_{2.5}$ and SO_4 concentrations (increments 25 and 15 $\mu g/m^3$ respectively) for the ACS study. The comparisons for the Six Cities and ACS studies have been translated from published RR for the most polluted vs. least polluted city for PM_{10}, $PM_{2.5}$, and SO_4. Results are shown by sex and smoking status. The AHSMOG subjects are classified as 'non-smokers', although some former smokers are included. The ACS study combines past and current smokers into an 'ever smoker' category, although long-term past smokers are at much lower risk than current smokers (U.S. Department of Health and Human Services, 1990). The number of subjects in these studies varies greatly, partially accounting for differences 8,111 subjects in the Six Cities study, compared to 295,223 subjects in the 50 fine particle cities and 552,138 subjects in the 151 sulfate cities of the ACS study.

Table 6-32 shows relative risks for total mortality at comparable standard increments. RR is generally highest for the Six Cities study. The AHSMOG study found a much smaller RR for women than did the other studies, whereas the effect for males was similar to non-smokers in the ACS study and marginally significant. RR among the three studies varied substantially with

TABLE 6-32. RELATIVE RISK (RR) OF TOTAL MORTALITY IN THREE PROSPECTIVE COHORT STUDIES, BY SEX AND SMOKING STATUS

Sex	Smoking Status	Study	PM Index	PM Inc.	RR	RR LCL	RR UCL
F	NON-SMOKER	Six Cities	PM_{10}	50	1.280	0.704	2.345
		ACS	$PM_{2.5}$	25	1.215	1.020	1.440
			SO_4	15	1.147	1.045	1.261
		AHSMOG	PM_{10}	50	0.879	0.713	1.085
	PAST	Six Cities	PM_{10}	50	1.999	0.704	5.632
	PAST + CURRENT	ACS	$PM_{2.5}$	25	1.102	0.898	1.338
			SO_4	15	1.104	0.977	1.240
	CURRENT	Six Cities	PM_{10}	50	1.442	0.719	3.166
M	NON-SMOKER	Six Cities	PM_{10}	50	1.568	0.674	3.678
		ACS	$PM_{2.5}$	25	1.245	1.000	1.554
			SO_4	15	1.104	0.977	1.247
		AHSMOG	PM_{10}	50	1.242	0.955	1.616
	PAST	Six Cities	PM_{10}	50	1.611	0.930	2.825
	PAST + CURRENT	ACS	$PM_{2.5}$	25	1.164	1.051	1.297
			SO_4	15	1.104	1.037	1.176
	CURRENT	Six Cities	PM_{10}	50	1.858	1.090	3.166

Sources: Dockery et al. (1993); Pope et al. (1995); Abbey et al. (1999).

sex and smoking categories. Six of the 16 independent analyses showed significant positive RR (LCL $\geq$ 1.0), but subsetting the data allowed less power to detect effects than the whole data sets would have allowed. Neither of the AHSMOG RR were significant using the mean as the PM_{10} index, but another PM_{10} index (exceedances over 100 $\mu g/m^3$) was significant for males.

Table 6-33 shows relative risks for cardiopulmonary mortality at comparable standard increments. RR is highest for the Six Cities study, which did not report separate effects by sex and smoking status. The AHSMOG study found a much smaller cardiopulmonary RR for

TABLE 6-33. RELATIVE RISK (RR) OF CARDIOPULMONARY MORTALITY IN THREE PROSPECTIVE COHORT STUDIES, BY SEX AND SMOKING STATUS

Sex	Smoking Status	Study	PM Index	PM Inc.	RR	RR LCL	RR UCL
F	NON-SMOKERS	ACS	$PM_{2.5}$	25	1.585	1.235	2.039
			SO_4	15	1.316	1.147	1.518
		AHSMOG	PM_{10}	50	0.841	0.639	1.107
		AHSMOG - CRC	PM_{10}	50	1.219	0.739	2.011
	PAST + CURRENT	ACS	$PM_{2.5}$	25	1.276	0.918	1.760
			SO_4	15	1.219	1.008	1.465
M	NON-SMOKERS	ACS	$PM_{2.5}$	25	1.245	0.929	1.668
			SO_4	15	1.205	1.023	1.412
		AHSMOG	PM_{10}	50	1.219	0.862	1.616
		AHSMOG - CRC	PM_{10}	50	1.537	0.879	2.688
	PAST + CURRENT	ACS	$PM_{2.5}$	25	1.235	1.061	1.440
			SO_4	15	1.126	1.037	1.233
F+M	ALL	Six Cities	PM_{10}	50	1.744	1.202	2.501

Sources: Dockery et al. (1993); Pope et al. (1995); Abbey et al. (1999).

women than did the other studies. However, the RR for male non-smokers was much more similar to the ACS studies than for female non-smokers. RR for the AHSMOG endpoint CRC ('contributing respiratory causes') was more similar to the ACS findings for women, but higher in men, although the confidence intervals are very wide. Seven of 13 of the independent analyses showed significant positive RR (LCL $\geq$ 1.0). The AHSMOG cardiopulmonary RR using mean PM_{10} were not significant. However, the 100 $\mu g/m^3$ exceedance index for males was nearly so.

Table 6-34 shows relative risks for lung cancer mortality at comparable standard increments. RR was highest for males in the AHSMOG study, and statistically significant. The AHSMOG study also found a larger RR for women than did the other studies. The only other

TABLE 6-34. RELATIVE RISK (RR) OF LUNG CANCER MORTALITY IN THREE PROSPECTIVE COHORT STUDIES, BY SEX AND SMOKING STATUS

Sex	Smoking Status	Study	PM Index	PM Inc.	RR	RR LCL	RR UCL
F	NON-SMOKERS	ACS	$PM_{2.5}$	25	0.644	0.203	2.091
			SO_4	15	1.432	0.731	2.800
		AHSMOG	PM_{10}	50	1.808	0.343	9.519
	PAST + CURRENT	ACS	$PM_{2.5}$	25	0.949	0.563	1.595
			SO_4	15	1.074	0.781	1.479
M	NON-SMOKERS	ACS	$PM_{2.5}$	25	0.483	0.086	2.714
			SO_4	15	1.261	0.501	3.190
		AHSMOG	PM_{10}	50	12.385	2.552	60.107
	PAST + CURRENT	ACS	$PM_{2.5}$	25	1.123	0.827	1.533
			SO_4	15	1.316	1.104	1.577
F+M	ALL	Six Cities	PM_{10}	50	1.744	0.689	4.390
		ACS	$PM_{2.5}$	25	1.031	0.796	1.338
			SO_4	15	1.261	1.082	1.465

Sources: Dockery et al. (1993); Pope et al. (1995); Abbey et al. (1999).

significant finding for lung cancer was in past and current male smokers in the ACS 151-city sulfate study. This pattern is in some contrast with the findings of the other studies, and merits further analysis.

There is no obvious statistically significant relationship between PM effect sizes, gender, and smoking status across these studies. The AHSMOG studies show no statistically significant relationships between PM_{10} and total mortality or cardiovascular mortality for either sex, and only for male lung cancer incidence and lung cancer deaths in a predominantly non-smoking sample. The ACS results, in contrast, show similar and significant associations with total mortality for both "never smokers" and "ever smokers", although the ACS cohort may include a substantial number of long-term former smokers with much lower risk than current smokers.

The Six Cities study cohort shows the strongest evidence of a higher PM effect in current smokers than in non-smokers, with female former smokers having a higher risk than male former smokers. This study suggests that smoking status may be viewed as an "effect modifier" for ambient PM, just as smoking may be a health effect modifier for ambient ozone (Cassino et al., 1999).

In summary, the recent AHSMOG studies find positive but non-significant excesses of total and cardiopulmonary mortality associated with mean PM_{10} exposure in males, but not in females. The male RR in AHSMOG are similar to those in male non-smokers in the ACS study. There is a large and statistically significant RR for lung cancer in males in the AHSMOG cohort, which is much larger than in the other studies. While all of these studies find some associations with mean PM_{10} or $PM_{2.5}$, there are differences among specific endpoints and subgroups that remain to be resolved.

It is interesting to note, in relation to the above discussion, that a comparison of the 6-Cities Study non-smoker RRs with the 6-Cities results in Table 6-32 for smokers indicates that larger and more significant effects of ambient PM pollution are found for smokers than non-smokers. This suggests that smoking is an effect modifier that increases the adverse effects of ambient pollution. This trend is consistent with air pollution effect causality, as smokers represent a compromised population, logically more likely to be adversely affected by air pollution. This may also explain why the reported AHSMOG study RRs are generally not significant, in contrast with the overall 6-Cities study (but consistent with the 6-Cities nonsmoker results), as there are no identified smokers among the AHSMOG study group to "drive up" the overall significance of the air pollution effect. This again indicates that more years of follow-up may be required to see any statistically significant total mortality effects in both the AHSMOG and 6-Cities studies' non-smoking populations.

When the ACS study results are compared with the AHSMOG study results for $SO_4^=$ (as PM_{10} was not considered in the ACS study), the total mortality effect sizes per 15 $\mu g/m^3$ $SO_4^=$ for the males in the AHSMOG population are seen to fall between the 6-Cities and the ACS effect estimates for males: RR=1.28 for AHSMOG male participants; RR=1.61 for 6-Cities Study male non-smokers, and; RR=1.10 for never smoker males in the ACS study. The AHSMOG study 95% confidence intervals encompass both of those other studies' sulfate RRs.

6.3.3.4 Population-Based Mortality Studies in Children

The older cross-sectional mortality studies suggest that the very young may represent an especially susceptible sub-population. Lave and Seskin (1977) found mortality among those 0-14 years of age to be significantly associated with TSP. More recently, Bobak and Leon (1992) studied neonatal (ages less than one month) and post-neonatal mortality (ages 1-12 months) in the Czech Republic, finding significant and robust associations between post-neonatal mortality and PM_{10}, even after considering other pollutants. Post-neonatal respiratory mortality showed highly significant associations for all pollutants considered, but only PM_{10} remained significant in simultaneous regressions. The exposure duration was longer than a few days, but shorter than in the adult prospective cohort studies. Thus, the limited available studies reviewed in the last PM Criteria documented were highly suggestive of an association between ambient PM concentrations and infant mortality, especially among post-neonatal infants.

Since the 1996 PM AQCD, Woodruff et al. (1997) used cross-sectional methods to follow-up on the reported post-neonatal mortality association with ambient PM_{10} pollution in a U.S. population. This study involved an analysis of a cohort consisting of approximately 4 million infants born between 1989 and 1991 in 86 metropolitan statistical areas (MSAs). Data from the National Center for Health Statistics-linked birth/infant death records were combined at the MSA level with measurements of PM_{10} from the EPA's Aerometric data base. Infants were categorized as having high, medium, or low exposures based on tertiles of PM_{10} averaged over the first 2 postnatal months. Total and cause-specific postneonatal mortality rates were examined using logistic regression to control for demographic and environmental factors. Overall postneonatal mortality rates per 1,000 live births were 3.1 among infants with low PM_{10} exposures, 3.5 among infants with medium PM_{10} exposures, and 3.7 among highly exposed infants. After adjustment for other covariates, the odds ratio (OR) and 95% confidence intervals for total postneonatal mortality for the high exposure versus the low exposure group was 1.10 (CI=1.04-1.16). In normal birth weight infants, high PM_{10} exposure was associated with mortality for respiratory causes (OR = 1.40, CI=1.05-1.85) and sudden infant death syndrome (OR = 1.26, CI=1.14-1.39). Among low birth weight babies, high PM_{10} exposure was associated, but not significantly, with mortality from respiratory causes (OR = 1.18, CI=0.86-1.61). However, other pollutants, such as O_3, were not considered as possible confounders. This study confirms past study results indicating that outdoor PM air pollution is associated with risk of

postneonatal mortality (e.g., Bobak and Leon, 1992), but the lack of consideration of other air pollutants in this new study reduces the certainty that PM is the specific causal outdoor air pollutant in this case.

6.3.3.5 Studies by Particulate Matter Size-Fraction and Composition

Particulate matter mass varies widely over time and from place to place in composition, and this should affect the toxicity of that mass. Unfortunately, only a limited number of the chronic exposure studies have included direct measurements of the chemical-specific constituents of the PM mass.

The semi-individual studies also investigated the relative roles of various PM components in the air pollution association with mortality. As shown in Table 6-35, the Harvard 6-Cities study (Dockery et al., 1993) results indicated that the $PM_{2.5}$ and $SO_4^=$ RR associations (as indicated by their respective 95% CI's and t-statistics) were stronger than those for the coarser mass components. However, the effects of sulfate and non-sulfate $PM_{2.5}$ are indicated to be quite similar. Acid aerosol (H^+) exposure was also considered by Dockery et al. (1993), but only less than one year of measurements collected near the end of the follow-up period were available in most cities, so the 6-Cities results were much less conclusive for the acidic component of PM than for these other PM metrics (that, in contrast, were measured over many years during the study). The 6-Cities study also yielded total mortality RR estimates for the reported range across those cities of $PM_{2.5}$ and $SO_4^=$ concentrations that, although not statistically different, were roughly double the analogous RR's for the TSP-PM_{15} and $PM_{15-2.5}$ mass components.

Table 6-36 presents comparative $PM_{2.5}$ and $SO_4^=$ results from the ACS study that indicate that, although the RR differences were not statistically significant across pollutants, the $SO_4^=$ RRs were in every case more strongly significant than those for the $PM_{2.5}$ across the various mortality cause classifications considered, especially for lung cancer ($SO_4^=$ t=2.92 vs. t=0.38 for $PM_{2.5}$).

The most recent AHSMOG study analysis (Abbey et al., 1999) employed PM_{10} as its PM mass index, finding significant associations with total and by-cause mortality, even after controlling for potentially confounding factors (including other pollutants). This analysis also considered $SO_4^=$ as a PM index for all health outcomes studied except lung cancer, but $SO_4^=$ was not as strongly associated as PM_{10} with mortality, and was not found to be statistically significant

TABLE 6-35. COMPARISON OF ESTIMATED RELATIVE RISKS FOR ALL-CAUSE MORTALITY IN SIX U.S. CITIES ASSOCIATED WITH THE REPORTED INTER-CITY RANGE OF CONCENTRATIONS OF VARIOUS PM METRICS (Dockery et al., 1993; U.S. Environmental Protection Agency, 1996)

PM Species	Concentration Range ($\mu g/m^3$)	Relative Risk Estimate	RR 95% CI	Relative Risk t-Statistic
SO_4=	8.5	1.29	(1.06-1.56)	3.67
$PM_{2.5}$ - SO_4=	8.4	1.24	(1.16-1.32)	8.79
$PM_{2.5}$	18.6	1.27	(1.06-1.51)	3.73
$PM_{15-2.5}$	9.7	1.19	(0.91-1.55)	1.81
TSP-PM_{15}	27.5	1.12	(0.88-1.43)	1.31

TABLE 6-36. COMPARISON OF REPORTED $SO_4^=$ AND $PM_{2.5}$ RELATIVE RISKS FOR VARIOUS MORTALITY CAUSES IN THE ACS STUDY (POPE et al., 1995)

Mortality Cause	$SO_4^=$ (Range = 19.9 $\mu g/m^3$)			$PM_{2.5}$ (Range = 24.5 $\mu g/m^3$)		
	Relative Risk	RR 95% CI	RR t-Statistic	Relative Risk	RR 95% CI	RR t-Statistic
All Cause	1.15	(1.09-1.22)	4.85	1.17	(1.09-1.26)	4.24
Cardiopulmonary	1.26	(1.15-1.37)	5.18	1.31	(1.17-1.46)	4.79
Lung Cancer	1.35	(1.11-1.66)	2.92	1.03	(0.80-1.33)	0.38

for any mortality category. The significant mortality associations found for PM_{10} contrasts with previously published AHSMOG study PM analyses that found weaker mortality associations with TSP (Abbey et al., 1991). Although the longer follow-up time in this new analysis may have also contributed, the greater strength of association by PM_{10} vs. TSP is consistent with the Harvard Six-City study results presented in Table 6-35, as well as with the Özkaynak and Thurston (1987) cross-sectional comparisons of mortality associations with the various PM fractions.

Overall, the semi-individual studies conducted to-date collectively confirm the cross-sectional study indications that, as opposed to the more coarse mass fractions, the fine mass component of PM (and sometimes including its acidic sulfate constituent) are strongly correlated with mortality.

6.3.3.6 Shortening-of-Life Associated With Long-Term Exposure to Particulate Matter of Ambient Origins

The public health burden of mortality associated with exposure to ambient PM depends not only on the increased risk of death, but also on the length of life shortening that is attributable to those deaths. However, the 1996 PM AQCD concluded that confident qualitative determination of years of life lost to ambient PM exposure is not yet possible; life shortening may range from days to years (U.S. Environmental Protection Agency, 1996). Fortunately, a new analysis has now provided a first estimate of the life-shortening associated with chronic PM exposure.

Life-Shortening Estimates Based on Semi-Individual Cohort Study Results

Brunekreef (1997) reviewed the available evidence of the mortality effects of long-term exposure to particulate matter air pollution and, using life table methods, derived an estimate of the reduction in life expectancy that is associated with those effect estimates. Based on the results of Pope et al. (1995) and Dockery et al. (1993), a relative risk of 1.1 per 10 $\mu g/m^3$ exposure over 15 years was assumed for the effect of particulate matter air pollution on men 25-75 years of age. A 1992 life table for men in the Netherlands was developed for 10 successive five-year categories that make up the 25-75 year old age range. Life expectancy of a 25 year old was then calculated for this base case, and then compared with the calculated life expectancy for the PM exposed case where the death rates were increased in each age group by a factor of 1.1. A difference of 1.11 years was found between the "exposed" and "clean air" cohorts' overall life expectancy at age 25. Looked at another way, this would imply that the expectation of the lifespan of the persons who actually died from air pollution was reduced by more than 10 years, since they represent a small percentage of the entire cohort population. A similar calculation by the authors for the 1969-71 life table for U.S. white males yielded an even larger reduction of 1.31 years for the entire population's life expectancy at age 25. Thus,

this study's table calculations imply that relatively small differences in long-term exposure to particulate matter of outdoor origins can have substantial effects on life expectancy.

Potential Effects of Infant Mortality on Life-Shortening Estimates

Deaths among children can logically have the greatest influence on a population's overall life expectancy, but the Brunekreef (1997) life table calculations did not consider any possible effects of long-term air pollution exposure on the population aged less than 25 years. As discussed above, some of the older cross-sectional studies and the more recent studies by Bobak and Leon (1992) and Woodruff et al. (1997) suggest that infants may be among the sub-populations that are especially affected by long-term PM exposure. Thus, although it is difficult to quantify, any premature PM associated mortality that occurs among children due to long-term PM exposure, as suggested by these studies, would significantly increase the overall population life shortening over and above that estimated by Brunekreef (1997) for long-term PM exposure to adults 25 years and older.

6.3.3.7 Effects of Exposure to Multiple Pollutants

Little is known about the effects of exposure to multiple pollutants in prospective cohort studies. While qualitative results of multiple-pollutant analyses have been reported for the AHSMOG study (Abbey et al., 1999; Beeson et al., 1998), the numerical values and the correlations of the regression coefficients have not been published. The AHSMOG study allows detailed evaluation of multiple-pollutant effects because each subject has an individual exposure "history" for PM and gaseous pollutants, based on his /her residence history and occupation. This allows some degree of inter-individual variation of exposures, even among individuals living in the same census tract. However, it must be acknowledged that there is still substantial correlation of pollutant concentration values because of the relatively small number of community air monitors from which the assigned exposure histories have been derived.

Many of the results from multiple-pollutant analyses in the AHSMOG study have been reported in terms of levels of exceedance frequencies, such as the number of days per year with $PM_{10} > 100\ \mu g/m^3$, the number of hours per year with ozone > 100 ppb, and so on. These are extremely useful indices, but not readily comparable to analyses reported by other investigators. The construction of comparable indices appears feasible for the Six Cities study, since PM and

gaseous co-pollutant measurements were made daily or every 2nd day during the course of the multi-year study. However, assignment of individual exposures would not result in variability among individuals in each of the Six Cities, unless additional air pollution information were available for the same communities from which differential exposure histories could be constructed. Otherwise, only 5 'degrees of freedom' would be available for statistical analyses.

It is unlikely that comparable indices of high-level exposure exceedance could be constructed for subjects in the ACS study, since the PM indices were observed only for a few years, mostly prior to the interval over which vital status was ascertained. Additional aerometric data would be needed for multi-pollutant analyses. If appropriate data for other air pollutants could be obtained for all cities, there could be up to 49 degrees of freedom in the fine-particle cities and 150 degrees of freedom in the sulfate cities from which multi-pollutant or other ecological analyses could be carried out, even without subject-specific exposure indices.

Analyses to address similar questions for the Six Cities and ACS studies are now being carried out by investigators at the University of Ottawa as part of a project sponsored by the Health Effects Institute. Results will be included when they become available.

Single-pollutant results about PM components are informative, however, as shown in Table 6-37 for total mortality, and in Table 6-38 for cardiopulmonary causes. The t-statistics are compared for studies where appropriate: mean PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, and sulfate for the Six Cities (Dockery et al., 1993); mean $PM_{2.5}$ and sulfate for ACS (Pope et al., 1995); mean PM_{10} and sulfate, and PM_{10} exceedances of 100 $\mu g/m^3$ for AHSMOG (Abbey et al., 1999).

Estimates for Six Cities parameters were calculated in two ways: (1) mortality RR for most versus least polluted city in (Table 3, Dockery et al., 1993) adjusted to standard increments; (2) ecological regression fits in (Table 12-18, U.S. Environmental Protection Agency, 1996). The eastern and mid-western Six Cities suggest a strong and highly significant relationship for fine particles and sulfates, a slightly weaker but still highly significant relationship to PM_{10}, and a marginal relationship to $PM_{10-2.5}$. The ACS study looked at a broader spatial representation of cities, and found a stronger statistically significant relationship to $PM_{2.5}$ than to sulfate (no other pollutants were examined).

The AHSMOG study at California sites where sulfate levels are typically low found significant effects in males for PM_{10} exceedances, and a marginal effect of mean PM_{10}, but no PM effects for females or for sulfates. These results are consistent in suggesting a statistically

TABLE 6-37. COMPARISON OF TOTAL MORTALITY RELATIVE RISK ESTIMATES AND T-STATISTICS FOR PM COMPONENTS IN THREE PROSPECTIVE COHORT STUDIES

PM Index	Study	Subgroup	Relative Risk	t Statistic
PM_{10} (50 $\mu g/m^3$)	Six Cities	All	1.504 (1); 1.530 (2)	**2.94**(1); **3.27** (2)
		Male Nonsmoker	1.280 (1)	0.81 (1)
	AHSMOG	Male Nonsmoker	1.242	1.616
$PM_{2.5}$ (25 $\mu g/m^3$)	Six Cities	All	1.364 (1); 1.379 (2)	**2.94**(1); **3.73** (2)
		Male Nonsmoker	1.207 (1)	0.81(1)
	ACS (50 cities)	All	1.174	**4.35**
		Male Nonsmoker	1.245	**1.96**0
SO_4= (15 $\mu g/m^3$)	Six Cities	All	1.504 (1); 1.567 (2)	**2.94**(1); **3.67** (2)
		Male Nonsmoker	1.359	0.81(1)
	ACS (151 cities)	All	1.111	**5.107**
		Male Nonsmoker	1.104	1.586
	AHSMOG	Male Nonsmoker	1.279	0.960
Days/y with PM_{10}>100 (30 days)	AHSMOG	Male Nonsmoker	1.082	**2.183**
$PM_{10-2.5}$ (25 $\mu g/m^3$	Six Cities	All	1.814 (1); 1.560 (2)	**2.94**(1,3); 1.816 (2)
		Male Nonsmoker	1.434 (1)	0.81 (1)

(1) Method 1 compares Portage vs. Steubenville (Table 3, Dockery et al., 1993).
(2) Method 2 is based on ecologic regression models (Table 12-18, U.S. Environmental Protection Agency, 1996).
(3) Method 1 not recommended for PM10-2.5 analysis due to high concentration in Topeka.

significant relationship of PM_{10} to excess mortality, less so for cardiopulmonary causes than for contributing respiratory causes, as shown in Table 6.3.3.7.2. The findings to date are more ambivalent about the role of sulfates, which tend to be much higher at eastern sites than at western sites. The AHSMOG investigators are currently investigating effects of fine and coarse particles.

TABLE 6-38. COMPARISON OF CARDIOPULMONARY MORTALITY RELATIVE RISK ESTIMATES AND T-STATISTICS FOR PM COMPONENTS IN THREE PROSPECTIVE COHORT STUDIES. 'MALE NON. - CRC' IDENTIFIES SUBJECTS WHO DIED OF ANY CONTRIBUTING NON-MALIGNANT RESPIRATORY CAUSE IN THE AHSMOG STUDY

PM Index	Study	Subgroup	Relative Risk	t Statistic
PM_{10} (50 $\mu g/m^3$)	Six Cities	All	1.744 (1)	**2.94**(1)
	AHSMOG	Male Nonsmoker	1.219	1.120
		Male Non. - CRC	1.537	**2.369**
$PM_{2.5}$ (25 $\mu g/m^3$)	Six Cities	All	1.527 (1)	**2.94**(1)
	ACS (50 cities)	All	1.317	**4.699**
		Male	1.245	**3.061**
		Male Nonsmoker	1.245	1.466
SO_4= (15 $\mu g/m^3$)	Six Cities	All	1.743 (1)	**2.94**(1)
	ACS (151 cities)	All	1.190	**5.470**
		Male	1.147	**3.412**
		Male Nonsmoker	1.205	**2.233**
	AHSMOG	Male Nonsmoker	1.279	0.072
		Male Non. - CRC	1.219	0.357
Days/y with PM_{10}>100 (30 days)	AHSMOG	Male Nonsmoker	1.082	1.310
		Male Non. - CRC	1.188	**2.370**
$PM_{10-2.5}$ (25 $\mu g/m^3$	Six Cities	All	2.251 (1)	**2.94**(1,2)

(1) Method 1 compares Portage vs. Steubenville (Table 3, Dockery et al., 1993).
(2) Method 1 not recommended for PM10-2.5 analysis due to high concentration in Topeka.

6.3.3.8 Discussion

Gamble (1998) presents a critique of the earlier prospective cohort mortality studies, structured around a substantially modified and altered version of Austin Bradford Hills's (1965) nine considerations for inferring causality from epidemiology studies. He ignores Hill's caveats and reservations about using the nine points as a check-list or set of criteria. The relevance of community stationary air monitoring concentrations as surrogates for individual exposure to PM of ambient origin was discussed at length in Chapter 5 of this document, and in the 1996 PM

AQCD. Individual differences in exposure to PM of non-ambient origin (such as cigarette smoke, cooking, and resuspended house dust) are sometimes important contributors to total PM exposure, but appear to be largely independent of exposure to PM of ambient origin. Gamble's (1998) emphasis on total personal exposure appears to be misplaced, since the toxicity of ambient PM may be quite different than the toxicity of non-ambient PM from indoor sources, occupations, and personal activities such as smoking tobacco and simple comparison of TWA daily PM concentrations may not adequately characterize differences in health effects from short-term (much less long-term) PM exposures from particles with different chemical properties. There is considerable direct observational evidence that short exposures to PM under certain conditions, as in London during the 1952 fog episode, can greatly increase mortality and sickness from cardio respiratory causes. The evidence presented earlier suggests some degree of coherence for respiratory and cardiovascular effects in susceptible populations: the elderly, children, and asthmatics. There is now also some evidence suggesting large PM mortality at a "midrange" of exposure time scales, roughly 30 to 120 days of exposure (Schwartz, 1999b; Zeger et al., 1998), as well as short-term effects over a few days, increasing the plausibility that there may be even larger effects over longer time-scales. Evidence from the well-conducted AHSMOG study (Beeson et al., 1998; Abbey et al., 1999) supports the earlier studies, with some differences (little or no excess mortality in the female cohort; little cardiovascular effect, considerable effects for lung cancer and for death with underlying respiratory causes). The AHSMOG study used individualized exposure metrics based on the subjects' residence and work history, and could therefore evaluate a number of multi-pollutant models, thus dealing with some of Gamble's (1998) concerns. Further analyses of data from Dockery et al. (1993) and Pope et al. (1995) being carried out under HEI sponsorship may also resolve some of Gamble's (1998) concerns.

Valberg and Watson (1998) question PM health effects, but their paper focuses upon raising possible alternative hypotheses that might confound the PM- health effects association. The three alternative pathways the authors propose as possible are: (1) weather conditions; (2) human behavior, and 3) indoor air pollution. No direct examples are provided of cases where published PM- health effects were actually explainable by these factors, but arguments are made, using largely anecdotal evidence, as to how these factors might be related to both health and daily variations in PM, and there by might explain away the PM- health effects relationships. As in

Gamble (1998), the authors do not distinguish between total personal exposure to all PM vs. total personal exposure to PM of outdoor origins only the latter of which is relevant to outdoor air pollution epidemiology. The authors conclude that their analysis "supports the importance of considering the factors that drive outdoor PM fluctuations in the first place to determine if the observed mortality/morbidity changes may be caused by pathways other than the hypothetical frank toxicity from inhalation of ambient PM."

6.3.3.9 Conclusions

A review of the studies summarized in the previous PM AQCD (U.S. Environmental Protection Agency, 1996) indicates that past epidemiologic studies of chronic PM exposures collectively indicate increases in mortality to be associated with long-term exposure to airborne particles of ambient origins. The PM effect size estimates for total mortality from these studies also indicate that a substantial portion of these deaths reflected cumulative PM impacts above and beyond those exerted by acute exposure events.

The new ASHMOG study (Abbey et al., 1999) provides all-cause mortality RR estimates for adult males that are quantitatively and qualitatively consistent with prior semi-individual studies, especially the similarly designed 6-Cities study. Extensive new by-gender, by-cause, and multiple pollutant sensitivity analyses, as well as a more comprehensive analyses of numerous potentially uncontrolled factors in this study (such as of the effects of variations in the time spent outdoors) provide important new evidence that is largely supportive of the mortality associations with PM of ambient origins previously reported by the 6-Cities and ACS studies.

Published cross-sectional studies collectively also indicate that older adults and infants are the age groups most affected by PM from ambient origins, while both the cross-sectional and semi-individual studies indicate that those deaths involving respiratory disease (either malignant or not) are especially associated with exposure to PM air pollution. These results are biologically plausible and consistent with a causal relationship between mortality and exposure to PM of outdoor origins.

With regard to the role of various PM constituents in the PM-mortality association, cross-sectional studies have generally found that the fine particle component, as indicated either by $PM_{2.5}$ or sulfates, was the PM constituent most consistently associated with mortality.
In addition, the Six-cities prospective semi-individual study also indicates that the fine mass

components of PM are more strongly associated with the mortality effects of PM than the coarse PM components.

Recent investigations of the public health implications of these PM mortality effect estimates were also reviewed. Life table calculations by Brunekreef (1997) found that relatively small differences in long-term exposure to airborne particulate matter of ambient origin can have substantial effects on life expectancy. For example, a calculation for the 1969-71 life table for U.S. white males indicated that a chronic exposure increase of 10 $\mu g/m^3$ PM was associated with a reduction of 1.31 years for the entire population's life expectancy at age 25. Also, new evidence of infant mortality associations with PM exposure (Bobak and Leon, 1992; Woodruff et al., 1997) may have the implication that life shortening in the entire population from long-term PM exposure could well be significantly larger than that estimated by Brunekreef (1997).

6.4 DISCUSSION OF EPIDEMIOLOGY FINDINGS

6.4.1 Overview of Section

The purpose of this section is to evaluate the results of the epidemiology studies reported above, and particularly to assess factors impacting the validity of the reported results (whether positive or negative). These factors take a number of forms. Section 6.4.2 discusses the specificity of the adverse health effects attributed to ambient PM exposure with respect to diagnosed outcomes. Section 6.4.3 evaluates the consistency of morbidity attributable to short-term and long-term ambient PM exposures. Section 6.4.4 similarly evaluates the consistency of mortality attributable to short-term and long-term ambient PM exposures. Section 6.4.5 discusses the coherence of the findings for different susceptible subpopulations.

The specificity of health effects attributed to PM size fraction is discussed in Section 6.4.6. A variety of methodological issues are discussed in Section 6.4.7. Section 6.4.8 discusses some of the approaches that have been used in synthesis of results from different cities. Finally, Section 6.4.9 discusses the attribution of health effects to ambient PM alone, to ambient PM in the presence of other air pollutants, and to PM as an index or co-indicator of a mixture of pollutants.

Evaluation of the Quantitative Consistency of Effect Size

The quantitative consistency of effect size across different studies lends credibility to the hypothesis that the partial contribution of a causal factor to the effect is the same under differing conditions. The appropriate metric for determining consistency depends on the health endpoint. For binary outcomes (e.g., $FEV_1 < 85\%$ of normal in a subject, versus normal), an odds ratio over a standard PM increment is used here. For counts of discrete events in a population (e.g., daily number of hospital admissions), a relative risk over a standard PM increment is used here. For continuous endpoints (e.g., FEV_1 as liters or as percent of expected value), either the percentage decrease or absolute decrease over a standard PM increment is used here. Many of the statistical analyses are appropriately carried out on a logarithmic scale, and the results could have been reported on a log-odds-ratio or log-relative-risk scale (or as excess risk). We prefer to report results as OR or RR, which we believe more clearly shows the relatively modest health risks for individuals or urban populations associated with current levels of PM (compared to the London smog episode of 1952, say), although the aggregate population risk may be substantial. This also shows that normally small biases of 2 or 3 percent attributable to methodology or study design may seriously alter the conclusions of any study. For this reason, findings of similar effects across studies as well as findings of differences between effect size estimates should be interpreted cautiously.

Certain factors facilitate the comparison of studies:

(1) similarity in study design (subject selection or recruitment, retention, follow-up);

(2) similarity in data analysis (methodology, criteria for covariate adjustment, smoothing or detrending);

(3) similarity in air pollution measurements (averaging times or lags, spatial averaging, representativeness of monitors, instrumentation);

(4) similarity in environmental factors that may modify PM health effects.

Evaluation of the Statistical Significance of Effect Size

Statistical significance plays an important role in assessment of study results, but we believe that it should not play a dominant role, particularly in the synthesis of results from multiple studies. Even if each study were regarded as an independent replicate of an exactly identical design, it would be normal to find some studies with statistically significant findings of

adverse health effects, some with findings of adverse health effects that are not statistically significant, and some studies with findings of beneficial effects (including those that are statistically significant). For this reason, causal conclusions about adverse health effects associated with PM or other environmental factors are strengthened when a number of independent studies find statistically significant adverse health effects, and when the majority of studies find adverse rather than beneficial effects. However, far more than simple 'vote counting' is required to interpret a body of evidence with mixed findings (see Section 6.4.8 on research synthesis).

In reality, any simple description of a specific study finding as 'positive' or 'negative' is likely to be misleading, in view of the large number of model selection and data analysis strategies that may be applied. It is hardly surprising that different analyses of the same data set may find greater or smaller statistical significance associated with a given PM effect size estimate. It is often possible to separate more adequate analyses from less adequate based on generally accepted strategies for data analysis, but some element of judgement is inevitably involved. For this reason, the results of different analyses are often presented in different forms, to assist the reader in drawing an independent conclusion.

Results are usually presented in two forms: (1) 95 percent confidence intervals of OR or RR for a standard PM increment, to express uncertainty (these can also be used to test statistical significance by comparing the lower confidence limit with 1.0); (2) a t-statistic for the PM or co pollutant regression coefficient in a generalized linear model, which allows a consistent single-digit plus single-decimal format for easy visual comparison, although P-values and other equivalent representations could be used. Any equivalent representation of statistical significance would be equally subject to the same criticism, that it combines elements of sample size, effect size, internal uncertainty (standard error), and model selection. We find t-statistics particular convenient for evaluating the sensitivity of alternative PM and co-pollutant models fitted to the same data sets.

6.4.2 Relationship of Ambient Concentrations to Specific Diseases and Age Groups

New studies have expanded the overall database for morbidity outcomes in relation to ambient PM concentration. A brief summary of age groups is followed by discussion of asthma, non-asthma, and finally, cardiovascular disease.

Most studies have been designated to examine age groups with the largest potential yield, the elderly (>65 years) in hospitalized studies, and children in panel studies of respiratory symptoms and pulmonary function outcomes. Since the subjects examined in most panel studies were a uniform age group such as 8 to 12 years of age, no difference by age can be drawn. Those studies with adults in the panels did not examine the data by age. Some age-related outcomes are available from emergency department (ED) visits and hospital admission studies. Delfino et al. (1997) report no significant associations between air pollution and ED respiratory visits for persons 2 to 6 years of age, but positive association for patients over 64 years of age. Medina et al. (1997) reported that the relationship between asthma visits and air pollution was strong for children. Spix et al. (1998) studied TSP and BS and hospital admissions data by older (>65) and younger (15 to 64 years) people which yielded mixed results. Sunyer et al. (1997) report nonsignificant outcomes for BS and age group 15 to 64 and <15 years. However, the majority of hospital admission studies report positive outcomes for the age group >65 years of age. Comparative analyses by age group have not been done, usually. Morbidity studies provide limited insight into potential age differences for outcome because age is usually part of the study design, to produce a more homogeneous study group with larger effects, such as age >65.

6.4.2.1 Asthma Studies

The asthma panel studies discussed in Section 6.2.2 were conducted by over 10 research teams in various locations world-wide. As a group the studies examine health outcome effects that are similar such as PEFR. Each study characterizes the clinical-symptomatic aspects in a community of a sample of asthmatics, mainly children age 5 to 16 years of age observed in their natural setting. Their asthma is "ideally" being treated to achieve the therapeutic purpose of keeping them symptom free, with "normal" pulmonary function rates, normal activity levels, and to prevent recurrent exacerbations of asthma (National Institutes of Health, 1991). They are mild to moderate asthmatics. Characterization of their asthma is by symptom, pulmonary function and

medication use. In the new severity classification (National Institutes of Health, 1997) these panel studies would be classified to include mild intermittent to mild persistent. As a group they may differ from asthmatics are examined in studies of hospitalization or doctor visits for acute asthmatic episodes who may have more severe asthma.

Severity of asthma is important in that these panel studies are examining primarily mild and moderate asthmatics, but still those who require medication for the condition seen to demonstrate enough disease or reaction to stimulus to be the appropriate group to study. The results for the study may represent only that segment of the asthma population with these levels of disease. Physician visits and hospitalization for asthma are better outcome measures for those with moderate or severe asthma (Schwartz et al., 1993; Gordian et al., 1996; Tseng et al., 1992).

Study Characteristics

Most of these studies used a single ambient monitoring site to characterize PM ambient exposure estimates. For PM_{10} and especially for $PM_{2.5}$, exposure derived from such sites (Janssen et al., 1997; U.S. Environmental Protection Agency, 1996; Wilson et al., 1998; Mage et al., 1999) provide an estimate of PM ambient exposure for a panel of subjects such as asthmatics. The study authors provide limited discussion of exposure estimates. While the opportunity for measurement error is an important consideration in this circumstance, the major potential effect is to weaken a possible association. Some of the studies used monitors that were located in more residential areas in the community and thus may provide a better exposure estimate for PM, others used multiple monitors and one examined personal exposure.

Most studies reported ambient PM_{10} results. $PM_{2.5}$ was examined in two studies. Other ambient PM measures (Black Smoke (BS) and SO_4) were also used. For these studies, mean PM_{10} levels range from a low of 13 $\mu g/m^3$ in Finland to a high of 167 $\mu g/m^3$ in Mexico City. This Mexico City level is over 3 times more than each of the other levels and is unique compared to the others. Related 95% CI for these means or ranges show one day maximums above 100 $\mu g/m^3$ in four studies with two of these above 150 $\mu g/m^3$. The studies thus provide a measure of differentiated levels of PM in the range of US cities. All the studies controlled for temperature and several controlled for relative humidity.

Most panel studies are analyzed using a design which takes advantage of the repeated measures. Linear models are often used for lung function and logistic models are used for

dichotomous outcomes. Meteorological variables are used as covariates. Perhaps the most critical choice in the model is the choice of the lag of the pollution variable. The use of medication is also an important confounder. Study subject number various from 12 to 164. Most of the studies had cohort samples over 50, and all had gathered adequate subject-day data to provide sufficient power for the conducted analysis. All the studies reported a positive outcome for either O_3 or PM.

Three asthma panel studies (Gielen et al., 1997; Peters et al., 1997b; Delfino et al., 1998) used symptom-scoring approaches as opposed to measuring, the presence or absence of cough, wheeze, sputum production (phlegm), shortness of breath and dyspnea (chest tightness). Since the complex of symptoms and their clinical expression varies between asthmatic subjects, outcome misclassification would be less in the symptom scoring approaches as opposed to symptom specific approach.

Presenting lag periods with the strongest associations introduces potential bias since the biological basis for lag structure may be related to effect. No biological basis for lag periods is known, but some hypotheses can be proposed. Acute asthmatic reaction can occur 4-6 hours after exposure and thus 0-day lag may be more appropriate than 1-day lags for that reaction. Lag 1 may be more relevant for morning measurement of asthma outcome from the day before and longer term lag, (i.e., 2-5 days may represent the outcome of an inflammatory mechanism). There is too little information to predetermine the appropriate lag period. Additional research is needed.

A qualitative summary of these studies examining ambient PM_{10} exposure on asthmatic health outcomes indicate that as a group, the majority of studies report a positive odds ratio for the relationship with almost half having 95% CI above 1.00. This is looking at the endpoints one at a time. Viewing all the indicators together within a study may be a better test of the relationship for an asthma attack. Examining all the studies as a group quantitatively describes a stronger relationship.

The available group of studies examined PM_{10} and other measures, but did not study outcomes for coarse, $PM_{10-2.5}$. One study (Romieu et al., 1996) examining both PM_{10} and $PM_{2.5}$ reported that $PM_{2.5}$ had a larger effect.

Peters et al. (1997c) is unique for two reasons: (1) they studied the size distribution of the particles in the range 0.01 to 2.5 μm, and (2) examined the number of particles. They report that

the health effects of 5 day means of the number of ultra fine particles were larger than those of the mass of the fine particles. In contrast Pekkanen et al. (1997) also examined a range of PM sizes but PM_{10} was more consistently associated with PEF. Mean PM_{10} levels were 18 $\mu g/m^3$. Delfino et al. (1998) is unique in that the report effects with 1-hr and 8-hr maximum PM_{10} having larger effects than the 24 hr mean.

Several new panel studies of asthmatic effects in relation to ambient PM_{10} concentration have been published since the 1996 PM AQCD. Some new studies of emergency department visits and hospitalizations for asthma have been published. The panel studies examine mild asthmatics while the hospitalization studies examine those with asthma attacks severe enough to result in hospitalization.

As a group, the results for the asthma panels (see Table 6-2 thru 6-5) of the peak flow analysis consistently show small decrements for both PM_{10} and $PM_{2.5}$. The effects using 2 to 5 day lags averaged about the same as did the zero to one day lags. The effects on respiratory symptoms in asthmatics (see Tables 6-5 thru 6-12) also tended to be positive. Most studies showed increases in cough, phlegm, difficulty breathing, and bronchodilator use. The only endpoint more strongly related to longer lag times was bronchodilator use which was observed in three studies. The peak flow decrements and respiratory symptoms are indicators for asthma episodes.

The group of studies examining emergency department visits and hospitalization for asthma were fewer in number for these studying ambient PM_{10} as compared to other ambient PM measures (TSP, BS). Lipsett et al. (1997) reported consistent relationships between ER visits for asthma and wintertime ambient PM_{10} in an area where one of the principal sources of ambient PM_{10} is residential wood combustion. Medina et al. (1997) report a relationship between asthma visits and daily concentrations of black smoke. Dab et al. (1996) report that asthma hospital admissions were significantly correlated with NO_2 levels, but not ambient PM_{13}. Wordley et al. (1997) report significant associations with mean ambient PM_{10} values for the past three days and asthma admissions. Sunyer et al. (1997) report, for BS and emergency admissions for asthma, a consistently positive but overall nonsignificant association in all cities they studied for both children and adults.

6.4.2.2 Other Non-Asthma Studies

Few new studies examine non-asthma outcomes. One review study, by Hoek et al. (1998), yields results of peak flow analysis that consistently show small decrements for increases in ambient PM_{10}. The results of limited chronic studies are not consistent. Specific endpoints examined are bronchitis, COPD, and pneumonia in hospital admission studies. The results of these new PM studies are generally consistent with, and supportive of, those examined in the last AQCD (U.S. Environmental Protection Agency, 1996).

6.4.2.3 Cardiovascular Effects of Ambient PM Exposure

About 75% of all U.S. deaths occur in persons at least 65 years old, and of these nearly 40% are for cardiac causes (nearly 45% if deaths from cerebrovascular causes are counted). Thus, if ambient PM exposure indeed produces increased total mortality in the elderly, it would seem possible that cardiovascular deaths may be involved.

Seaton et al. (1995) hypothesized that inhalation of very fine ambient particles might provoke alveolar inflammation, with release of chemical mediators. In some susceptible individuals, such mediators might induce both aggravation of underlying lung disease and increase in blood coagulability. These mechanisms could serve to explain the observed association of ambient PM exposure with increased cardiovascular deaths in the elderly. Interestingly, in the European MONICA study, Peters et al. (1996) observed a short-term increase in blood viscosity in men and women, in association with an episode of high TSP and SO_2 levels in Augsburg, Germany. This observation lends some weight to the hypothesis of Seaton et al., especially since blood viscosity has been independently associated with risk of a first myocardial infarction and with incidence of coronary heart disease. At the same time, size-specific PM measurements were not available in Peters et al., and effects of TSP and SO_2 could not be statistically separated. Also, high ambient CO levels were associated with increased blood viscosity in women. Also, it is not known whether an increase in mortality or other adverse health effect was temporally associated with the observed increase in blood viscosity in Augsburg.

6.4.2.4 Issues in the Interpretation Of Acute Cardiovascular Effects Studies

Three recent analyses of daily PM_{10} and CO in U.S. cities suggest that elevated concentrations of both PM_{10} and CO may enhance risk of cardiovascular morbidity leading to acute hospitalizations (Morris and Naumova, 1998; Schwartz, 1997, 1999a). Schwartz (1999a) argued that independent effects of both pollutants are biologically plausible. For CO, the argument is based on the well-established effects of CO on oxygen transport by hemoglobin, albeit at relatively high concentrations. In the case of PM_{10}, Schwartz' plausibility argument draws upon the emerging literature which has demonstrated: effects of ambient PM on pulmonary inflammation in laboratory animals and human volunteers (Gilmour et al., 1996; Salvi et al., 1997); toxicity of transition metals carried by combustion-generated particles (Costa and Dreher, 1999); effects on cardiac dysfunction in animals with pre-existing cardiopulmonary disease (Godleski et al., 1996; Watkinson et al., 1998); and new epidemiologic evidence of associations between ambient PM and physiologic changes in cardiac function (Pope et al., 1999a,b; Liao et al., 1999; Peters et al., 1998; Gold et al., 1998) and plasma viscosity (Peters et al., 1997d) in humans. While a great deal more research is needed to confirm the hypothesized linkages among these new findings, these arguments provide an initial foundation for inferring that ambient levels of PM may play a causal role in cardiovascular illness.

Another mechanistic hypothesis, relating to enhanced blood viscosity, is suggested in a recent analysis of plasma viscosity data collected over time in a population of 3256 German adults in the MONICA study (Peters et al., 1997d). Each subject provided one blood sample over the period from October 1984 to June 1985. An episode of unusually high air pollution concentrations occurred over a 13 day period while these measurements were being collect. The authors reported that, among the 324 persons who provided blood during the episode, there was a statistically significant elevation in plasma viscosity as compared with the 2932 persons studied at other times. The odds ratio for plasma viscosity exceeding the 95th percentile was 3.6 (CI 1.6-8.1) among men and 2.3 (CI 1.0-5.3) among women. Analysis of the distribution of blood viscosity data suggested that these findings were driven by changes in the upper tail of the distribution rather than by a general shift in mean viscosity. This is consistent with the presence of a susceptible sub-population of individuals.

Because they lack data on individual subject characteristics, ecologic time series studies provide only limited information on susceptibility factors based on stratified analyses. The

relative impact of PM on cardiovascular (and respiratory) admissions reported in ecologic time series studies are generally somewhat higher than those reported for total admissions. This provides some limited support for the hypothesis that the acute effects of PM operate via cardiopulmonary pathways or that persons with pre-existing cardiopulmonary disease have greater susceptibility to PM, or both. Although there is some data from the ecologic time series studies showing larger relative impacts of PM on cardiovascular admissions in adults 65 and over as compared with younger populations, the differences are neither striking nor consistent. Individual-level studies of cardiophysiologic function suggest that elderly persons with pre-existing cardiopulmonary disease are susceptible to subtle changes in HRV in association with PM exposures. However, because younger and healthier populations have not yet been assessed, it is not possible to delineate clearly the extent to which the elderly have increased susceptibility, although this does represent a reasonable working hypothesis.

It is unlikely that all acute cardiovascular effects can be attributed to weather rather than air pollution. The ecologic time series studies published since 1996 have controlled adequately for weather influences. Some recent studies (Morris and Naumova, 1998) have extensively explored the bivariate effects of weather and CO, and deemed it unlikely that residual confounding by weather is responsible for the PM associations observed. Also, Pope et al. (1999a) evaluated the role of barometric pressure and other meteorological factors in the individual-level studies of cardiac function, but many of these factors have not yet been studied in conjunction with air pollution. Thus, the possibility of confounding by weather, although unlikely, cannot be entirely discounted at present.

Co-pollutants have been analyzed rather extensively in many of the recent time-series studies of hospital admissions and PM. In some studies, PM clearly carries an independent association after controlling for gaseous co-pollutants. In others, the PM "effects" are markedly reduced once co-pollutants are added to the model. Among the gaseous criteria pollutants, carbon monoxide has emerged as the one most consistently associated with cardiovascular hospitalizations. The CO effects are generally robust in multi-pollutant models; however, in spite of this, the EPA CO AQCD (U.S. Environmental Protection Agency, 1999) did not find compelling toxicological evidence to support a finding of biological plausibility for the reported epidemiologic observations of CO effects at the current very low ambient CO concentrations typically seen in the United States.

The temporal patterns of cardiovascular response appear more consistent than for many respiratory responses. The evidence from recent time series studies of CVD admissions suggests rather strongly that PM effects, if any, are maximal at lag 0, with some carryover to lag 1. There is little evidence for important effects beyond lag 1.

The characterization of PM attributes associated with acute CVD is incomplete. Insufficient data exist from the time series CVD admissions literature or from the emerging individual-level studies to provide guidance as to which PM attributes, defined either on the basis of size or composition, determine potency. The epidemiologic studies published to date have been constrained by the limited availability of multiple PM metrics. Where multiple metrics exist, they often are of differential quality due to differences in numbers of monitoring sites and in monitoring frequency. Until more extensive and consistent data become available for epidemiologic research, the question of PM size and composition, as they relate to acute CVD impacts, will remain epidemiologically unanswerable.

6.4.3 Consistency of Health Effects for Short-Term and Long-Term Exposure

Morbidity health effect outcome measures are demonstrated for ambient PM exposure in asthmatic panel studies for respiratory symptoms and pulmonary function decrements. New studies that look at primary care settings of doctor visits show effects related to PM levels. Effects are also reported for increased hospitalization rates for ambient PM exposure for COPD, asthma, and cardiovascular disease. Hospitalization can be a more severe outcome for an asthmatic than the increase in symptoms or medication use observed in panel studies. These effects may be related to the disease status of the individual in the studies group. The effects are consistent between studies. They are consistent at different locations, and times. Lipfert and Wyzga (1998) and Wyzga and Lipfert (1998) note a lack of coherence among endpoints in long-term studies, in part, because of the lack of long-term studies of hospitalization rates. The studied health effects of ambient PM (i.e., lung function decrements, symptoms, hospitalization utilization, death) may not occur on the same mechanistic pathway and thus there is no reason to expect a quantitative consistency across outcomes.

It is not necessarily the case that there is uniformity in effects seen, such as deaths due to respiratory causes with different time scales for ambient PM exposures. For example, PM

exposures on a short time scale are reported as associated with excess cardiopulmonary deaths and respiratory hospital admissions. At this time, however, it is not clear that such deaths or hospital admissions in association with high ambient PM concentrations represent a long-term difference in the mortality rate, or a displacement of events that would have occurred a few days later without the high PM levels. The prospective cohort mortality studies do not yet allow assessment as to whether the occurrence and frequency of deaths from short-term exposures are consistent with a larger rate of occurrence of deaths that is associated with longer-term exposures, on a scale of months or years.

There is as yet little basis (conceptual, experimental, or mathematical) that allows direct quantitative linkage of endpoints between mortality attributable to short ambient PM exposures ("acute") and mortality attributable to longer ambient PM exposures ("chronic" or "sub-chronic"). Exposure indices are more easily compared at different time scales when endpoints are identified (Evans et al., 1984). One hypothesis for discussion is that an individual with high susceptibility to ambient PM at a given moment (e.g., elderly, with an acute respiratory infection as well as COPD or other serious pre-existing conditions) may succumb to a moderately elevated ambient PM exposure or to some coincident cause, when that individual would have survived the same PM exposure if it had occurred during a time of lesser susceptibility to ambient PM.

The 1996 PM AQCD reported that excess daily mortality associated with a large PM increment (50 μg/m3 for PM_{10}; or 25 $\mu g/m^3$ for $PM_{2.5}$) was only about 1.05, whereas the excess risk associated with 20 $\mu g/m^3$ $PM_{2.5}$ between Portage and Steubenville was 1.26 in the Six Cities study, and a comparable $PM_{2.5}$ increment yielded a mortality RR of 1.17 in (Pope et al., 1995) for 50 U.S. cities. This is consistent with (but does not prove) the hypothesis that there is a substantial baseline risk from long-term exposure to PM that is much larger than the accumulation of mortality from elevated PM episodes.

The recent analyses of the long-term AHSMOG study continue to show serious adverse health effects associated with ambient PM_{10} exposure for which a substantially greater level of individualized ambient PM_{10} information is available, but also demonstrates some differences with the earlier Six Cities and ACS studies (Dockery et al., 1993; Pope et al., 1995). Statistically significant increases in lung cancer incidence (Beeson et al., 1998), and statistically significant increases in lung cancer deaths and in deaths associated with any contributing respiratory causes

(CRC) were found in AHSMOG males, but not females. The results were generally very robust to different confounder specifications, population subsets, and inclusion of co-pollutants, and were larger for and more significant PM exceedance indices (number of days per year with PM_{10} greater than a cut point, typically 100 $\mu g/m^3$) than with the mean PM_{10} concentration. However, PM_{10} was estimated from TSP rather than measured in the earlier part of the study.

Using the same mean PM_{10} increment of 50 $\mu g/m^3$, total mortality attributable to long-term ambient PM_{10} RR was similar to that of the ACS study for $PM_{2.5}$ for male nonsmokers (1.24) and smaller than that for the Six Cities study (1.57), albeit only significant for the ACS study (Table 6-31). The AHSMOG RR for females (Table 6-31) is smaller and non-significant (0.88), whereas the ACS RR for female non-smokers is significant and only somewhat smaller than the male RR (1.22 in the 50-city $PM_{2.5}$ study, 1.15 in the 151-city SO_4 study) and 1.28 in the Six Cities.

The AHSMOG findings for cardiopulmonary mortality attributable to long-term ambient PM_{10} are positive for males, but not statistically significant, whereas the ACS findings are significant for female nonsmokers in both studies and in male nonsmokers for the 151-city study (Table 6-32). However, the male RR in AHSMOG (1.22 for cardiopulmonary deaths, 1.54 for CRC deaths) is similar to that of ACS male non-smokers (1.24 for the 50-city study, 1.21 for the 151-city study) and smaller than that for all Six Cities subjects (1.74, includes smokers and non-smokers). The ACS female non-smokers have RR of 1.58 and 1.32 respectively, both significant, compared to 0.84 in AHSMOG.

Lung cancer mortality attributable to long-term ambient PM_{10} is not significant for females in any of the female studies (Table 6.3.3.3.3), nor for male nonsmokers in ACS, but is significant for male nonmokers in AHSMOG and male smokers in ACS 151-city. Lung cancer mortality attributable to long-term ambient PM_{10} is not significant for both genders in the ACS and Six Cities studies, but would be more significant if combined in AHSMOG.

The AHSMOG studies also found indications of adverse effects associated with other air pollutants, particularly high concentrations of ozone. Including co-pollutants in PM_{10} models with exceedance days as the indicator tended to slightly attenuate the PM_{10} effect, but usually left it significant. This may suggest that long-term PM_{10} exposures may be better modeled by a non-linear concentration-response function, where data such as in AHSMOG allow this analysis.

Some SO_4 analyses were carried out by Abbey et al. (1999). No statistically significant results were found, unlike in the ACS and Six Cities studies. However, SO_4 levels tend to be lower in California than in many Eastern cities, and the $SO_4/PM_{2.5}$ ratio is much different.

Several recent analyses have started to bridge the gap between the short-term and long-term mortality studies. A relatively transparent approach has been applied by Schwartz (1999b) to the Boston daily mortality data, using the Six Cities data base. This approach, discussed in Section 6.3.2, is to filter out long time trends from the data using a LOESS smoother with a 120 window, then to use weighted moving averages of mortality, $PM_{2.5}$, and meteorological covariables over longer averaging times. This extends the daily time series studies, predicting daily counts from predictors in the preceding few days, to averages of mortality compared to averages of pollution and weather variables over longer periods of time. The windows evaluated by Schwartz (1999b) were 0, 15, 30, 45, and 60 days (weighted moving averages over 1, 31, 61, 91, 121 days resp.). RR for some endpoints, such as COPD mortality, showed relatively little change from 0 and 15 d windows, suggesting that these may be predominantly determined by short-term events. RR for pneumonia, ischemic heart disease, and all cause mortality showed substantial and systematic increases from 0 d to 60 d windows, suggesting that there are mortality effects attributable to prolonged $PM_{2.5}$ and weather exposures that greatly exceed a few days. The excess mortality over a 60-d window can be nearly twice as large as those over a 0 d window, thereby providing a substantial degree of plausibility for even larger differences for multi-year mortality studies which do not require seasonal and secular detrending.

A different approach was used by Zeger et al. (1999), who decomposed total mortality and TSP time series into Fourier components with distinct time scales, roughly year, season, month, week, day. The decomposition allows each daily term to be represented as the sum of its components. By discarding long-term and very short-term (i.e. “Harvesting”) frequencies, a “harvesting-resistant” estimator may be calculated. The analyses in (Zeger et al., 1999) suggest that only a small part of the variation in mortality time series may be attributed to short-term events, such as daily fluctuations in TSP and weather. A large part of the total variation appears to be associated with time scales of 5 to 100 days. Lag times of 0 to 3 days had little effect.

While Zeger et al. (1999) establish the existence of a mid-frequency signal (scale of months), they do not establish the absence of a harvesting effect, since the “harvesting-resistant” estimator only allows detection of the longer-term signals that are not simply harmonics of

high-frequency signals. It is entirely feasible that short-term harvesting does occur, along with excess mortality attributable to accumulated ambient PM exposures on a scale of months or longer, as suggested by the prospective cohort studies.

The daily time-series studies in fact contain a great deal of information about long-term effects. The results of detrending the daily time-series produces a series with substantial variations in relative risk, which are sometimes shown graphically, but never used to evaluate adverse health effects associated with long-term exposure. Quantitative assessment of the large seasonal and secular variations, often larger than the short-term RR, would be of interest.

As yet there is little methodology for quantifying the relationship between short-term and long-term PM epidemiology studies. McMichael et al. (1998) have pointed out some difficulties in assuming that long-term exposure effects can be estimated accurately by summing up day-to-day increments from short-term exposure. The long-term issue requires further study, because extensive life-shortening is an extremely serious adverse health effect.

Effects from extremely short-term exposures to ambient PM have not yet received much attention. A number of hypotheses have been raised (Michaels et al., 1998, 1999), but data are extremely scarce because of the relative absence of short-term PM monitoring. An important recent study on asthmatics (Delfino et al., 1998) suggests substantially stronger PM_{10} effects in asthmatic children in response to 8-hr events than to 24-hr concentrations.

6.4.4 Susceptible Populations

6.4.4.1 Summary Of Previous Criteria Document

The 1996 PM AQCD identified several potentially susceptible sub-populations: (1) the elderly (age 65+), particularly those with pre-existing respiratory conditions such as COPD, or previous cardiovascular disease; (2) asthmatics, possibly including both adults and children. Recent research summarized in sections 6.2 and 6.3 often report higher relative risks or odds ratios for adverse effects in these groups associated with ambient PM exposure. More recent studies, summarized in Sections 6.2.4 and discussed in Section 6.4.2.3, find a variety of cardiovascular responses in the elderly associated with ambient PM exposure. Therefore, these findings will not be further discussed, as they tend to confirm the findings in the 1996 AQCD (U.S. Environmental Protection Agency, 1996).

The most important addition to the last document is in the area of children's health. Many recent studies have looked at larger and more general populations of children, in a variety of locations. The findings in (U.S. Environmental Protection Agency, 1996) were somewhat mixed about effects in children, particularly in healthy children. A number of recent studies have shown serious endpoints, including physician visits, hospital admissions, and even mortality associated with various ambient PM indices. The evidence on children's health effects from previous sections is summarized here.

6.4.4.2 Children as a Susceptible Subpopulation

New publications provide a much stronger basis for identifying children as a susceptible sub-population. General overviews of child health air pollution studies include (Raizenne et al., 1998; Romieu, 1998). A quantitative summary of PM effects in many recent studies is presented in (Anderson et al., 1998; esp. Table 7), complementing materials presented in Section 6.2 of this document. Recent evidence suggests a variety of effects: (1) reduced pulmonary function or increased respiratory symptoms in asthmatics and non-asthmatics; (2) an increased incidence of doctor's visits, emergency department visits, and hospital admissions for respiratory symptoms, including asthma, upper and lower respiratory infection (URI, LRI) associated with short-term PM exposures; (3) Increased infant and child mortality associated with short-term PM exposures; (4) Reduced pulmonary function or increased respiratory symptoms associated with longer-term PM exposures; (5) Increased infant mortality, intrauterine growth reduction, or preterm delivery associated with long-term PM exposures. Unfortunately, the wide variety of endpoints and PM indices complicates the estimation of composite effects.

Most studies have carried out only single-pollutant analyses. The most commonly used indices are PM_{10}, TSP, and BS, although significant effects are sometimes reported for $PM_{2.5}$, SO_4, H+. Column 4, labeled "PM Effects" in each of the tables in this section briefly describes the statistical significance of the PM index or indices used in the analyses, with effect sizes reported earlier in Sections 6.2 and 6.3. Column 5, labeled "Pollutants", lists all of the pollutants that were used or were available for use in the analyses. Sensitivity of the PM effect to co-pollutant models is also shown in Column 4, where reported.

Reduced Pulmonary Function or Increased Respiratory Symptoms in Asthmatics and Non-Asthmatics

The studies are discussed in detail in Section 6.2.2. The findings for children are summarized in Table 6-39. The tables are generally organized so as to characterize populations in the U.S. and Canada first, then Mexico and other western hemisphere countries, Europe, and Asia, roughly in order of relevance to U.S. population demographics. There is a somewhat patchy pattern of symptom effects in asthmatics, particularly in U.S. studies in California. Delfino's findings of significant effects for 1-h and 8-h PM_{10} exposures is noteworthy. Many asthmatics self-medicate with bronchodilators, which may also be a useful indicator of respiratory distress in these subjects. Cough, phlegm, and LRI are also sometimes found. A number of investigators have found statistically significant peak expiratory flow reduction (PEFR) associated with PM_{10} and other indices, and sometimes significant reduction in FEV_1 and FVC.

There is an overall indication that respiratory symptoms in children are exacerbated by exposure to airborne particles, and may be more serious in asthmatics or other susceptible groups. There appear to be large numbers of children who may be susceptible to more-or-less serious adverse health effects from brief exposures to airborne particles leading to exacerbation of asthmatic responses. The investigations summarized here generally focus on respiratory endpoints in school-age children.

Increased Incidence of Doctor's Visits, Emergency Department Visits, Hospital Admissions

Table 6-40 summarizes studies described in more detail in Sections 6.2.3 and 6.2.4. Several of the studies using PM_{10} as an index are statistically significant, suggesting that serious symptomatic responses to PM requiring explicit medical intervention may occur in a number of locations. However, some of these associations became statistically non-significant when gaseous co-pollutants were included in the model, including O_3, SO_2, NO_2, CO. This suggests that specific local conditions, possibly related to the co-pollutant mixture, may play a role in the effects of PM on children. Norris et al. (1999) is the only U.S. study using an index of fine or ultra-fine particles.

TABLE 6-39. RECENT PM STUDIES OF PULMONARY FUNCTION TESTS OR ACUTE RESPIRATORY SYMPTOMS IN SCHOOL-AGE CHILDREN, GENERALLY USING PANEL STUDIES

Study	Endpoint	Ages (years)	PM Effects	Pollutants	Remarks (N)
Ostro et al. (1995) Los Angeles, CA	Asthma symptoms for at least six weeks	7-12	Shortness of breath risk, 9% per 10 $\mu g/m^3$ PM_{10}	PM_{10}, TSP, SO_4, NO_3, O_3, SO_2, NO_2	African-American (N = 83)
Delfino et al. (1998) Alpine, CA	Bothersome asthma symptoms	9-17	Symptoms signif. 1-h, 8-h PM_{10}, 24-h less signif.	PM_{10}, O_3 (others low)	Panel of asthmatics (N = 25) higher elevation
Delfino et al. (1997) Alpine CA	Symptom score, bronchodilator use		PM_{10} signif. dilator use	PM_{10}, O_3	Asthmatics (N = 13)
Delfino et al. (1996), San Diego, CA	Symptom scores, broncho-dilator use		Signif. O_3 personal monitor, N.S. SAM O_3, $PM_{2.5}$	$PM_{2.5}$, O_3	Asthmatics (N = 12)
Linn et al. (1996) southern CA	Pulmonary function		Morning FVC signif. PM5?, NO_2	PM5?, NO_2	School children (N = 269)
Thurston et al. (1997) NY summer camps	lung function, symptoms, dilator use		PM_{10} N.S., SO_4, O_3 rel. symptoms, dilator use	PM_{10}, SO_4, H+, O_3,	PM_{10}, TSP, SO_4, H+, SO_2
Hoek et al. (1998) re-analyses of other studies in the U.S. and the Netherlands	PEF, large changes related to symptoms	Utah Valley	Signif. PEFR, Cough	PM_{10}	N = 39
		Bennekom	PEFR N.S..		N -= 67
		Uniontown	PEFR N.S.		N = 83
		State College	PEFR N.S.		N = 108
Romieu et al. (1997) Mexico City	PEF, respiratory symptoms	5-13	N.S. for PM. Strongest effect w. O_3	PM_{10}, O_3	Mild asthmatics (N = 65)
Romieu et al. (1996) Mexico City	PEF, respiratory symptoms	5-7	PM_{10} signif. PEFR, LRI	PM_{10}, O_3	Mild asthma (N = 71)
Gold et al. (1999) Mexico City	PEF, respiratory symptoms	8-11	$PM_{2.5}$, O_3 signif. PEFR, phlegm	PM_{10}, $PM_{2.5}$, O_3	School children (N = 40)
Peters et al. (1996) Erfurt and Weimar, Germany; Sokolov, Cz.	PEF, daily symptoms, medication	7-15	0.43% decrease with 52 $\mu g/m^3$ PM_{10}	PM_{10}, TSP, SO_2	Mild and moderate asthmatics (N = 155)
Tittanen et al. (1999) Kuopio Finland	PEF, cough	8-13	N.S. for PM	PM0.1, PM1.0	Chronic resp. symptoms (N = 49)

TABLE 6-39 (cont'd). RECENT PM STUDIES OF PULMONARY FUNCTION TESTS OR ACUTE RESPIRATORY SYMPTOMS IN SCHOOL-AGE CHILDREN, GENERALLY USING PANEL STUDIES

Study	Endpoint	Ages (years)	PM Effects	Pollutants	Remarks (N)
Pekkanen et al. (1997) Kuopio, Finland	PEF	7-12	PEFR signif. for difft. PM measures, w. difft. lags	PM0.03, PM0.1, PM0.32, PM1, PM_{10}	Asthmatic (N = 39)
Timonen and Pekkonen (1997) Kuopio, Finland	PEF, respiratory symptoms	7-12	Morning PEF and PM_{10} signif, not evening; N.S. symptoms	PM_{10}	Asthmatic (N = 74) or dry cough (N = 95)
Segala et al. (1998) Paris, France	PEF, respiratory symptoms, bronchodilator use	7-15	PM13 N.S. in mild asthma, signif. inhaler in moderates. PM13< other	PM13, SO_2, NO_2	Mild (N = 43), moderate (N = 43) asthmatics
Gielen et al. (1997) Amsterdam, the Netherlands	PEF, respiratory symptoms	7-13	PEF, symptoms, dilator use > for BS than PM_{10}	PM_{10}, BS, O_3	Meds. (N = 47) or hospitalized (N = 14)
PEACE studies, the Netherlands	changes in respiratory symptoms		Assessed by group rates; N.S.PM	PM_{10}, BS, SO_2, NO_2	Chronic resp. disease, usu. Dry cough
Roemer et al. (1993) the Netherlands	PEF, respiratory symptoms, medication	6-12	PM_{10} signif. broncho-dilator, marg. Signif. PEFR	PM_{10}, BS, SO_2	Chronic respiratory symptoms (N = 73)
Hoek and Brunekreef (1994) the Netherlands	PEF, respiratory symptoms		Weak assoc. PEFR, N.S. symptoms	PM_{10}, SO_4, NO_3, H+, SO_2, NO_2	Non-asthmatics (N = 1079)
Boezen et al. (1999) the Netherlands	PEF, respiratory symptoms	7-11	PM_{10} N.S.	PM_{10}	N = 632 w and w/o bronchial hyperresp.
Agócs et al. (1997) Budapest HU	PEFR		TSP N.S.	TSP, SO_2	Asthmatic children (N = 60)
Scarlett et al. (1996)	Pulmonary function		PM_{10} signif. FEV, FVC	PM_{10}, O_3, NO_2	School children (N = 154)
Studnicka et al. (1995)	Pulmonary function		Pulmonary function related to H+, not PM_{10}	PM_{10}, SO_4, H+, NH3, O_3	Three panels of children at summer camp.

Note abbreviations: EF, peak expiratory flow; PEFR, reduction in PEF; N.S., not statistically significant (two-tailed, P = 0.05).

TABLE 6-40. RECENT PM STUDIES OF EMERGENCY DEPARTMENT VISITS (EDV), HOSPITAL ADMISSIONS, OR DOCTOR'S VISITS IN CHILDREN, ATTRIBUTABLE TO SHORT-TERM PM EXPOSURE

Study	Endpoint	Ages (years)	PM Effects	Pollutants	Remarks (N)
Norris et al. (1999) Seattle WA	EDV for asthma	0-17	PM_{10} signif. all hosp., lt.-scatter each	PM_{10}, light scatter, CO, SO_2, NO_2	PM_1 index from light scattering
Delfino et al. (1997) Montreal PQ	EDV, 1992-1993	0-1	H+ signif. only 1993	PM_{10}, $PM_{2.5}$, SO_4, H+, O_3	
Rosas et al. (1998) Mexico City	emergency admissions for asthma	0-15	PM_{10} N.S.	PM_{10}, TSP, O_3, SO_2, NO_2	grass, fungal spores signif.
Lin et al. (1999) São Paulo, Brazil	Respiratory emergency visits	0-12	PM_{10} signif. w. and w/o co-pollutants	PM_{10}, O_3, SO_2, NO_2, CO	LRI, URI, wheezing w. co-pollutants
Braga et al. (1999) São Paulo, Brazil	Hospital admissions	0-12	PM_{10} signif., not w. O_3, CO	PM_{10}, SO_2, NO_2, CO	
Ostro et al. (1999) Santiago, Chile	Medical visit for LRI, URI	0-2	LRI 4-12%	PM_{10}, O_3	
		3-15	LRI 3-9%		
Garty et al. (1998) Israel	EDV for asthma	1-18	PM_{10} N.S.	PM_{10}, O_3, SO_2, NO_2	N = 1076
Atkinson et al. (1999) London UK	EDV for respiratory complaints	0-14	PM_{10} signif. total resp., asthma	PM_{10}, BS, O_3, SO_2, NO_2, CO	N.S. in 2-poll. models w. SO_2, NO_2
Medina et al. (1997) Paris, France	Doctor's house calls	0-14	Asthma signif. BS.	PM13, BS, SO_2, NO_2, O_3	Similar RR for PM13, SO_2, NO_2
Hajat et al. (1999) London U.K.	GP visits for asthma, LRI	0-14	PM_{10} N.S., BS signif. LRI	PM_{10}, BS, O_3, SO_2, NO_2, CO	
Sunyer et al. (1997) Barcelona Helsinki London, Paris	emergency admissions for asthma	0-14	BS positive, N.S. NO_2 and SO_2 signif.	BS, NO_2, SO_2	

Increased Infant and Child Mortality Associated with Short-Term PM Exposures

Table 6-41 shows the results of four recent studies, none in the U.S., in which excess mortality was associated with PM. Significant mortality was reported in three of the four studies, using $PM_{2.5}$ exposure for infants in Mexico City (Loomis et al., 1999), TSP exposure for school-age children (but not younger children) in Delhi (Cropper et al., 1997), and PM_{10} exposure for a composite group of children 0-14 years in Bangkok (Ostro et al., 1999). Pereira et al. (1998) did not find excess stillbirths associated with PM_{10} in São Paulo. These studies are highly diverse in terms of age group, location, and environment. As with adult mortality, there are no known biological mechanisms that specifically account for excess child mortality from short exposures to PM at levels found in these Latin American and Asian countries. However, the studies suggest that short-term PM exposure in general may cause deaths of some children in certain urban environments. The mortality findings are consistent with findings of less serious health effects from short-term particle exposure, represented by respiratory endpoints from lung function deficits through respiratory symptoms, medical encounters, and death, that may affect substantial numbers of children.

TABLE 6-41. NEONATAL, INFANT, AND CHILD MORTALITY ATTRIBUTABLE TO SHORT-TERM PM EXPOSURE

Study	Mortality	Ages	PM Effects	Pollutants	Remarks (N)
Loomis et al. (1999) Mexico City	Total	0-11 mo	$PM_{2.5}$ signif. w and w/o copollutant	$PM_{2.5}$, O_3, NO_2	
Pereira et al. (1998) São Paulo, Brazil	Intrauterine	0 d	PM_{10} N.S.	PM_{10}, O_3, SO_2, NO_2, CO	
Cropper et al. (1997) Delhi, India	Total, cardiovascular, respiratory	0-4 yr	TSP N.S. for total mort.	TSP, SO_2, NO_x	Similar RR in both age groups, s.e. not given
		5-14 yr	TSP signif. for total mort		
Ostro et al. (1998) Bangkok, Thailand	Total, cardiovascular, respiratory	0-5 yr	PM_{10} signif. all	PM_{10}, $PM_{2.5}$	

Pulmonary Function or Respiratory Symptoms Associated with Longer-Term PM Exposures

Table 6-42 shows a number of studies related to longer-term PM exposures. All of these studies involve school-age children, and many use PM_{10} as an index. PM_{10} is not always significantly associated with adverse health effects, although other indicators sometimes are (SO_4, H+). There are no known biological mechanisms by which elevated PM exposure over long periods of time may be associated with increased risk of respiratory symptoms or decreased pulmonary function in children, although such mechanisms may exist. However, the epidemiology findings from different sites are too diverse to allow simple conclusions about underlying causes.

TABLE 6-42. RECENT PM STUDIES OF PULMONARY FUNCTION TESTS OR RESPIRATORY SYMPTOMS IN SCHOOL-AGE CHILDREN ATTRIBUTABLE TO LONG-TERM PM EXPOSURE

Study	Endpoint	Ages (years)	PM Effects	Pollutants	Remarks (N)
Dockery et al. (1996) 24 U.S., Canad. Communities	Various	8-12	SO_4 signif. bronchitis; PM_{10} N.S. any endpoint	PM_{10}, PM2.1, SO_4, H+, SO_2, O_3	
Braun-Fahrlander (1997) 10 Swiss comm.	Various	6-15	Cough, bronchitis, wheeze signif. pollut.	PM_{10}, O_3, NO_2, SO_2	
von Mutius (1995) Leipzig, Ger.	URI	9-11	PM signif. winter	PM beta, SO_2, NO_2	(N = 1854)
Raizenne et al. (1996) 24 U.S., Canad. Communities	Pulmonary function	8-12	Strong signif. H+, signif. PM_{10}	PM_{10}, PM2.1, SO_4, H+, SO_2, O_3	
Lewis et al. (1998) N.S.W. Australia	Night cough, chest colds, wheeze	8-10	PM_{10} signif. chest colds, night cough. N.S. wheeze.	PM_{10}, SO_2	(N = 3023)
Peters et al. (1999a,b) 12 So. CA communities	Asthma, bronchitis, cough, wheeze, lung function	Grades 4, 7 (9, 12 years)	PM_{10} signif. FVC, MMFR N.S. FEV_1, symptoms, PEFR,		(N =150 each in grades 4, 7)

Increased Infant Mortality, Intrauterine Growth Reduction, or Preterm Delivery

Finally, a number of recent studies associated with children less than one year old is pointing toward the possibility of adverse consequences to the mother, fetus, and infant, from prolonged PM exposure during and shortly after pregnancy. Some of the studies shown in Table 6-43 were discussed in Section 6.3.3. There appears to be a possible relationship between preterm birth (< 37 weeks gestational age) or low birth weight (< 2,500 g) and PM exposure in several locations. A significant relationship with PM_{10} and $PM_{2.5}$ was found in Teplice, Czech Republic (Dejmek et al., 1999), but not with PM_{10} in Los Angeles (Ritz and Yu, 1999). Bobak and Leon (1999) did not find a relationship of low birth weight to TSP. There was a significant risk of low birth weight and preterm delivery in Beijing (Xu et al., 1995; Wang et al., 1997) associated with TSP, but SO_2 was the only co-pollutant available. However, low birth weight is known to be an important risk factor for infant mortality, so that the findings of excess mortality in U.S. and Czech infants (Woodruff et al., 1997; Bobak and Leon, 1992) is consistent with many of the other findings on intrauterine growth reduction (IUGR).

Several issues still require resolution. Dejmek et al. (1999) characterize IUGR as low-weight-for-gestational-age, whereas others use a fixed weight for full-term infants (37 to 44 weeks) without adjusting for gestational age. Dejmek et al. (1999) also find the average PM during the first month of pregnancy as the index of fetal exposure, whereas Xu et al. (1995), Wang et al. (1997), and Ritz and Yu (1999) use final trimester averages. This is difficult to interpret in terms of underlying biological mechanisms. In spite of these methodological differences, there appears to be an identifiable PM risk to the fetus and infant.

The findings of adverse health effects in infants or young children associated with air pollution exposures of one month to one year is of particular importance in interpreting findings of long-term effects in adults. The duration of exposure in infants and young children is much than that used to characterize adult exposure in long-term prospective cohort studies. While the biological mechanisms for PM-related health effects in children are not necessarily the same as in adults, the child studies do suggest less-than-chronic exposures may be harmful to adults as well as to children. This hypothesis merits further investigation.

TABLE 6-43. OTHER NEONATAL AND INFANT EFFECTS ATTRIBUTABLE TO LONGER TERM PM EXPOSURE

Study	Effects	Ages	PM Effects	Pollutants	Remarks (N)
Woodruff et al. (1997)	Total infant mortality, SIDS, resp.	1-11 mo	PM_{10} signif. total, SIDS, respir. NBW	PM_{10}	PM_{10} avg over 2 mos.
Bobak and Leon (1992) Czech. Repub.	Total infant mortality, respir. mort.	0+ d neonatal	TSP-10 N.S.	TSP-10, SO_2, NO_x	Ecologic study; TSP indexed as 90th percentile
		post-neonatal	TSP signif.		
		post, respir.	TSP signif.		
Bobak and Leon (1999) Czech. Rep.	Low birth wt. Stillbirth	0 d	TSP N.S.	TSP, SO_2, NO_x	
Dejmek et al. (1999) Teplice, Czech. Rep.	Intrauterine growth reduction	0 d	First month $PM_{2.5} > 37$, $PM_{10} > 40$ signif.	PM_{10}, $PM_{2.5}$, SO_2, NO_x, PAH	30-d avg PM per month of pregnancy
Ritz and Yu (1999) Los Angeles, CA	Low birth weight (adj. Gest age)	0 d	Last trimester PM_{10} N.S.	PM_{10}, O_3, NO_2, CO	CO signif., more signif. with co-pollutants
Wang et al. (1997) Beijing, PRC	Low birth weight	0 d.	TSP signif. increases risk of LBW	TSP, SO_2 in third trimester	SO_2 also signif. Small reduc. mn.wt.
Xu et al. (1995) Beijing, PRC	Preterm gestational age	0 d	TSP signif. lag 5-10 days	TSP, SO_2	SO_2 also signif.

6.4.5 Consistency of Mortality and Morbidity Effects (Coherence)

The criterion of *coherence* was emphasized by Bates (1992) and it was discussed in detail by U.S. Environmental Protection Agency (1996; Section 12.6.4.3). It consists of the assessment of the entire body of epidemiology data, as well as supporting medical and toxicological data, for consistency in a variety of health outcomes by its repeated observation in different populations of individuals, under different circumstances of duration and level of ambient PM concentration, and in different places. The adverse health effects associated with PM are: (1) lung function decrements; (2) respiratory symptoms, or exacerbation of symptoms requiring bronchodilator therapy; (3) hospital admissions for respiratory and cardiovascular causes; (4) emergency medical visits; and (5) death from cardiopulmonary causes. None of the currently available time series studies are based on a temporal sequence of these outcomes in single individuals. Panel studies

of respiratory symptoms look at the repeated occurrence of symptoms in individuals, but not at the progression of, for example, repeated respiratory symptoms into hospital admissions, or repeated hospital admissions into cardiopulmonary mortality. Indeed, the extent to which this progression occurs in individuals is uncertain. While some studies are currently underway that will examine large public health data bases, no preliminary results have been published. It is therefore necessary to look at indirect indicators of the quantitative consistency at a group level.

For example, in asthmatic panel studies, mild asthmatics rarely go to the hospital. Asthmatic symptoms may be controlled by medication use, or may be sufficiently mild that changes in pulmonary function or occurrence of symptoms can be detected and self-treated, but not so severe that they lead to a hospital or emergency department visit. Moderate to severe asthmatics usually are not assessed in panel studies, but these are the subjects more likely to go to a hospital or emergency department for asthmatic episodes. Ambient PM concentrations may not be associated with a progression from mild to severe asthmatic symptoms, since mild and severe asthmatics are distinct sub-groups.

It is by no means self-evident that the numbers of events on some appropriate baseline of time and reference group will follow a sequence (1) > (2) > (3) > (4). There are many causes other than PM for each of these endpoints. Long-term lung function decreases with age and chronic respiratory illness. It is affected by cigarette smoking behavior and exposure to occupational air pollution. A number of studies have found an association of mortality with reduced ventilatory function (Strachan, 1992; Higgins and Keller, 1970). Strachan (1992) notes that little is known about the constitutional or environmental determinants of ventilatory function decline. Longitudinal studies such as the Harvard Six Cities study could be used to evaluate a hypothetical causal pathway. Ambient PM concentration $\longrightarrow$ PM exposure $\longrightarrow$ FEV_1 decrease $\longrightarrow$ death in individuals. The decline of FEV_1 may be either a precursor of ambient-PM-induced health effects, or an independent factor in susceptibility to air pollution effects leading to hospital respiratory admissions or mortality.

The relationship of hospital admissions and mortality in independent studies has been studied. Hospital admissions may be affected by health status as well as by environmental factors. For an individual, the relationship of prior hospital admissions to mortality is uncertain. In general non-environmental studies (Seneff et al., 1995), hospitalization in the preceding few months or year is a good predictor of subsequent hospital admissions or death. The major risk

factor for subsequent death was the development and severity of non-respiratory organ system dysfunction. It is possible that medical intervention is provided to the most seriously ill individuals, but if these interventions reduce the likelihood of death associated with elevated ambient PM concentration and exposure, then many of the deaths attributed to ambient PM may occur in a less frequently hospitalized population. Quantitative consistency would be suggested if there were more cause-specific hospital admissions than deaths from respiratory or cardiovascular causes as described in U.S. Environmental Protection Agency (1996).

An Ecological Assessment

In the absence of appropriate multi-endpoint cohort studies, some evaluations looking at group-level outcomes may provide some insight. Figure 6-3 shows three indicators for the Harvard Six Cities, using data from Dockery et al. (1993); Ferris et al. (1979) . The vertical axis is the relative risk of mortality from (Dockery et al., 1993), the x-axis is the mean $PM_{2.5}$ concentration for each city from the same paper, and the y-axis is the mean deviation from expected FEV_1 (not necessarily in the same subjects in each city) (Ferris et al., 1979). The close linear relationship of mortality RR to $PM_{2.5}$ was noted in U.S. Environmental Protection Agency (1996). The 2-dimensional relationships to $PM_{2.5}$ are shown in Figure 6-4. The relationship of mean FEV_1 to $PM_{2.5}$ shows a general trend of greater FEV_1 decrements with increasing $PM_{2.5}$, but the relationship is weaker and appears nonlinear. As did the cohort in Strachan (1992), the cohort in Dockery et al. (1993) should show a relationship between pulmonary function and mortality unrelated to ambient PM, although this has not yet been evaluated. Further evaluation using other ambient PM indices such as $PM_{2.5}$ is needed.

6.4.6 Effects of PM Size Distribution and Composition

6.4.6.1 Summary of Previous 1996 PM AQCD

Most of the information about size-fractionated PM health effects in U.S. Environmental Protection Agency (1996) was based on PM_{10}, with supporting studies using BS, SO_4, or BS. The only daily time series study on mortality (Schwartz et al., 1996) evaluated the single-pollutant effects of $PM_{2.5}$, $PM_{10-2.5}$, and PM_{10} in the Harvard Six Cities study. While two-pollutant models with both $PM_{2.5}$ and $PM_{10-2.5}$ were fitted, the only results reported were that,

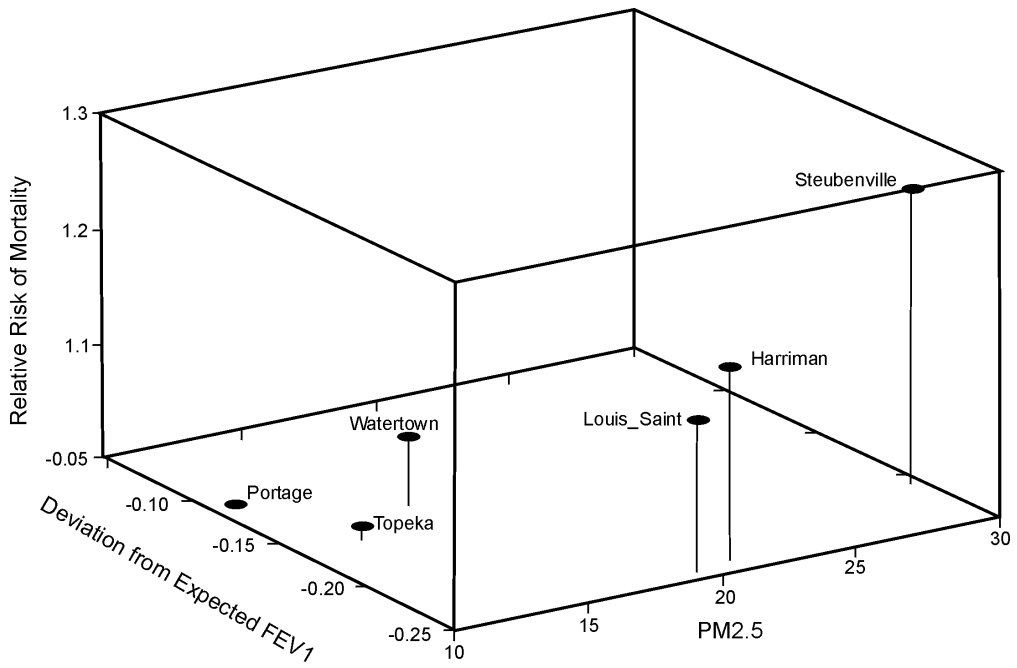

Figure 6-3. Relationship of ambient $PM_{2.5}$ to relative risk of mortality and to deviations of FEV_1 from its expected (standard) value in the Harvard Six Cities study (Ferris et al., 1979; Dockery et al., 1993).

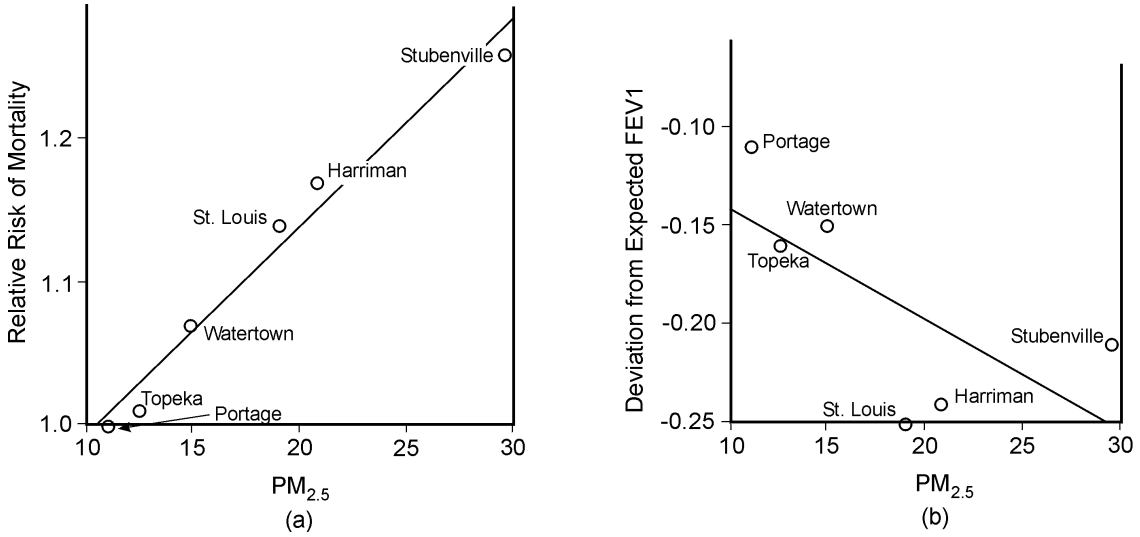

Figure 6-4. Relationship of two health endpoints to $PM_{2.5}$ in the Six Cities study. (a) strong linear relationship between relative risk of mortality and mean $PM_{2.5}$; (b) nonlinear or weakly linear relationship between mean FEV_1 decrement and $PM_{2.5}$. Data from (Dockery et al., 1993; Ferris et al., 1979).

"The estimated effects of the 5th to the 95th percentile increase for $PM_{2.5}$ (5.8%, CI 4.3% to 7.4% [excess mortality per 38.8 $\mu g/m^3$]) was unchanged while the estimate for CM [coarse matter, $PM_{10-2.5}$] (-0.6%, 95% CI -2.2% to 1.0% [excess mortality per 29.1 $\mu g/m^3$]) was essentially zero." Significant or marginally significant $PM_{2.5}$ effects on mortality were identified in most of the cities, and very significant effects in the combined analysis. Only one city suggested a significant effect of $PM_{10-2.5}$.

Long-term prospective cohort studies used single-pollutant $PM_{2.5}$, $PM_{10-2.5}$, PM_{10}, SO_4 or H+ (Dockery et al., 1993) or $PM_{2.5}$ and SO_4 (Pope et al., 1995). Neither study evaluated effects of gaseous co-pollutants.

The studies cited in Sections 6.2 and 6.3 include a number of studies in which $PM_{2.5}$ was observed, or estimated using site-specific data. A few studies have even included $PM_{1.0}$ as an indicator of the effects of ultrafine particles. These studies are tabulated below in extensive detail because of the importance of characterizing the health effects of fine particles. Many of the new $PM_{2.5}$ studies include one or more gaseous co-pollutants, and (Fairley, 1999) included both $PM_{2.5}$ and PM_{10-25}, the nitrate (NO_3) component of PM_{10}, and gaseous co-pollutants. The new studies thus greatly expand the information available compared to U.S. Environmental Protection Agency (1996).

6.4.6.2 Assessment of Effects of $PM_{2.5}$ and Gaseous Co-Pollutants

Several recent studies in Santa Clara County, Toronto, and Mexico City have been reported in sufficient detail to allow evaluation of the sensitivity of $PM_{2.5}$ health effects estimates to co-pollutants and lag times or moving averages used in the model. These analyses generally use Poisson regression models for daily mortality counts or hospital admissions, non-parametric smoothers for temporal detrending, and adjustments for temperature and other meteorological variables, thus are likely to provide adequate control of non-pollution factors that affect health endpoints. The hospital admissions studies in Toronto are discussed first (Burnett et al., 1997b, 1999), then the mortality studies in Toronto (Burnett et al., 1998) and in Mexico City (Borja-Abuto et al., 1998; Loomis et al., 1999).

Hospital Admissions in Toronto

Burnett et al., 1997 Study

There is an extensive reporting of results for 1-, 2-, and 4-pollutant models for summer hospital admissions for respiratory causes (Table 6-44) and cardiovascular causes (Table 6-45) separately. Table 6-44 shows the respiratory admissions relative risks (RR) and confidence limits (LCL, UCL) for three PM indices (estimated $PM_{2.5}$ or $EPM_{2.5}$, estimated PM_{10} or EPM_{10}, and estimated coarse fraction $PM_{10-2.5}$ or ECF), and for four co-pollutants (O_3, NO_2, SO_2, CO). All of the single-pollutant models from Table 2, 2-pollutant models with one of the PM indices from Tables 4 and 5, and 4-pollutant models in Table 6 in (Burnett et al., 1997) are shown. The sensitivity of the PM and co-pollutant predictors of daily respiratory admissions may be assessed by use of the t-statistics in the last 5 columns. Although t-statistics are less useful for comparisons across studies, they are extremely helpful for within-study assessments shown here.

The $PM_{2.5}$ t-statistic for respiratory admissions shows slight attenuation when CO is included in the model, moderate attenuation from single-pollutant estimates when O_3 and SO_2 are included in the model, but major attenuation when NO_2 or 3 co-pollutants are included. There appears to be a substantial collinearity involving $PM_{2.5}$ (averaged 1+2+3+4 days) and NO_2 (averaged 0+1+2+3+4 d). There is little collinearity of $PM_{2.5}$ with CO (averaged 2+3+4 d).

The PM_{10} t-statistic for respiratory admissions shows slight attenuation when CO and O_3 are included in the model, moderate attenuation from single-pollutant estimates when SO_2 is included in the model, but major attenuation when NO_2 or 3 co-pollutants are included. There appears to be a substantial collinearity involving PM_{10} (averaged 0+1+2+3 d) and NO_2 (averaged 0+1+2+3+4 d). There is little collinearity of PM_{10} with CO or O_3 in summer.

The $PM_{10-2.5}$ t-statistic for respiratory admissions shows slight attenuation when CO or O_3 are included in the model, moderate attenuation from single-pollutant estimates when SO_2 is included in the model, but major attenuation when NO_2 or 3 co-pollutants are included. There appears to be a substantial collinearity involving $PM_{10-2.5}$ (averaged 0+1+2+3+4 d) and NO_2 (averaged 0+1+2+3+4 d). There is little collinearity of $PM_{10-2.5}$ with CO or O_3 in summer.

The $PM_{2.5}$ t-statistic for cardiovascular admissions shows slight attenuation when CO is included in the model, moderate-to-large attenuation from single-pollutant estimates when O_3, NO_2, SO_2 or are included in the model, but major attenuation when 3 co-pollutants are included.

TABLE 6-44. SENSITIVITY OF PM RELATIVE RISK ESTIMATE TO CO-POLLUTANTS MODELS (IN BURNETT ET AL., 1997b; TABLES 2, 4, 6)

ENDPOINT: Hospital admissions for respiratory causes.

SITE: Toronto, Canada, summers.

	PM Relative Risk			t-statistics for RR				
PM Index	RR	LCL	UCL	PM	O_3	NO_2	SO_2	CO
$EPM_{2.5}$ (25) Moving average lag days 1+2+3+4	1.086	1.034	1.141	3.3				
	1.062	1.010	1.118	2.3	4.6			
	1.030	0.972	1.091	1.0		3.1		
	1.062	1.003	1.125	2.1			1.9	
	1.081	1.025	1.141	2.8				0.5
	0.998	0.954	1.043	-0.1	4.7	2.3	1.6	
EPM_{10} (50) Moving average lag days 0+1+2+3	1.109	1.045	1.177	3.4				
	1.098	1.036	1.164	3.2	5.0			
	1.021	0.945	1.104	0.5		2.8		
	1.079	1.005	1.159	2.1			1.7	
	1.106	1.035	1.181	3.0				0.5
	1.014	0.940	1.094	0.4	4.7	1.8	1.5	
E. Coarse fraction (25) Moving average lag days 0+1+2+3+4	1.127	1.052	1.207	3.4				
	1.110	1.038	1.187	3.0	4.9			
	1.048	0.957	1.149	1.0		3.0		
	1.098	1.016	1.188	2.4			2.0	
	1.121	1.041	1.208	3.0				0.7
	1.037	0.950	1.133	0.8	4.7	1.7	1.5	

Other PM indices: CoH, $SO_4^=$, H+

Note: $PM_{2.5}$, avg. lags 1-4 days; PM_{10}, avg. lags 0-3 d; CP, avg. lags 0-4 d; SO_4, avg. lags 1-4 d; H+, avg. lags 0-1 d; CoH, dayt. avg. lags 0-4 d; O_3, dayt. avg. lags 1-3 d; NO_2, dayt. avg. lags 0-4 d; SO_2, max. avg. lags 0-3 d; CO, max. avg. lags 2-4 days.

1 There appears to be a substantial collinearity involving $PM_{2.5}$ with NO_2, SO_2, and possibly O_3.

2 There is little collinearity of $PM_{2.5}$ with CO (averaged 2+3+4 d).

TABLE 6-45. SENSITIVITY OF PM RELATIVE RISK ESTIMATE TO CO-POLLUTANTS MODELS IN (BURNETT ET AL., 1997b; TABLES 2, 5, 6)

ENDPOINT: Hospital admissions for cardiovascular causes.

SITE: Toronto, Canada, summers.

	PM Relative Risk			t-statistics for RR				
PM Index	RR	LCL	UCL	PM	O_3	NO_2	SO_2	CO
$EPM_{2.5}$ (25) Moving average lag days 1+2+3+4	1.072	0.994	1.156	1.8				
	1.032	0.953	1.117	0.8	3.5			
	1.039	0.960	1.125	1.0		2.7		
	1.046	0.966	1.133	1.1			2.2	
	1.065	0.983	1.154	1.5				0.8
	0.984	0.895	1.082	-0.3	3.7	1.7	1.6	
EPM_{10} (50) Moving average lag days 0+1+2+3	1.121	1.014	1.1238	2.2				
	1.091	0.986	1.206	1.7	3.6			
	1.036	0.922	1.163	0.6		2.3		
	1.072	0.964	1.192	1.3			1.9	
	1.109	1.001	1.229	2.0				0.7
	0.986	0.875	1.112	-0.2	3.8	1.6	1.6	
E. Coarse fraction (25) Moving average lag days 0+1+2+3+4	1.205	1.082	1.341	3.4				
	1.192	1.073	1.325	3.3	3.7			
	1.139	0.992	1.308	1.8		1.4		
	1.168	1.037	1.317	2.6			1.4	
	1.198	1.072	1.340	3.2				0.5
	1.121	0.981	1.282	1.7	3.8	0.6	1.4	

Note: Other PM indices CoH, $SO_4^=$, H+

Note: $PM_{2.5}$, avg. lags 1-4 days; PM_{10}, avg. lags 0-3 d; CP, avg. lags 0-4 d; SO_4, avg. lags 1-4 d; H+, avg. lags 0-1 d; CoH, dayt. avg. lags 0-4 d; O_3, dayt. avg. lags 1-3 d; NO_2, dayt. avg. lags 0-4 d; SO_2, max. avg. lags 0-3 d; CO, max. avg. lags 2-4 days.

The PM_{10} t-statistic for cardiovascular admissions shows slight attenuation when CO and O_3 are included in the model, moderate attenuation from single-pollutant estimates when SO_2 is included in the model, but major attenuation when NO_2 or 3 co-pollutants are included. There

appears to be a substantial collinearity involving PM_{10} (averaged 0+1+2+3 d) and NO_2 (averaged 0+1+2+3+4 d). There is little collinearity of PM_{10} with CO or O_3 in summer.

The $PM_{10-2.5}$ t-statistic for respiratory admissions shows slight attenuation when CO, O_3 or SO_2 are included in the model, but major attenuation when NO_2 or all 4 co-pollutants are included. There appears to be a substantial collinearity involving $PM_{10-2.5}$ (averaged 0+1+2+3+4 d) and NO_2 (averaged 0+1+2+3+4 d). There is little collinearity of $PM_{10-2.5}$ with CO or O_3 in summer.

The averaging times used for PM indices and for the gaseous pollutants are all much longer than is found in many other studies. Results for shorter averaging times would also be of interest, but were not reported. The longer averaging times may have corresponded to summer episodes, or may have been necessary in order to find statistically significant relationships in the relatively short time series data sets (summers, 1992-1994).

Inferences that may be drawn from the data set are limited by the use of estimated $PM_{2.5}$ and PM_{10} data. This introduces an unknown measurement error into these PM indices. Other measured PM indices are also available in the paper (H^+, SO_4, Coefficient of Haze).

The $PM_{2.5}$ estimates achieve statistical significance for respiratory admissions, but not for cardiovascular admissions, and even then, are not significant when NO_2 is included as a co-pollutant. Conversely, the coarse fraction $PM_{10-2.5}$ estimates are highly significant predictors for both respiratory and cardiovascular admissions, except when NO_2 is included as a co-pollutant. Even then, ECF is positive and marginally significant ($0.05<P<0.10$) for cardiovascular causes when NO_2 is included as a co-pollutant. The greater significance for the estimated coarse fraction effect is unexpected, since coarse fraction mass may have greater measurement error than $PM_{2.5}$.

Burnett et al., 1999 Study

This study assessed the effects of particles and gaseous pollutants on hospital admissions over a much longer time span, 1980-1994, than did Burnett et al. (1997a). There is an extensive reporting of results for 1-, 2-, and multi-pollutant models for annual daily hospital admissions for respiratory infection (Table 6-46), asthma (Table 6-47), obstructive lung disease (Table 6-48), heart failure (Table 6-49), ischemic heart disease (Table 6-50), and dysrhythmias (Table 6-51). There were no systematic PM effects on cerebral vascular disease and diseases of the peripheral

TABLE 6-46. SENSITIVITY OF PM RELATIVE RISK ESTIMATE TO CO-POLLUTANTS MODELS IN (BURNETT ET AL., 1999; TABLES 3, 4, 5)

ENDPOINT: Hospital admissions for respiratory infections.

SITE: Toronto, Canada.

		PM Relative Risk			t-statistics for RR				
Pollutant	Lags, d averaged	RR	LCL	UCL	PM	O_3	NO_2	SO_2	CO
$EPM_{2.5}$ (25)	0+1+2	1.108	1.072	1.145	6.09				
EPM_{10} (50)	0+1+2	1.112	1.074	1.152	5.96				
ECF (25)	0+1+2	1.093	1.046	1.142	4.00				
O_3	1+2					4.29			
NO_2	0						5.53		
SO_2	0+1+2							5.04	
CO	0								4.25
$NO_2 + SO_2 + O_3$						4.04	3.38	3.43	
$NO_2 + SO_2 + O_3 + EPM_{2.5}$		1.098	1.034	1.166	3.03	3.88	2.94	1.04	
$NO_2 + SO_2 + O_3 + E_{PM10}$		1.113	1.010	1.227	2.16	3.44	3.03	1.56	
$NO_2 + SO_2 + O_3$ + ECF		1.018	0.915	1.133	0.33	3.63	3.34	3.06	
Table 5: $NO_2 + O_3 + EPM_{2.5}$		1.121	1.066	1.178	4.46	3.80	3.31		

circulation, which are not shown here. Tables 6-46 through 6-51 show the admissions relative risks (RR) and confidence limits (LCL, UCL) for three PM indices (estimated $PM_{2.5}$ or $EPM_{2.5}$, estimated PM_{10} or EPM_{10}, and estimated coarse fraction $PM_{10-2.5}$ or ECF), and for four co-pollutants (O_3, NO_2, SO_2, CO), along with the optimal moving average or lag times for each endpoint and each pollutant. All of the single-pollutant models from Table 3, and multipollutant models from Tables 4 and 5 in (Burnett et al., 1999) are shown. Burnett et al. (1999) drew conclusions based on their Table 5 models. The Table 4 models all use the "optimal" model with gaseous pollutants as their starting point, with each PM index added to this model. The sensitivity of the PM and co-pollutant predictors of daily respiratory admissions may be assessed

TABLE 6-47. SENSITIVITY OF PM RELATIVE RISK ESTIMATE TO CO-POLLUTANTS MODELS IN (BURNETT ET AL., 1999; TABLES 3, 4, 5)

ENDPOINT: Hospital admissions for asthma.

SITE: Toronto, Canada.

		PM Relative Risk			t-statistics for RR				
Pollutant	Lags, d averaged	RR	LCL	UCL	PM	O_3	NO_2	SO_2	CO
$EPM_{2.5}$ (25)	0+1+2	1.064	1.024	1.106	3.22				
E_{PM10} (50)	0+1+2	1.089	1.037	1.144	3.39				
ECF (25)	2+3+4	1.111	1.058	1.166	4.20				
O_3	1+2+3					4.63			
NO_2	0						2.37		
SO_2	2+3+4							1.76	
CO	0								3.92
CO + SO_2 + O_3						4.56		1.53	3.72
CO + SO_2 + O_3 + $EPM_{2.5}$		1.027	0.965	1.093	0.85	4.40		1.13	3.15
CO + SO_2 + O_3 + E_{PM10}		1.031	0.937	1.135	0.63	4.20		1.27	3.32
CO + SO_2 + O_3 + ECF		1.170	1.041	1.314	2.63	3.49		0.25	3.84
Table 5: CO + O_3 + ECF		1.179	1.036	1.342	3.04	3.48			3.86

by use of the t-statistics in the last 5 columns. Burnett et al. (1999) presented coded t-statistics for co-pollutant models, so only single-digit t values may be inferred.

The PM t-statistics for respiratory infections in Table 6-46 show substantial attenuation when NO_2, SO_2, and O_3 are included in the models. The estimated coarse fraction loses almost all effect when gaseous pollutants are included. However, when SO_2 is omitted as not consistently significant, then the Table 5 model with $EPM_{2.5}$ is less attenuated, and appears to be more significant than when SO_2 is included is included in the Table 4 co-pollutant model. Thus, there appears to be a significant $PM_{2.5}$ effect on respiratory infection admissions that is not wholly attributable to gaseous pollutants.

TABLE 6-48. SENSITIVITY OF PM RELATIVE RISK ESTIMATE TO CO-POLLUTANTS MODELS IN (BURNETT ET AL., 1999; TABLES 3, 4, 5)

ENDPOINT: Hospital admissions for obstructive lung disease.

SITE: Toronto, Canada.

		PM Relative Risk			t-statistics for RR				
Pollutant	Lags, d averaged	RR	LCL	UCL	PM	O_3	NO_2	SO_2	CO
$EPM_{2.5}$ (25)	1+2	1.048	0.998	1.100	1.89				
E_{PM10} (50)	2	1.069	1.013	1.128	2.44				
ECF (25)	2+3+4	1.128	1.049	1.213	3.26				
O_3	2+3+4					4.23			
NO_2	1						1.07		
SO_2	2							0.05	
CO	0								1.48
CO + O_3						3.80			1.50
CO + O_3 + $EPM_{2.5}$		1.046	0.986	1.110	1.28	3.69			1.22
CO + O_3 + EPM_{10}		1.077	0.978	1.186	1.59	3.41			1.39
CO + O_3 + ECF		1.172	0.952	1.443	1.90	2.74			1.52
Table 5: CO + O_3 + ECF		1.172	0.952	1.443	1.90	2.74			1.52

The PM t-statistics for asthma admissions in Table 6-47 show substantial attenuation when CO, SO_2, and O_3 are included in the models. Only the estimated coarse fraction retains statistical significance when gaseous pollutants are included. However, when SO_2 is omitted as not consistently significant, then the Table 5 ECF effect is slightly larger, and significance of the coarse fraction is greater than the Table 4 co-pollutant model. Thus, there appears to be a significant $PM_{10-2.5}$ effect on asthma admissions that is not wholly attributable to gaseous pollutants.

The PM t-statistics for obstructive lung disease in Table 6-48 show substantial attenuation when CO and O_3 are included in the models. The estimated $PM_{2.5}$, PM_{10}, and coarse fractions lose their statistically significant effects on admissions for obstructive lung disease when gaseous pollutants are included, although the coarse fraction is still marginally significant.

TABLE 6-49. SENSITIVITY OF PM RELATIVE RISK ESTIMATE TO CO-POLLUTANTS MODELS IN (BURNETT ET AL., 1999; TABLES 3, 4, 5)

ENDPOINT: Hospital admissions for heart failure.

SITE: Toronto, Canada.

		PM Relative Risk			t-statistics for RR				
Pollutant	Lags, d averaged	RR	LCL	UCL	PM	O_3	NO_2	SO_2	CO
$EPM_{2.5}$ (25)	0+1+2	1.066	1.025	1.108	3.20				
EPM_{10} (50)	0+1+2	1.097	1.042	1.155	3.51				
ECF (25)	0+1+2	1.079	1.023	1.314	2.79				
O_3	1+2					1.42			
NO_2	0						6.33		
SO_2	0							3.85	
CO	0+1								5.71
CO + NO_2							3.44		2.08
CO + NO_2 + $EPM_{2.5}$		1.019	0.959	1.082	0.60		3.33		1.83
CO + NO_2 + EPM_{10}		1.050	0.954	1.155	1.00		3.18		1.84
CO + NO_2 + ECF		1.071	0.956	1.201	1.18		3.11		2.04
Table 5: CO + NO_2							3		2

The PM t-statistics for heart failure admissions in Table 6-49 show substantial attenuation when NO_2 and CO are included in the models. The $PM_{2.5}$, PM_{10}, and estimated coarse fractions lose even marginal statistically significant effects on admissions for heart failure when these gaseous pollutants are included.

The very significant single PM t-statistics for ischemic heart disease admissions in Table 6-50 show almost complete attenuation when NO_2 and SO_2 are included in the models. The NO_2 and SO_2 effects are somewhat attenuated, but remain statistically significant when PM_{10} only 1 of the 3 respiratory endpoints (admissions for asthma) retains a clearly significant effect of $PM_{10-2.5}$, after specific co-pollutants are included in the models. None of the cardiovascular or

TABLE 6-50. SENSITIVITY OF PM RELATIVE RISK ESTIMATE TO CO-POLLUTANTS MODELS IN (BURNETT ET AL., 1999; TABLES 3, 4, 5)

ENDPOINT: Hospital admissions for ischemic heart disease.

SITE: Toronto, Canada.

		PM Relative Risk			t-statistics for RR				
Pollutant	Lags, d averaged	RR	LCL	UCL	PM	O_3	NO_2	SO_2	CO
$EPM_{2.5}$ (25)	0+1+2	1.080	1.054	1.105	6.08				
EPM_{10} (50)	0+1+2	1.084	1.053	1.115	5.55				
ECF (25)	2+3+4	1.037	1.013	1.062	3.02				
O_3	1+2+3					0.99			
NO_2	0						8.40		
SO_2	2+3+4							6.13	
CO	0								6.46
$NO_2 + SO_2$							6.10	2.07	
$NO_2 + SO_2 + EPM_{2.5}$		1.031	0.985	1.080	1.32		5.45	1.20	
$NO_2 + SO_2 + EPM_{10}$		0.996	0.967	1.025	-0.3		5.56	1.98	
$NO_2 + SO_2$ + ECF		0.985	0.871	1.112	-0.2		5.94	2.03	
Table 5: $NO_2 + SO_2$							6.10	2.07	

circulatory endpoints appear to show clearly significant effects for any PM index when specific co-pollutants are included in the model. Marginally significant effects of the coarse fraction for COPD and PM_{10} for dysrhythmia are also noteworthy in this context.

The differences between the previous study (Burnett et al., 1997a) and this study require further elaboration. The early study looked only at summer outcomes, for combined respiratory causes and combined cardiovascular causes, rather than year-round effects for more specific causes. Combining the specific causes, and looking for seasonal effects, might have found more similar results in this study.

Differences in PM and co-pollutant moving averages might also account for different findings. The $PM_{2.5}$ moving average in (Burnett et al., 1997) was 1+2+3+4 days, whereas the moving averages for the significant effect for $PM_{2.5}$ in Table 6-46 was 0+1+2 days, the

TABLE 6-51. SENSITIVITY OF PM RELATIVE RISK ESTIMATE TO CO-POLLUTANTS MODELS IN (BURNETT ET AL., 1999; TABLES 3, 4, 5)

ENDPOINT: Hospital admissions for dysrhythmias.

SITE: Toronto, Canada.

		PM Relative Risk			t-statistics for RR				
Pollutant	Lags, d averaged	RR	LCL	UCL	PM	O_3	NO_2	SO_2	CO
$EPM_{2.5}$ (25)	0	1.061	1.019	1.104	2.91				
EPM_{10} (50)	0	1.084	1.029	1.142	3.03				
ECF (25)	0	1.051	0.998	1.108	1.88				
O_3	2+3+4					1.71			
NO_2	0+1+2						1.73		
SO_2	0							1.43	
CO	0+1								3.60
CO + O_3						1.58			3.52
CO + O_3 + $EPM_{2.5}$		1.048	0.985	1.115	1.49	1.63			2.50
CO + O_3 + EPM_{10}		1.089	0.991	1.197	1.77	1.58			2.58
CO + O_3 + ECF		1.072	0.961	1.195	1.24	1.53			3.29
Table 5: CO + O_3 + $EPM_{2.5}$		1.048	0.985	1.115	1.49	1.63			2.50

non-significant effects for $PM_{2.5}$ in Tables 6-47 through 6-51 were 0+1+2, 1+2, and 0 days. The $PM_{10-2.5}$ moving average in (Burnett et al., 1997a) was 0+1+2+3+4 days, whereas the moving averages for the significant effect for $PM_{2.5}$ in Table 6-47 was 2+3+4 days, the non-significant and the coarse PM fraction are included. Including $PM_{2.5}$ reduces the NO_2 effect slightly, and the SO_2 effect becomes non-significant.

The PM t-statistics for dysrhythmias in Table 6-51 show substantial attenuation when CO and O_3 are included in the models. The estimated $PM_{2.5}$, PM_{10}, and coarse fractions lose much of their effect when gaseous pollutants are included. However, there appears to be a positive

marginally significant PM_{10} effect on admissions for dysrhythmias that is not wholly attributable to gaseous pollutants.

The results of this study provide a rather mixed picture, Only 1 of the 3 respiratory endpoints (admissions for respiratory infections) retains a clearly significant effect of $PM_{2.5}$, and effects for $PM_{2.5}$ in Tables 6-46 and 6-48 through 6-51 were 0+1+2, 2+3+4, and 0 days. The co-pollutant moving averages and lag times were much more diverse across the health endpoints than the PM moving averages. It is not possible to generalize these findings into a single statement about the potential effect of gaseous pollutants as confounders of PM health effects for various endpoints at various time lags.

Mortality Studies

Fairley (1999) in Santa Clara County, California

This paper evaluates the effects of $PM_{2.5}$ and its co-pollutants in considerable detail, using data for 1989-1996, updating earlier studies (Fairley, 1990, 1994) discussed in (U.S. Environmental Protection Agency, 1996). Santa Clara County (SCC) is a major metropolitan area centered on the city of San Jose, just south of the San Francisco MSA. While particle concentrations from mobile sources, wood smoke and other stationary sources are relatively high during the winter, SO_2 concentrations are so low that they are no longer monitored in SCC. However, $PM_{2.5}$, $PM_{10-2.5}$, and PM_{10} were measured on an every-sixth-day schedule at the SCC San Jose 4th Street site from 1990. The analyses did not used imputed PM data, so that the sample sizes are only N = 408 for fine and coarse fractions from a dichot sampler, N = 823 for PM_{10} from dichot and hi-vol samplers, N = 523 for sulfate and 534 for nitrate (NO_3) samples from PM_{10}. The dichotomous sampling at this site also allowed collection of PM_{10} nitrate and sulfate species data. Daily measurements of CoH were also available for comparison with the 1980-1986 study (Fairley, 1990). Poisson regression models were fitted to daily mortality data, as well as to cardiovascular and respiratory mortality data, but extensive assessments for sensitivity to co-pollutant models are only reported for total mortality. Daily measurements were available for gaseous co-pollutants. Because of the sparse PM measurements, only concurrent-day and previous-day effects are considered.

The results are shown in Table 6-52. All of the $PM_{2.5}$ coefficients with gaseous co-pollutants are statistically very significant, and practically unchanged in magnitude, as are the

TABLE 6-52. SENSITIVITY OF PM RELATIVE RISK ESTIMATE TO CO-POLLUTANT MODELS IN (FAIRLEY, 1999; TABLE 4)

ENDPOINT: Mortality

SITE: Santa Clara County, California, 1989-1996.

	PM Relative Risk			t-statistics for RR								
PM Index	RR	LCL	UCL	PM	O_3	NO_2	SO_2	CO	CoH	NO_3	SO_4	CF
$PM_{2.5}$ 25 $\mu g/m^3$	1.085	1.034	1.138	3.3								
	1.091	1.036	1.148	3.3	1.1							
	1.108	1.049	1.171	3.7		-1.2						
	1.097	1.035	1.163	3.1				-0.8				
	1.098	1.021	1.180	2.5					-0.2			
	0.999	0.913	1.095	-0.0						1.9		
	1.090	1.031	1.153	3.0							0.0	
	1.100	1.043	1.160	3.5								-0.9
	1.117	1.049	1.190	3.4	1.4	-1.0		-0.1				
PM_{10} (50)	1.080	1.035	1.127	3.6								
CF (25)	1.045	0.933	1.171	0.8								
SO_4 (15)	1.328	1.059	1.665	2.5								
NO_3				3.4								
				3.5	1.5							
				3.3		-0.5						
				3.0				0.4				
				3.4	2.0	-0.9		1.6				

Note: All pollutants lag 0 except for CoH, CO, or NO_2 (lag 1 where they fit better). Ozone is 8-hr average.

$PM_{2.5}$ coefficients with CoH, SO_4, and $PM_{10-2.5}$, and these co-pollutant effects are greatly attenuated in size and significance when $PM_{2.5}$ is included. This suggests that $PM_{2.5}$ has an effect on mortality that is largely independent of all co-pollutants in the model *except* for the thoracic nitrate fraction (NO_3) in PM_{10}. The thoracic nitrate fraction appears slightly more significant as a predictor of total mortality than does $PM_{2.5}$. Further elaboration of the possible role of $PM_{2.5}$ and

nitrate in SCC would be of interest, such as the mortality effects of the non-nitrate thoracic particles (PM_{10}-NO_3) and the non-sulfate fine particles ($PM_{2.5}$-SO_4). Cause-specific mortality effects with co-pollutants included in the model would also be of interest.

Burnett et al. (1998) in Toronto, Canada

Although this paper emphasizes the role of CO in mortality, a great deal of information about PM effects is also provided. The paper emphasizes short-term exposure lags, either same-day or previous day (0 or 1) or their average. The results are shown in Table 6-53. There is an extensive reporting of results for 1- and 2-pollutant models for total mortality. Table 6-53 shows the relative risks (RR) and confidence limits (LCL, UCL) for five PM indices (estimated $PM_{2.5}$ or $EPM_{2.5}$, estimated PM_{10} or EPM_{10}, sulfates, TSP, and coefficient of haze or CoH). No results are reported for the estimated coarse fraction $PM_{10-2.5}$, a major omission. The t-statistics are given for models with and without CO as a co-pollutant for the five PM indicators, and for three gaseous pollutants (O_3, NO_2, SO_2).

All five PM indicators have a statistically significant relationship to mortality, although the significance is greatly reduced by inclusion of CO as a co-pollutant. None of the gaseous pollutants are statistically significant with inclusion of CO. The statistical significance of CO is only slightly diminished by the inclusion of a PM indicator, with the exception of CoH (an indicator of elemental fine carbon that is often highly correlated with CO). In every case, CO has greater statistical significance than the PM index, although both are significant.

The two most significant particle indicators of mortality are CoH and $EPM_{2.5}$, which have the same t-statistic of 3.5 with CO as a co-pollutant. A more thorough co-pollutant assessment of $PM_{2.5}$ for Toronto, with particular attention to NO_2 and O_3 effects, seasonal effects, and specific causes of death, would be of interest.

Borja-Abuto et al. (1998) in Southwest Mexico City, Mexico

The authors carried out a detailed assessment of non-accidental mortality for the period 1 January 1993-31 July 1995 in a populous section of Mexico City with historically high ozone levels, but lower levels of PM than in heavily industrialized areas. In addition to total mortality, the authors also examined mortality for age > 65 years, mortality from respiratory causes, from cardiovascular causes, and from other causes. The results are shown in Table 6-54, for a $PM_{2.5}$

TABLE 6-53. SENSITIVITY OF PM RELATIVE RISK ESTIMATE TO CO-POLLUTANTS MODELS IN (BURNETT, ET. AL., 1998: TABLE 2)

ENDPOINT: Total mortality from all natural causes.

SITE: Toronto, Canada.

		PM Relative Risk			t-statistics for RR					
PM Index or Pollutant	Lag or average (days)	RR	LCL	UCL	PM	O_3	NO_2	SO_2	CO	CO RR (1.4 ppm)
CO	0+1								8.4	1.070
$EPM_{2.5}$ 25 μg/m3	0+1	1.048	1.033	1.064	6.0					
		1.030	1.014	1.047	3.5				6.3	1.056
EPM_{10} 50 μg/m3	0	1.035	1.018	1.053	3.9					
		1.021	1.004	1.039	2.4				7.1	1.063
SO_4= 15 μg/m3 Lag 0 d	0	1.027	1.012	1.043	3.4					
		1.020	1.005	1.035	2.8				7.9	1.066
TSP 100 μg/m	0	1.023	1.008	1.038	3.1					
		1.017	1.002	1.032	2.3				6.7	1.056
CoH (0.6 per kft)	0+1	1.059	1.043	1.075	7.5					
		1.035	1.016	1.055	3.5				4.3	1.043
O_3	1					0.7				
						1.4			8.7	1.072
NO_2	0						3.2			
							0.7		8.0	1.067
SO_2	0							2.6		
								1.5	8.0	1.067

Note: Multiple-pollutant models have 2 or more t-values in the same row, for each pollutant.

Note: Average of lags 0 and 1 days used for CO, CoH. $EPM_{2.5}$. Lag 0 (same day) used for EPM_{10}, TSP, SO_4, NO_2, SO_2. Lag 1 used for O_3.

lag of 4 days (largest effect), with co-pollutants O_3 (average 1+2 d) and NO_2 (average 1+2+3+4+5 d). We will examine the choices of lag structures later. The authors reported results of single-pollutant models, and all 2- and 3-pollutant models with $PM_{2.5}$.

TABLE 6-54. SENSITIVITY OF PM RELATIVE RISK ESTIMATE FOR TOTAL MORTALITY TO CO-POLLUTANT MODELS (BORJA-ABUTO ET AL., 1998, TABLE 5)

PM INDEX: $PM_{2.5}$, lag 4 days.

SITE: Southwest Mexico City, Mexico

	$PM_{2.5}$ Relative Risk (25 μg/m3, lag 4 d)			t-statistics for RR				
Endpoint	RR	LCL	UCL	PM	O_3	NO_2	SO_2	CO
Total mortality from all natural causes	1.034	1.005	1.064	2.3				
					0.6			
						1.1		
	1.036	1.006	1.067	2.4	0.9			
	1.034	0.997	1.071	1.8		0.0		
	1.043	1.006	1.080	2.3	1.0	-0.0		
Age > 65	1.040	1.001	1.080	2.0				
					1.3			
						0.7		
	1.041	1.000	1.082	2.0	0.9			
	1.046	0.997	1.096	1.8		-0.4		
	1.058	1.008	1.109	2.3	1.1	-0.6		
Respiratory	1.064	0.972	1.160	1.4				
					-0.5			
						0.9		
	1.067	0.973	1.166	1.4	-0.6			
	1.051	0.939	1.170	0.9		0.4		
	1.043	0.930	1.163	0.7	-0.7	1.0		
Cardiovascular	1.056	1.000	1.113	2.0				
					2.0			
						0.9		
	1.056	0.999	1.116	1.9	1.8			
	1.043	0.930	1.163	0.7		-0.3		
	1.088	1.017	1.162	2.4	2.0	-0.2		
Other natural causes	1.020	0.983	1.057	1.0				
					0.5			
						0.7		
	1.021	0.984	1.060	1.1	0.2			
	1.018	0.971	1.065	0.7		0.1		
	1.022	0.975	1.069	0.9	0.2	-0.0		

Note: $PM_{2.5}$ lag 4 days; O_3 mean of lags 1 and 2 days; NO_2 mean of lags 1 through 5 days.

The t-statistics for $PM_{2.5}$ were generally stable across co-pollutant models within each endpoint. For total mortality, $PM_{2.5}$ had a significant effect when O_3, and both O_3 and NO_2 were included. When NO_2 was the only co-pollutant, the $PM_{2.5}$ effect was of about the same magnitude, but only marginally significant.

For elderly mortality, $PM_{2.5}$ had a significant effect when O_3, and both O_3 and NO_2 were included. When NO_2 was the only co-pollutant, the $PM_{2.5}$ effect was of about the same magnitude, but only marginally significant. The relative risks were somewhat higher than for total mortality, but showed a similar pattern.

Neither $PM_{2.5}$ nor the co-pollutants had a significant effect on respiratory mortality. However, the $PM_{2.5}$ relative risk was higher than all-cause mortality. The lack of statistical significance may reflect the small number of deaths in this category.

For cardiovascular mortality, $PM_{2.5}$ had a larger and even more significant effect when both O_3 and NO_2 were included. When O_3 or NO_2 was the only co-pollutant in the model, the $PM_{2.5}$ effect was of about the same magnitude, but not significant with NO_2 and marginally significant with O_3. The O_3 effects were stable and significant or marginal for cardiovascular mortality. This was the only endpoint for which O_3 effects were significant, with or without $PM_{2.5}$ as a co-pollutant.

The $PM_{2.5}$ relative risks for other natural causes were lower than for respiratory or cardiovascular causes. None of the pollutants had a significant effect on other-cause mortality.

The time lags and moving averages selected are somewhat atypical. The authors present information on risk estimates at various lags. Figure 6-5 shows a pattern of relative risks, with confidence limits, that is not readily interpretable. Positive, statistically significant RR of roughly similar magnitude are shown at lag days 0 and 4, and for the moving average of 1+2+3+4+5 days. The other lags do not show significant effects. Other results may have been obtained by other choices.

In summary, this study suggests that $PM_{2.5}$ is associated with moderately elevated risks of cardiovascular mortality, and total mortality, to an extent that cannot be attributed to the gaseous pollutants O_3 and NO_2. The effects of CO and other co-pollutants remains to be evaluated. The lag structure may have been chosen to maximize the $PM_{2.5}$ effect and other forms might be worthy of investigation.

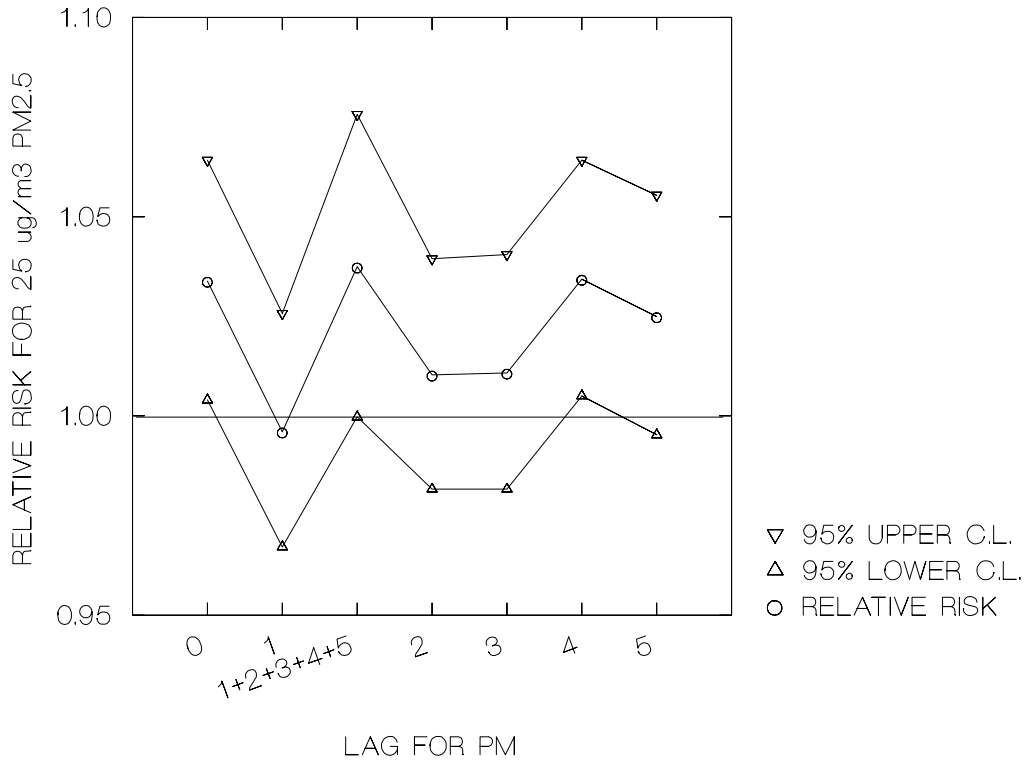

Figure 6-5. Relative risk of total mortality from $PM_{2.5}$ in southwest Mexico City as a function of PM lag or moving average, with 95% confidence limits.

Source: Borja-Abuto et al. (1998).

Loomis et al. (1999) Infant Mortality in Southwest Mexico City, Mexico

This study parallels that of Borja-Abuto et al. (1998) for mortality in children less than one year of age. The results are shown in Table 6-55, for a $PM_{2.5}$ moving average of 3+4+5 days (largest effect), with co-pollutants O_3 (average 2+3 d) and NO_2 (average 3+4+5 d). We will examine the choices of lag structures later. The authors reported results of single-pollutant models, and all 2- and 3-pollutant models with $PM_{2.5}$.

The $PM_{2.5}$ relative risk is statistically very significant with no co-pollutants, but is somewhat attenuated by including O_3 (still significant), NO_2, and both NO_2 and O_3 (marginally significant) as co-pollutants. Neither of the gaseous pollutants is a significant predictor of infant mortality when $PM_{2.5}$ is included as a co-pollutant. The results are only moderately robust to the inclusion of gaseous co-pollutants.

TABLE 6-55. SENSITIVITY OF PM RELATIVE RISK ESTIMATE FOR INFANT MORTALITY TO CO-POLLUTANT MODELS (LOOMIS ET AL., 1999, TABLE 5)

PM INDEX: $PM_{2.5}$, mean of lag days 3+4+5

SITE: Southwest Mexico City, Mexico

$PM_{2.5}$ Relative Risk (25 μg/m3, mean of lag days 3+4+5)			t-statistics for RR				
RR	LCL	UCL	PM	O_3	NO_2	SO_2	CO
1.181	1.063	1.306	3.2				
1.163	1.034	1.302	2.6	0.8			
1.154	0.981	1.345	1.8		0.4		
1.165	0.987	1.362	1.9	0.8	0.1		
				1.7			
					2.5		

Note: $PM_{2.5}$, mean of lags 3, 4, 5 days; O_3, mean of lags 2 and 3 days; NO_2, mean of lags 3, 4, 5 days.

The time lags and moving averages selected are somewhat atypical. The authors present information on risk estimates at various lags. Figure 6-6 shows a pattern of relative risks, with confidence limits, that is reasonably interpretable. Positive, statistically significant RR are shown for the 7 moving averages on the right side, ranging from single days (lags 3, 4, 5) up to 2+3+4+5 days. The other lags do not show significant effects. The two best choices are averages of 3+4+5 and 2+3+4+5 days. These findings are reasonably consistent with the long-delayed effects in the total mortality study of Borja-Abuto et al. (1998).

Summary: Sensitivity of $PM_{2.5}$ Effect Estimates to Inclusion of Gaseous Co-Pollutants

The findings of this discussion are shown in Table 6-56. It is often the case that inclusion of gaseous co-pollutants attenuates the estimated $PM_{2.5}$ effect size and statistical significance, but the attenuation is occasionally modest or negligible, and the effect remains statistically significant. Examples include: Hospital admissions for respiratory infection (Burnett et al., 1999); total mortality (Burnett et al., 1998; Fairley, 1999); total mortality, age > 65 mortality and cardiovascular mortality (Borja-Abuto et al., 1998); and marginally, infant mortality (Loomis et al., 1999).

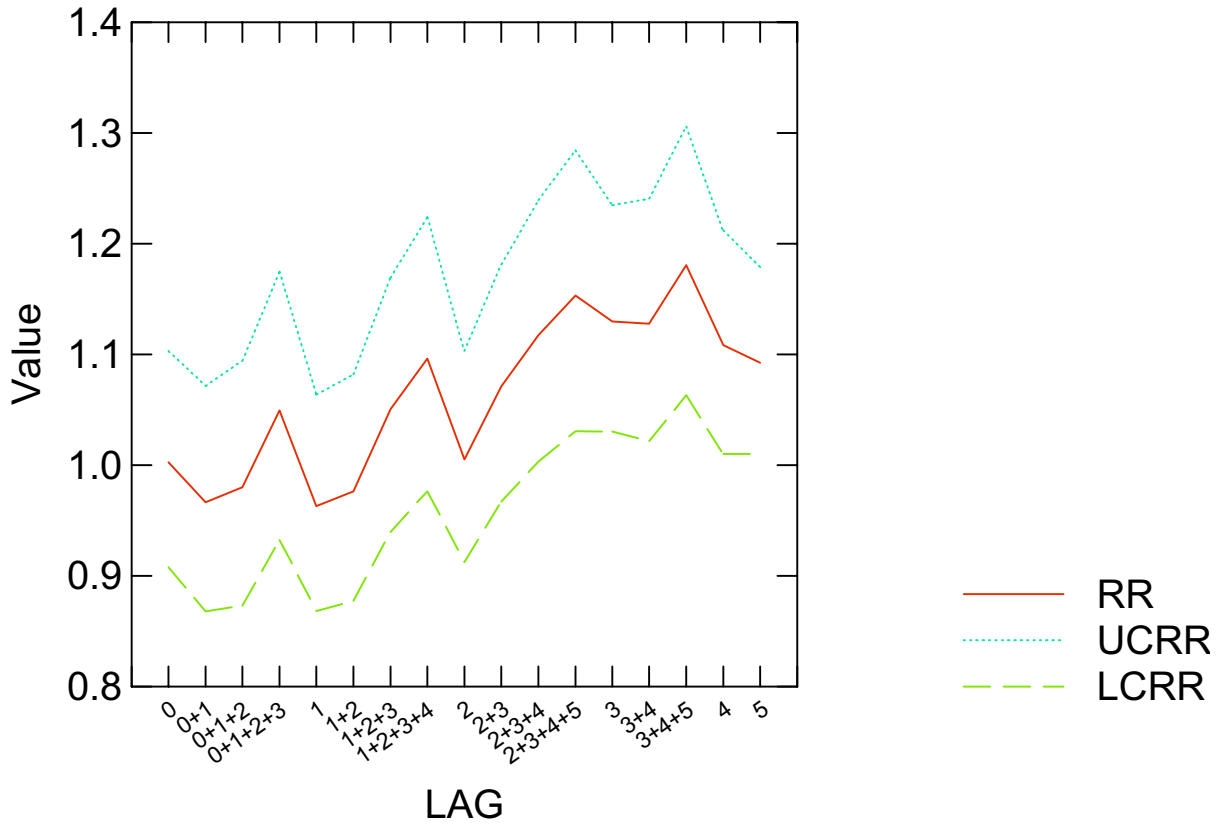

Figure 6-6. Relative risk of infant mortality from $PM_{2.5}$ in southwest Mexico City as a function of PM lag or moving average, with 95 percent confidence limits.

Source: Loomis et al. (1999).

These form a body of evidence that the effects are moderately robust to the inclusion of certain co-pollutants. This evidence applies to 5 or 6 of 16 independent endpoints in the 6 studies. However, the biological meaning of the 6 significant or marginally significant robust $PM_{2.5}$ effects is limited by two factors: (1) differences in the gaseous co-pollutants used as covariates across the studies, and (2) differences in $PM_{2.5}$ and co-pollutant averages used as predictors of effects. The multipollutant model used in (Burnett et al., 1997) includes O_3, NO_2, and SO_2, whereas only CO is used as a co-pollutant for $PM_{2.5}$ in Burnett et al. (1998). All four co-pollutants are considered in Burnett et al. (1999), but different models are reported for different endpoints, some with different moving average lags as well. Fairley (1999) evaluates many

TABLE 6-56. EFFECTS OF INCLUDING ONE OR MORE GASEOUS CO-POLLUTANTS ON $PM_{2.5}$ RELATIVE RISK ESTIMATES FOR HOSPITAL ADMISSIONS AND MORTALITY IN TORONTO, SANTA CLARA COUNTY, AND SOUTHWEST MEXICO CITY

			$PM_{2.5}$ only		With 1 Gaseous Co-Pollutant			With 2+ Gaseous Co-Pollutants		
Study	End-point	Avg. lag d. for $PM_{2.5}$	t	RR	min. t	RR	Co-Poll.	t	RR	Co-Poll.
Burnett et al. (1997)	Respiratory Admission	1+2+3+4	3.3	1.086	1.0	1.030	NO_2	-0.1	0.998	NO_2 O_3 SO_2
	Cardiovasc. Admissions	1+2+3+4	1.8	1.072	0.8	1.032	O_3	-0.3	0.984	NO_2O_3 SO_2
Burnett et al. (1999) hospital admissions in Toronto	Respiratory Infection	0+1+2	6.1	1.108				4.5	1.085	NO_2 O_3
	Asthma	0+1+2	3.2	1.064				0.8	1.027	O_3 SO_2 CO
	Obstructive Lung Dis.	1+2	1.9	1.048				1.3	1.031	O_3 CO
	Heart failure	0+1+2	3.2	1.066				0.6	1.019	NO_2 CO
	Ischemic Heart Dis.	0+1+2	6.1	1.080				1.3	1.031	NO_2 SO_2
	Dysrhythmia	0	2.9	1.061				1.5	1.048	O_3 CO
Burnett et al. (1998)	Total mortality	0+1	6.0	1.048	3.5	1.030	CO			
Fairley (1999) Santa Clara County	Total mortality	0	3.3	1.085	3.1	1.097	CO	3.4	1.117	CO NO_2 O_3
Borja-Abuto et al. (1998) Mexico City	Total mortality	4	2.3	1.034	1.8	1.034	NO_2	2.3	1.043	NO_2 O_3
	Age> 65 mortality	4	2.0	1.040	1.8	1.046	NO_2	2.3	1.058	NO_2 O_3
	Respiratory mortality	4	1.4	1.064	0.9	1.051	NO_2	0.7	1.043	NO_2 O_3
	Cardiovasc. Mortality	4	2.0	1.056	0.7	1.043	NO_2	2.4	1.088	NO_2 O_3
	Other mortality	4	1.0	1.020	0.7	1.018	NO_2	0.9	1.022	NO_2 O_3
Loomis et al. (1999) Mexico City	Infant mortality	3+4+5	3.2	1.181	1.8	1.154	NO_2	1.9	1.165	NO_2 O_3

Note: t-statistics $\geq$ 1.96 are generally taken as statistically significant.

co-pollutants, including a model with CO, NO_2, and O_3. The Mexico City analyses (Borja-Abuto et al., 1998; Loomis et al., 1999) use only NO_2 and O_3 as co-pollutants, and all include longer lags (4 d and 3+4+5 d) than the Toronto analyses (0+1 d, 0+1+2 d). Thus, the evidence suggests that there may be adverse health effects associated with $PM_{2.5}$, but does not suggest that a single mechanism or time structure applies to all locations.

6.4.6.3 Factors and Components Including PM

Many of the concerns about attribution of health effects to ambient is that ambient PM is closely associated with co-pollutants and weather, an intrinsic causal association for which standard epidemiologic methods of covariate adjustment may not be adequate. Certain sources produce PM of specific size or composition, as well as gaseous pollutants. Weather affects ambient concentrations of particles and gases, affects the rate of formation of secondary particle components, and may affect human exposure patterns. Several new approaches have been developed that directly confront these issues: (1) construct common factors involving PM, co-pollutants, and weather variables, and use these common factors as nominal predictors of health effects; (2) Use elemental or other compositional components of PM as markers of sources from which the PM was derived. Both approaches are potentially useful.

The first approach is illustrated by a study of daily mortality in Toronto, Canada, carried out by Özkaynak et al. (1996). Factor analysis methods were applied to construct composite indicators as linear combinations of relative humidity, temperature, CoH, TSP, SO_2, CO, NO_2, and maximum O_3. Results are given in Sec. 6.3.3. Relationships between total and cardiovascular mortality were much stronger for composite factors 1, 4, and 5 than the relationships for individual components. Factor 1 was interpreted as an automobile factor, Factor 4 as a TSP factor, Factor 5 as a Temperature factor. Interestingly, Factor 3 (Ozone) predicted excess total mortality, but not cardiovascular mortality. Factor 1 involved mainly CoH and NO_2, with lesser weights on CO, TSP and SO_2. The method used by Özkaynak et al. (1996) produced plausible and interpretable combinations of the original variables.

An alternative method is described briefly by Laden et al. (1999) in an abstract. This method uses elemental components of $PM_{2.5}$ and *a priori* characterizations of sources by elemental profiles to estimate the contributions attributable to "crustal" materials (Al and Si), and

so on. Laden et al. (1999) found that little excess mortality in the Harvard Six Cities could be attributed to the "crustal" component of $PM_{2.5}$.

The preliminary findings of these methods suggest possible direction for improved characterization of ambient PM components with differential toxicity, whether defined by size, source, or composition. The Özkaynak et al. (1996) approach uses components of air pollution and weather. The approach of Laden et al. (1999) uses elemental components of $PM_{2.5}$. The findings of Laden et al. (1999) are also discussed in Section 8.4.

These methods may also be advantageous in comparing results across cities, using factors. The correlations between air pollutants may differ substantially from one city to another. Therefore, cross-city comparisons using only two pollutant correlations at a time, such as in the Schwartz (1999a) eight-cities assessment, may not adequately characterize effects such as hospital admissions or mortality in multi-pollutant models. Comparisons of factors from different cities' correlation matrix or covariance matrix decompositions may provide useful information, particularly if site-specific source profiles are appropriate.

6.4.6.4 Chemical Components of $PM_{2.5}$ and PM_{10}

The new studies continue to identify sulfates (and presumably acidity) as predictive of adverse health effects in some cases, such as $SO_4^=$ in the Burnett et al. (1998) and Fairley (1999) time-series mortality studies, and not predictive in other situations, such as $SO_4^=$ in Abbey et al. (1999). It is possible that sulfate acidity is a major factor in causing health effects under certain conditions, but not always. The conditions under which adverse effects occur may require conditions external to PM (such as weather or co-pollutant concentrations), or conditions specific to the particles (size range, concentration of transition metals, organic carbon, and so on).

The study by Fairley et al. (1999) also finds a strong effect of PM_{10} nitrates on mortality. The nitrates may also occur in coarse particles, but $PM_{10-2.5}$ was not predictive of mortality, whereas the $PM_{2.5}$ and NO_3 effects were of approximately equal strength in predicting mortality. This suggests nitrate acidity in $PM_{2.5}$ may be an important factor in locations such as Santa Clara County, where SO_2 and sulfate levels are very low, NO_2 and nitrate levels relatively high. Toxicology studies of PM with high nitrate acidity would clarify this question.

There is increasing interest in evaluating the effects of iron or other transition metals associated with PM. There are few epidemiology studies in which ambient metal concentrations

are used explicitly as predictors of health endpoints. Dusseldorp et al. (1994) identified adverse effects associated with Fe. Other studies in progress will evaluate human health endpoints in relation to metals. This is of particular interest in locations such the Utah Valley, where the major point source of particle emissions was a steel mill, and in other metal processing communities. The question then arises as the effects of different physical and chemical types of particles, including mixtures of metal, metals and acids, and mineral matrix embedding of metals within particles.

There is also important new epidemiology evidence that certain types of particles may be much less toxic than other types of particles. Papers by Schwartz et al. (1999), Pope et al. (1999b), Ostro et al. (1999), and Laden et al. (1999) all suggest that particles of crustal or geological origin may be much less toxic than other particles more typical of urban combustion products. These ambient concentrations of crustal particles are particularly high in the coarse $PM_{10-2.5}$ fraction during wind-blown dust episodes, and may even be a major component of $PM_{2.5}$ in the "intermodal" $PM_{2.5-1.0}$ fraction during such episodes. Under these conditions, the concentration of ambient particles in a certain size class may not be a unique indicator of risk. While high concentrations of acid sulfates, metals, and other potentially toxic components of $PM_{2.5}$ in eastern U.S. cities are presumed to be a health risk, high concentrations of fine particles may cause fewer or less serious health effects under other conditions. It is not possible at this time to provide a general definition of the conditions under which crustal particles are not harmful to human health, and non-crustal particles from different sources are harmful to health.

6.4.7 Effects of Exposure Estimation and Model Specification Errors in Epidemiology Studies

The interpretation of statistical associations between ambient PM and adverse health effects reviewed in Sections 6.2 and 6.3 depends on the appropriate attribution of effects to ambient PM exposures and to other environmental factors. Some questions have been raised about the adequacy of the air pollution concentration measurements to carry; this inferential burden. It is known that the measurements of ambient air pollution may have instrumental errors, spatial variability, and temporal uncertainties that affect statistical and causal inferences. Individual variation in personal exposure to ambient PM provide a different kind of "error". These are called "measurement errors", and include a wide variety of issues that are discussed in this

section. Incorrect specification of the statistical model also constitutes a "characterization error", and the combination of measurement errors and characterization errors may be important.

A number of authors have raised questions about the effects of mis-specification of the statistical models used in various epidemiology studies. We discuss several of these issues here, with regard to particular aspects of the data analyses in the studies. The modeling failures most often cited as relevant to daily time series or prospective cohort epidemiology studies are: (1) PM indicators and indicators of other air pollutants measured at a central monitor, do not adequately characterize the exposure of the population, or of individuals in the study group (2) important covariates are not included in the model, or are replaced by error-prone surrogates; (3) the functional relationship of the exposure-response (ER) function or the distributional model is incorrectly specified.

6.4.7.1 Measurement Errors in Air Pollution Exposure Surrogates: General Issues

The term "measurement error" has been applied to a number of distinct concepts, and it is useful to distinguish several kinds of "error" to which the term might apply: (a) analytical or instrument errors, apart from exposure imputation; (b) spatial errors arising from assignment of a measurement at a stationary air monitor (SAM) as an index of exposure to ambient air pollution among all members of the population; (c) assignment of a time- averaged value to an individual who is exposed to ambient air pollution over a space-time variable range; (d) assignment of the same air pollution exposure index to individuals with different patterns of biological and behavioral intake of ambient air. The differences are sketched in Figure 6-7. The first error (Figure 6-7a) is that two so-called "identical" instruments (denoted A and A') located at the same place ("collocated") will almost surely give different values of the ambient air pollution concentration over any given time interval. Instruments that use different measurement techniques or methodologies are expected to show systematic as well as random differences. A different form of exposure measurement error is suggested in Figure 6-7b. Here we show measurements at different locations (A, B, C, D) in a hypothetical region, along with concentration isopleths to suggest spatial differences at various locations. Any combination of these measurements to produce a single regional value introduces an error in the spatial interpolation of the pollutant concentration field to a given point, for example, to the average ambient concentration at the subject's residence (denoted PR). Figure 6-7c suggests an even

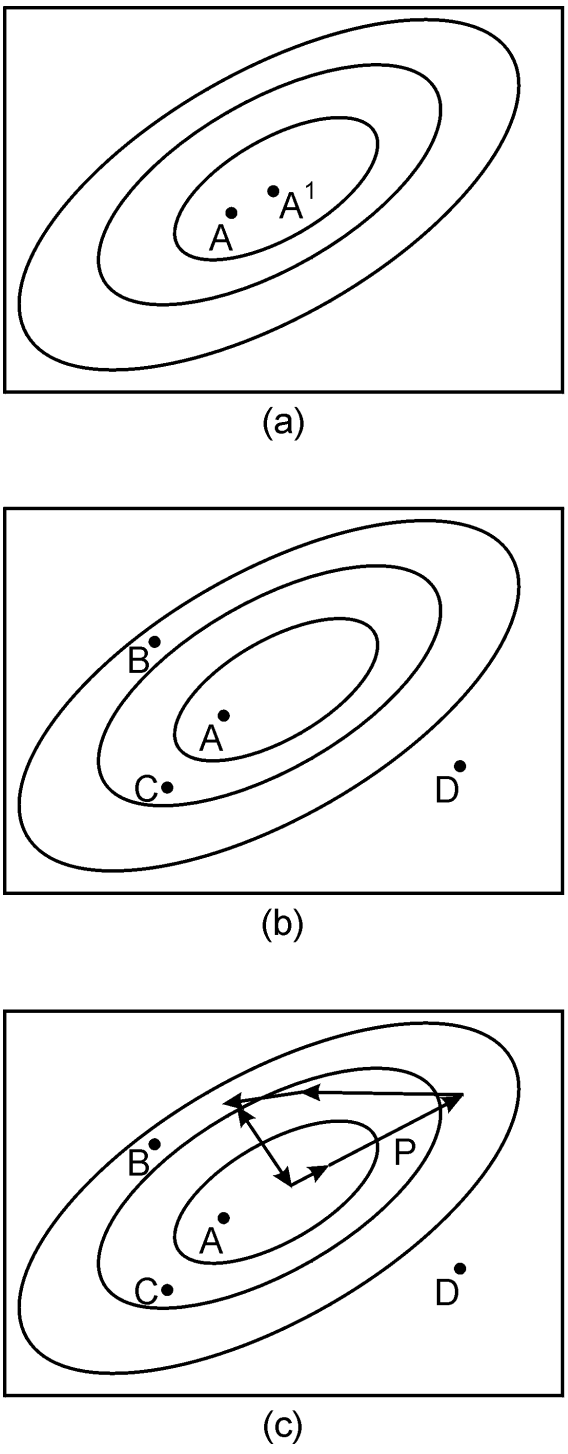

Figure 6-7. Ambient PM concentration isopleths and monitoring sites in a hypothetical urban area. Figure (a): two colocated monitors. Figure (b): Four regional monitors. Figure (c): personal exposure trajectory of a subject with a residence at PR and a moving personal exposure monitor PEM.

more complicated and realistic situation, in which both the individual and the spatial concentration move over time so that a hypothetical personal monitor (denoted PEM) on the individual would measure a space-and-time-weighted exposure averaged concentration. We do not show an example of (d), in which two otherwise hypothetical individuals with different levels of physical activity might inhale different amounts of pollutants, even if they had the same space-time trajectory as PEM.

The statistical consequences of using imprecisely measured indicators of air pollution exposure have long been known. Suppose that X is the true individual exposure to pollution of ambient origin, measured without error (a) along trajectory PEM. However, this is not observed, and cannot be observed with perfect accuracy. All that is observed is an error-prone surrogate measurement denoted W. W could be any of: the central monitor A; the average M over several sites (for example, M = (A + B + C + D)/4); the residential monitor PR; or the personal monitor PEM. Each choice induces a different statistical model for an observed outcome.

Since X can't be measured accurately, all we have is a surrogate measurement W, where W is one of the observed values A, M, PR, or PEM. No hospital admissions or mortality studies have used PEM. *Classical measurement error models* have assumed that the measurement error in X (denoted U) is additive and normally distributed, so that W = X + U. Type (a) errors might be of this form, although a more complicated structure such as a combination of additive or multiplicative errors with unequal variance seems more likely. Studies in progress should soon clarify the nature and distribution of these errors.

The exposure measurement errors of type (b) or type (c) have a different statistical structure. The true exposure X is not observed. However, all individuals are assigned the same value W (again, A or M). The linear error model in this case is defined by X = W + U. This is sometimes called *Berkson error structure*. Both Berkson and classical errors may be present.

6.4.7.2 New Theoretical Assessments of Consequences of Measurement Error

Since the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996) there have been some advances in the conceptual framework to investigate the effects of measurement error on PM health effects estimated in time-series studies. These studies evaluated the extent of bias caused by measurement errors under a number of scenarios with various error variances and covariance structure between co-pollutants.

Zidek et al. (1996) investigated the joint effects of multicollinearity and measurement error in Poisson regression models with two covariates, through simulations over error size and correlation. Their error model was of classical error form (W=X+U where W and X are surrogate and true measurements, respectively, and the error U is normally distributed). The results illustrated the transfer of effects from the "causal" variable to the confounder. However, for the confounder to have larger coefficients than the true predictor, the correlation between the two covariates had to be large ($r = 0.9$), with moderate error ($\sigma > 0.5$) for the true predictor, and no error for the confounder in their scenarios. The transfer-of-causality effect was mitigated when the confounder also became subject to error. Another interesting finding that Zidek et al. reported is the behavior of the standard errors of these coefficients: (1) when the correlation between the covariates are high ($r = 0.9$), and both covariates have no error, the standard errors for both coefficients were inflated by factor of 2; (2) however, this phenomenon disappeared when the confounder had error. Thus, the multicollinearity influences the significance of the coefficient of the causal variable only when the confounder is accurately measured.

Zeger et al. (1999) illustrated the implication of the classical error model and the Berkson error model in the context of time-series study design. Their simulation of the classical error model with two predictors, with various combination of error variance and correlation between the predictors/error terms, showed results similar to those reported by Zidek et al. (1996). Most notably, for the transfer of the effects of one variable to the other (i.e., error-induced confounding) to be large, the two predictors or their errors need to be substantially correlated. Also, for the spurious association of a null predictor to be more significant than the true predictor, their measurement errors have to be extremely negatively correlated. Zeger et al. also laid out a comprehensive framework for evaluating the effects of exposure measurement error on estimates of air pollution mortality relative risks in time-series studies. The error, the difference between personal exposure and the central station's measurement z, was decomposed into three components: (1) the error due to having aggregate rather than individual exposure; (2) the difference between the average personal exposure and the true ambient level; and, (3) the difference between the true and measured ambient level. By aggregating individual risks to obtain expected number of deaths, they showed that the first component of error (the aggregate rather than individual, or, the Berkson error) is not a significant contributor to bias in the estimated risk. The second error component is a classical error and can introduce bias if there are

short-term associations between indoor source contributions and ambient levels. The third error component is also of the classical error type, and includes spatial and instrumental error. Using this framework, the investigators then used PTEAM Riverside, CA data to estimate the second error component and its influence on estimated risks. The correlation between the average population PM_{10} exposure and the ambient PM_{10} level was estimated to be 0.58. By simulating the average personal exposure from the measured ambient PM_{10} levels using this relationship, they compared the estimated mortality relative risks in a log-linear model for the measured ambient PM_{10} data and the simulated average population PM_{10} exposure for Riverside, CA, during the period 1987-1994. They found that the relative risk (1.20% per 10 $\mu g/m^3$ increase in PM_{10} 95% CI: -0.38 - 2.77%) estimated using the simulated population average exposure was larger but less precise than the relative risk (0.78%; 95% CI: -0.17 - 1.75%) estimated using the ambient data.

Zeger et al., in the analyses described above, also suggested that the error due to the difference between the average personal exposure and the ambient level (the second type described above) are likely the largest source of bias in estimated relative risk. This suggestion at least partly comes from the comparison of PTEAM data and site-to-site correlation (the third type of error described above) for PM_{10} and O_3 in 8 US cities. While PM_{10} and O_3 both showed relatively high site-to-site correlation (~0.6-0.9), we do not necessarily expect similar extent of site-to-site correlation for other pollutants. Ito et al. (1998) estimated site-to-site correlation (after adjusted for seasonal cycles) for PM_{10}, O_3, SO_2, NO_2, CO, temperature, dewpoint temperature, and relative humidity using multiple stations' data from seven Central and eastern states (IL, IN, MI, OH, PA, WV, WI), and found that, in a geographic scale of less 100 miles, these variables could be categorized into three groups in terms of the extent of correlation: (1) weather variables ($r > 0.9$); (2) O_3, PM_{10}, NO_2 (r: 0.6 - 0.8); CO and SO_2 ($r < 0.5$). These results suggest that the contribution from the third component of error as described in Zeger et al. would vary among pollution and weather variables. Furthermore, the contribution from the second component of error would also vary among pollutants, as the contributions from indoor sources are expected to be different for each pollutants. Thus, more data on personal exposures for multiple pollutants is needed in order to assess the effects of these errors. Some of the ongoing exposure studies are expected to shed some light on this issue.

With regard to the PM exposure, the longitudinal part of the PTEAM data discussed above, as well as other studies (e.g., Tamura et al., 1996) show reasonable correlation (r = 0.6 - 0.9) between ambient and average population PM exposure, lending support for the use of ambient data as a surrogate for personal exposure to outdoor PM in time-series mortality or morbidity studies, under conditions similar to these non-smoking Japanese households. Furthermore, fine particles are expected to show even better correlation. Wilson and Suh (1997) examined site-to-site correlation of PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ in Philadelphia and St. Louis, and found that site-to-site correlations for $PM_{2.5}$ were high (r ~0.9) , but low for $PM_{10-2.5}$ (r ~ 0.4), indicating that fine particles have smaller errors in representing community-wide exposures. This finding supports Lipfert and Wyzga's (1997) speculation that the stronger mortality associations for fine particles than coarse particles found in Schwartz et al.'s (1996) study may be due to larger measurement error for coarse particles.

However, as Lipfert and Wyzga (1997) suggested, the issue is not whether the fine particle association with mortality is a "false positive", but rather, whether the weaker mortality association with coarse particles is a "false negative". Carrothers and Evans (1999) also investigated the joint effects of correlation and relative error, but they specifically addressed the issue of fine (FP) versus coarse particle (CP) effects, by assuming three levels of relative toxicity of fine versus coarse particles (β_{FP} / β_{CP} = 1, 3, and 10), and then evaluating the bias, ($B = \{E[\beta_{F'}] / E[\beta_{C'}]\} / \{\beta_F / \beta_C\}$, as a function of FP-CP correlation and relative error associated with FP and CP. Their results indicate: (1) if the FP and CP have the same toxicity, there is no bias (i.e., B=1) as long as FP and CP are measured with equal precision, but, if, for example, FP is measured more precisely than CP, then FP will appear to be more toxic than CP (i.e, B > 1); (2) when FP is more toxic than CP (i.e., β_{FP} / β_{CP} = 3 and 10), however, the equal precision of FP and CP results in downward bias of FP (B < 1), implying an relative overestimation of the less toxic CP. That is, to achieve non-bias, FP must be measured more precisely than CP, even more so as the correlation between FP and CP increases. They also applied this model to real data from the Harvard Six-Cities Study, in particular, the data from Boston and Knoxville. Estimation of spatial variability for Boston was based on an external data, and a range of spatial variability for Knoxville (since there was no spatial data available for this city). For Boston (where estimated FP-CP correlation was low (r = 0.28), estimated error was smaller for FP than for CP (0.85 versus 0.65, as correlation between true versus error-added series), and the observed

FP to CP coefficient ratio was high (11)), the calculated FP to CP coefficient ratio was even larger (26), providing evidence against the hypothesis that FP is absorbing some of the coefficient of CP. For Knoxville, where FP-CP correlation was moderate (0.54), the error for FP was smaller than for CP (0.9 versus 0.75), and the observed FP to CP coefficient ratio was 1.4), the calculated true FP to CP coefficient ratio was smaller (0.9) than the observed value, indicating that the coefficient was overestimated for the better-measured FP, while the coefficient was underestimated for the worse-measured CP. Since the amount (and the direction) of bias depended on several variables (i.e., correlation between FP and CP; the relative error for FP and CP; and, the underlying true ratio of the FP toxicity to CP toxicity), the authors concluded "...for instance, it is inadequate to state that differences in measurement error among fine and coarse particles will lead to false negative findings for coarse particles".

Fung and Krewski (1999) conducted a simulation study of measurement error adjustment methods for Poisson models, using scenarios similar to those used in the simulation studies that investigated implication of joint effects of correlated covariates with measurement error. The measurement error adjustment methods employed in this analysis were Regression Calibration (RCAL) method (Carroll et al., 1995) and Simulation Extrapolation (SIMEX) method (Cook and Stefanski, 1995). The RCAL algorithm consists of: (1) estimation of the regression of X on W (observed version of X, with error) and Z (covariate without error); (2) replacement of X by its estimate from (1), and conducting the standard analysis (i.e., regression); and (3) adjustment of the resulting standard error of coefficient to account for the calibration modeling. SIMEX algorithm consists of: (1) addition of successively larger amount of error to the original data; (2) obtaining naive regression coefficients for each of the error added data sets; and, (3) back extrapolation of the obtained coefficients to the error-free case using a quadratic or other function. Fung and Krewski examined the cases for : (1) $\beta_X = 0.25$; $\beta_Z = 0.25$; (2) $\beta_X = 0.0$; $\beta_Z = 0.25$; (3) $\beta_X = 0.25$; $\beta_Z = 0.0$, all with varying level of correlation (-0.8 to 0.8) with and without classical additive error, and also considering Berkson type error. The behaviors of naive estimates were essentially similar to other simulation studies. In most cases with the classical error, RCAL performed better than SIMEX (which performed comparably when X-Z correlation was small), recovering underlying coefficients. In the presence of Berkson type error, however, even RCAL did not recover the underlying coefficients when X-Z correlation was large (> 0.5). This is the first study to examine the performance of available error adjustment methods that can

be applied to time-series Poisson regression. The authors recommend RCAL over SIMEX. Possible reasons why RCAL performed better than SIMEX in these scenarios were not discussed, nor are they clear from the information given in the publication. There has not been a study to apply these error adjustment methods in real time-series health effects studies. These methodologies require either replicate measurements or some knowledge on the nature of error (i.e., distributional properties, correlation, etc.). Since the information regarding the nature of error is still being collected at this time, it may take some time before applications of these methods become practical.

Another issue that measurement error may affect is the detection of threshold in time-series studies. Lipfert and Wyzga (1996) suggested that measurement error may obscure the true shape of the exposure response curve, and that such error could make the concentration-response curve to appear linear even when a threshold may exist. Burnett et al. (1999) investigated methods to detect and estimate threshold levels in time series studies. Based on the realistic range of error observed from actual Toronto pollution data (average site-to-site correlation: 0.90 for O_3; 0.76 for CoH; 0.69 for TSP; 0.59 for SO_2; 0.58 for NO_2; and 0.44 for CO), pollution levels were generated with multiplicative error for six levels of exposure error (1.0, 0.9, 0.8, 0.72, 0.6, 0.4, site-to-site correlation). Mortality series were generated with three PM_{10} threshold levels (12.8 $\mu g/m^3$, 24.6 $\mu g/m^3$, and 34.4 $\mu g/m^3$). LOESS with a 60% span was used to observe the concentration-response curves for these 18 combinations of concentration-response relationships with error. A parameter threshold model was also fit using non-linear least squares. Graphical presentations indicate that LOESS adequately detects threshold under no error, but the thresholds were "smoothed out" under the extreme error scenario. Parametric threshold model were adequate to give "nearly unbiased" estimates of threshold concentrations even under the conditions of extreme measurement error, but the uncertainty in the threshold estimates increased with the degree of error. They concluded that "if threshold exists, it is highly likely that standard statistical analysis can detect it".

Other issues related to exposure error that have not been investigated include potential differential error among subpopulations. If the exposure errors are different between susceptible population (i.e., people with COPD) and the rest of the population, need to take into account for such difference. Also, the exposure errors may vary from season to season, due to the seasonal differences in the use of indoor emission sources and air exchange rate due to air conditioning

and heating. This may possibly explain the reported season specific effects of PM and other pollutants. Such season specific contributions of errors from indoor and outdoor sources are also expected to be different from pollutant to pollutant.

In summary, the studies that examined joint effects of correlation and error suggest that PM effects are likely underestimated, and that spurious PM effects (i.e., qualitative bias such as change in the sign of coefficient) due to transferring of effects from other covariates require extreme conditions, and therefore unlikely. A simulation study suggests that the under the likely range of error for PM, it is unlikely that a threshold is ignored by the common smoothing methods. More data is needed to examine the exposure errors for other pollutants since their relative error contributions and correlations with PM will influence their relative significance in relative risk estimates.

6.4.7.3 Concentration-Response Relationships

New research allows some conclusions about methodology for the shape of the concentration-response function to be used in PM epidemiology studies. Lipfert and Wyzga (1995), Lipfert (1997), and Carroll and Galindo (1998) have raised questions about the role of measurement error in attenuating and linearizing intrinsically non-linear relationships in air pollution epidemiology studies. Piecewise linear or "threshold" models in ambient PM studies have been most often evaluated, but similar issues may affect other models, such as the use of non-parametric smoothers introduced by Schwartz (1994). A few studies compare the goodness of fit of non-parametric models and linear models, but these have not been adjusted for the effects of measurement error in ambient PM and other predictors with which PM is correlated.

Schwartz (1998) discusses the threshold issue in detail, plotting a non-parametric smooth fit of total mortality versus $PM_{2.5}$ in the Boston component of the Harvard Six Cities study for which (log) linear models were fitted in earlier (Schwartz et al., 1996; Schwartz, 1999b). Schwartz (1996), Pope et al. (1999a) and Ostro et al. (1999) also extensively explore the change in the linear slope when higher $PM_{2.5}$ or PM_{10} concentration days are deleted in daily time series mortality studies. They find that the linear regression coefficient in a log-linear model is either little changed or increases somewhat when PM concentrations are restricted to lower values. Schwartz (1998) interprets this as evidence against a threshold in the lower range of concentrations. Effects of measurement errors in co-pollutants are not evaluated in these papers.

Çakmak et al. (1999) suggest the following two-step approach (discussed in Section 6.4.6) using mortality data for Toronto. First, examine a non-parametric smoothed fit to the data and attempt to identify thresholds or other non-linearities graphically. Secondly, fit a (log)linear model where indicated, and both linear and threshold models where a threshold is suggested. Simulations showed that standard Poisson methods using a threshold model had a high success rate in detecting threshold models with moderately large thresholds versus linear models with zero threshold. Çakmak et al. (1999) conclude that "... standard statistical methods of regression modeling and diagnostic plots of the association between air pollution and daily mortality rates are adequate to detect the presence of a threshold if it exists. Using these methods, the investigator is likely to correctly identify the form of the association even in the presence of exposure measurement error." It would be useful to extend this work to multiple correlated predictors with measurement errors.

The parameters estimated in the time-series models are based on population-level responses, such as daily hospital admissions or deaths. The parameters in the prospective cohort studies are based on individual deaths in relation to risk factors, such as ambient PM, smoking status, and BMI. A threshold parameter for an individual is interpretable, whereas a population-level threshold is difficult to interpret if individual thresholds differ over a wide range, or vary over time. If the "population threshold" is a "non-concept", inconsistent findings about thresholds in different time-series studies is readily understood.

Nonlinear concentration-response functions using log(ambient air pollutant concentration) for the pollution predictors is recommended in many analyses by Lipfert and Wyzga (1997, 1999). In cases where preliminary graphical assessment suggests a concentration-response function that bends downward with increasing concentration, this might be attempted. It is obviously necessary to restrict this logarithmic model at some lower bound, since it implies that RR = 0 when any concentration = 0 (from the log-log model log [RR] = b * log [concentration] + ...).

In summary, it is not possible to confidently assert that the concentration-response model for PM indices in time series or long-term studies is (log)linear, threshold, other nonlinear, or different from site to site. New methods being developed may allow resolution of this issue.

6.4.7.4 Methodology Issues in Modeling Time Series Studies

There has been a considerable convergence of thought on the most appropriate methods for modeling daily time series epidemiology studies. Many authors use generalized estimating equation (GEE) models to control for autocorrelation (Zeger and Liang, 1986; Samet et al., 1995). The methods now most commonly used in recent studies follow some variation of the following structure:

- The daily mortality or hospital admissions counts are smoothed by a nonparametric smoother, in lieu of filtering the counts or other approaches. This amounts to calculating a regression function S(t) as a function of the number Y(t) of events on day t, using either local regression functions (LOESS) or spline functions. The smoothing span for loess smoothers is usually 5% to 10% of the length of the time series. The spline function is usually chosen to maximize some criterion such as AIC (Akaike Information Criterion) or BIC (Bayes Information Criterion), and the typical span is 30 to 90 days per degree of freedom. Other non-environmental terms, such as the day of the week or the season, may also be included at this stage. Such functions are implemented in the S-Plus statistical package (Mathsoft, 1998), although similar analyses can be done using other packages. S-Plus has become the instrument of choice for most modelers. The most basic Poisson regression model is specified by $E\{Y(t)\} = \exp(S(t))$, where S(t) is the smoothed or detrended mortality at time t. S-Plus allows use of non-parametric smoothers in generalized linear models (GLM) that are appropriate for Poisson or over-dispersed Poisson data.
- Various weather variable specifications are evaluated. The variables frequently include: mean, minimum, or maximum daily temperature; mean dewpoint temperature; relative or specific humidity. Barometric pressure or changes in barometric pressure are used less often. These variables are evaluated for several lag functions (days t, t-1, t-2, etc.) or moving averages. Parametric functions are sometimes fit, typically low-order polynomials or piecewise linear functions, to account for the fact that weather-attributable deaths increase at very high temperatures and at very low temperatures. Newer analyses more often use non-parametric smoothers as well. The next level of model using generalized additive (Poisson) model (GAM) for Y(t) is now specified by its mean $E\{Y(t)\} = \exp(S(t) + W(t))$, where W(t) is a linear combination of terms involving the weather variables and their interactions (for example, 'hot and humid' weather). Adjustable parameter coefficients of the

smoothers or polynomials in S(t) and W(t) are implicit in these models, and the S(t) term is re-estimated. This next level model may include model selection so as to minimize deviance (variance) or index of dispersion of the fitted model, or to maximize AIC or BIC.

- Various air pollution variable specifications are evaluated. The variables frequently include: mean or maximum concentrations of gaseous pollutants measured hourly; daily PM concentrations, or mean hourly concentration of PM if measured more frequently (e.g., by TEOM®). These variables are evaluated for several lag functions (days t, t-1, t-2, etc.) or moving averages. Parametric functions are sometimes fit, typically linear or piecewise linear functions, to account for a possible 'threshold' in the data. Newer analyses sometimes use non-parametric smoothers of air pollution as well. The generalized additive (Poisson) model (GAM) for Y(t) is now specified by its mean $E\{Y(t)\} = \exp(S(t) + W(t) + P(t))$, where P(t) is a linear combination of terms involving the air pollution variables. This is a higher order model, usually with re-estimation of S(t) and W(t). Selection of air pollution variables may be done at this stage, or – if the number of candidates is not too large – results of several models are reported. It is not always clear that the models reported are "best" in any statistically objective sense. While any mathematical model in epidemiology can only be an approximation to reality, some models will fit a given data set better than other models, even though the best-fitting models are not necessarily "true". While EPA does not subscribe to "the tyranny of the optimal" (a remark attributed to Prof. John Tukey), there is often little information provided in published papers about the goodness of fit of the selected model(s) relative to other candidate models. The models reported may be the best of the models that include some statistically significant PM index, but there may be other models that are "good". The "good" models may or may not include some PM index. More information on goodness-of-fit would benefit an objective comparison of the model(s) reported in the study.
- The final stage consists of detailed sensitivity analyses with respect to alternative model specifications. If season was not included earlier, season and seasonal interactions may be evaluated at this stage. Data-specific estimates may be carried out, such as excluding all days with PM greater than some cut-point, or estimating a PM effect in different subsets (strata) of values of a co-pollutant.

Unless explicitly stated otherwise, the studies reviewed here have used this approach.

6.4.7.5 General Issues in Modeling Prospective Cohort Studies

The prospective cohort studies have generally been modeled using the Cox proportional hazards regression model for discrete outcomes such as death, or various regression and repeated measures analyses for continuous outcomes, such as pulmonary function decrements. The studies have used a variety of covariates specific to the individual, including age, sex, various indices of current or past smoking behavior, other indices of potential health problems or conditions such as body-mass index, and some indices of current or past alcohol use where available. These studies do not use measured individual indicators of air pollution, so may be regarded as "semi-individual" studies of air pollution risk. The ambient air pollution indices are surrogates for exposure that vary in terms of their ability to characterize individual exposure to air pollution of ambient origin. Sulfates and $PM_{2.5}$ of ambient origin are good indicators of personal exposure to sulfates (which have no significant indoor sources), and to $PM_{2.5}$ of ambient origin, because $PM_{2.5}$ has a reasonably uniform regional distribution, and it has a high penetration rate into indoor locations (Wilson and Suh, 1997). In locations with significant local sources of coarse particles, PM_{10} may include a substantial contribution from coarse particles, in which case ambient PM_{10} may not be as good an index of exposure to personal PM_{10} of ambient origin. Recent analyses of the AHSMOG study (Beeson et al., 1998; Abbey et al., 1999) use individually estimated air pollution exposure studies.

Other prospective study designs should be considered. Multi-level mixed models allow for random effects of community not accounted for by the measured ambient pollution levels and the individual covariates. The USC/CARB study (Peters et al., 1999a,b) illustrates use of these models.

Questions may always be raised about the selection of the subjects in the study, and about the adequacy of the adjustments for individual risk factors. EPA's assessment is that these were generally adequate, although extensive independent re-analyses of the data in (Dockery et al., 1993) and (Pope et al., 1995) are being carried out under the sponsorship of HEI. It is hoped that the new analyses will clarify the role of many of the issues raised here.

6.4.7.6 Effects of Co-Pollutants on Estimated PM Effects

One of the more important areas of uncertainty is in the assessment of the effects of co-pollutants on the estimated ambient PM effect. As noted in Section 6.3.2, the effect of

inclusion of co-pollutants in the time series mortality studies is to reduce the estimated effect attributable to ambient PM in some cases (often found for SO_2 in eastern U.S. cities), to increase the estimated effect attributed to PM (found for NO_2 at some sites), or to have little effect on the PM coefficient. The expected effect, based on analogies with effects of collinearity and measurement error in ordinary linear regression models, would be to find an attenuated estimate of ambient PM effect when positively correlated co-pollutants with small measurement error are included in the model. There is a general awareness that omission of co-pollutants that may have mortality effects and inclusion of co-pollutants that may have no mortality effect can bias the estimated PM effect.

A variety of methods have been proposed that may allow more complete assessment of the separability of ambient PM effects from those of other pollutants where this is possible, and better identification of those cases where separation is not possible. Much could be learned by use of principal components of ambient air pollution concentrations, as discussed in Section 6.4.6.3. Section 6.4.6.2 identifies a number of studies in which $PM_{2.5}$ effects were little attenuated by co-pollutants.

One issue that has received remarkably little attention is the possible interaction of PM and co-pollutants as effect modifiers. This is simply included in log-linear Poisson regression models by use of linear interaction terms, such as PM*CO and so on. Although "interactions" are sometimes identified as elements in an analysis, no results for linear co-pollutant interactions appear to have been published. Interactions of PM indices and weather or season indices are sometimes reported.

The only published co-pollutant interaction model appears to be in (Samet et al., 1996), reproduced by the U.S. Environmental Protection Agency (1996a). They presented three-dimensional plots of non-parametric surfaces, showing expected excess mortality as a function of TSP and SO_2, by season. The joint effect of TSP and SO_2 appeared to vary by season. Although software for these analyses is readily available, no subsequent investigations have been carried out.

A variety of analytical methods are available for exploring co-pollutant effects in time-series studies, and in prospective cohort studies where there are enough sites to produce enough variation among PM and co-pollutant correlations that their effects can be separated.

These methods have not yet been widely used, and many important questions about the separate effects of specific pollutants in an urban air mixture remain unresolved.

6.4.8 Synthesis of Information from Multiple Studies: Meta-Analyses

6.4.8.1 General Issues

There is now an extensive literature on methods for summarizing results of diverse research studies into a single evaluation or synthesis, this being one of the most important aims of this document. Some earlier documents provided a qualitative synthesis, or a "study of studies". Much of the emphasis in the recent literature has been on methods for providing quantitative summaries, often called "meta-analysis". However, there is not yet any consensus on how this should be done. There is some question as to whether quantitative summaries can be overly concise, implying greater precision and confidence in the quantitative summary than may be justified (Bailar, 1997; Weed, 1997a). The basic question is: do meta-analytic summaries of epidemiology studies provide findings of effect that can be subsequently verified using more definitive studies, such as interventions, chamber experiments, or large-scale randomized clinical trials?

The possibilities for verifying causal inferences about health effects from ambient air pollution in human populations are very limited, due to the large-scale nature of any interventions, the variety and complexity of atmospheric processes, and the general difficulty of defining appropriate control groups. Clinical random trials are frequently restricted to highly selected groups (an analogy with chamber studies), often excluding susceptible subjects who are of the greatest interest in environmental epidemiology studies.

Absent one or two "natural experiments", the best alternative is in the comparison of individual and population-based rates of adverse health effects in relation to differences in air pollution mixtures at different locations. At this time, there are few such multi-city comparisons with sufficient commonality in design and analysis that comparisons of effect sizes are believed to be meaningful, notably the half-dozen APHEA studies. Even among the APHEA studies, effects of differences in air pollutant indices, adjustments for season and weather, and differences in study populations pose complications for their interpretation.

Extensive meta-analyses of asthmatic responses are reported in Section 6.2, along with some published syntheses of hospital admissions studies (Schwartz, 1999a). Some APHEA

meta-analyses are also described in Sections 6.2 and 6.3. No attempt was made at this time to synthesize mortality studies in this Chapter, since extensive studies sponsored by the Health Effects Institute (HEI) are currently underway for 20 U.S. cities, soon to be expanded to 100 cities, using sophisticated new statistical methods.

There is an extensive literature on meta-analysis, much of it in the biomedical fields. Specific applications to environmental epidemiology are given by (Blair et al., 1995; Wong and Raabe, 1996). Although not necessarily representing EPA's views on meta-analyses, the criteria in (Blair et al., 1995) provide a useful and relevant basis for evaluating meta-analyses. Methodological issues in research synthesis require some discussion. Several critical questions in any research synthesis are:

(1) Are the summarized studies sufficiently comparable in characterization of effect, design, and analysis that a composite numeric estimate of the ambient PM effect has a meaningful interpretation across all of the studies being summarized?

(2) Are the summarized studies sufficiently comparable in characterization of effect, design, and analysis that a composite numeric estimate of the uncertainty of the estimated ambient PM effect is operationally meaningful: do we know what the 'between-study' variation indicates?

(3) Does the methodology allow for identification of distinctive sub-groups of studies (such as western Europe vs. eastern Europe in the APHEA meta-analyses), should the data suggest that more than one sub-group is involved?

(4) Do the studies synthesized include all studies available? If not, are the study selection criteria unbiased with respect to effect?

The general procedures in use allow the summary estimate to be a "weighted" combination of estimates from the individual studies, where the "weights" depend on statistical uncertainty or likelihood of the individual studies and on differences of their estimates from a central estimate or weighted average. Many sophisticated extensions of this basic idea have been proposed, including methods for estimating the effects of including hypothetical unpublished studies with less significant or non-significant findings compared to the published studies from which the estimates were assembled (Givens et al., 1997). Studies with negative or non-significant effects may be less likely to be published than studies with significant positive findings, or may be longer delayed before publication. Likelihood-based methods and Bayesian methods have also

been proposed for reviewing PM studies (Hasselblad et al., 1992; Clyde, 1999). However, no single method is generally accepted although simple "vote counting" is clearly inadequate. Any assessment of the value of specific methods for meta-analysis would probably require knowing the "right" answer from a definitive evaluation carried out separately from the studies being summarized.

Under some circumstances, one may have greater confidence in a research synthesis. Sometimes a synthesis or meta-analysis is based on studies by a single investigator or investigative team using virtually identical methods on each individual study; or, at times, a meta-analysis may be based on studies by different investigators using a generally similar analytical strategy, such as in the APHEA studies. Conversely, all studies in the group of analyses may have the same biases.

Assessment of the uncertainty of the estimated effect introduces other problems. Most estimates of ambient PM effect size depend on the regression model that was fitted to the data set in the individual study. These models include adjustments for a wide variety of covariates, with choices about which covariates to use, the shape or form of the adjustment for each covariate, the time-lag structure of the model for time series data, the method for smoothing mortality or morbidity counts, and so on. Uncertainty about the estimate of an ambient PM effect from the study clearly depends on the model that was finally selected in obtaining the PM effect estimate, but the uncertainty introduced in the model selection process is hardly ever explicitly included in assessing uncertainty of a composite estimate of effect. Published summaries of models rarely provide enough information to allow any assessment of the uncertainty in selection of the "best" model for estimation.

Finally, in any research synthesis, there may be a substantive basis for dividing estimates into subgroups based on location, inclusion or exclusion of common groups of covariates, or other group-level differences. These can be treated by hierarchical regression models or by empirical clustering methods. However, such approaches are not widely used.

In summary, no clear consensus currently exists regarding explicit criteria for assessing meta-analyses. Some issues in evaluating research reviews are discussed by Weed (1997b). The criteria that he suggests for evaluating review papers should also be applicable, with reasonable modifications, to the assessment of meta-analyses: These include:

(1) Explicit statement of the purpose of the review [meta-analysis];

(2) Literature search methods objective and subjective criteria for inclusion or exclusion of studies;

(3) Explicit statement of criteria for evaluating validity or quality of the studies;

(4) Methods for summarizing evidence;

(5) Criteria used in the review for drawing causal or preventive inferences;

The purposes of a review may include: making research recommendations; making causal scientific inferences; making recommendations for public health preventive action or intervention. For example, the purposes of this Chapter are to review the evidence relating adverse health effects in humans with environmental exposure to ambient PM, to draw conclusions about the role of ambient PM concentrations in causing the adverse effects, and to quantify the relationship between ambient PM and health effects where possible.

Literature searches were carried out in support of the substantive reviews in Sections 6.2 and 6.3. In general, this Chapter includes mainly studies published since the last PM Criteria Document was completed early in 1996. Earlier studies are included when there is reason to expand the discussion over that in U.S. Environmental Protection Agency (1996) so as to emphasize the interpretation of the more recent studies. The material selected for review here includes: publications in peer-reviewed journals, books, and conference proceedings; peer-reviewed publications that are in press or accepted for publication; abstracts of papers; Ph.D. dissertations; and in some cases, peer-reviewed technical reports where there is an institutional mechanism for publishing these reports in lieu of journal publication. However, some consideration has also been given to unpublished material that has a high probability of being published by the time of ultimate completion of this document. Clearly, much additional material submitted for publication and accepted for publication or published is expected to be included in the next external review draft of this Criteria Document expected to be released in mid 2000 (incorporating revisions in response to public comment and CASAC review of the present external review draft, as well as new information accepted by mid-2000 for publication).

A number of criteria have been used for placing greater reliance on the results of some studies than others in this draft document. The paramount criteria are:

(1) Studies in the United States, or in Canadian populations with air mixtures and demographics similar to those of the United States;

(2) Study populations are clearly identified (for example, by counties of residence or death; by recruitment and exclusion criteria in prospective cohort studies);

(3) Health endpoints are clearly identified (for example, by ICD codes);

(4) Statistical analyses are described with a sufficiently detailed description of covariate adjustments, ambient PM and co-pollutant exposure indices, effect size and uncertainty, and goodness of fit of the model, such that the informed reader can carry out assessments of study quality and validity, and perform secondary statistical analyses for comparison and synthesis.

6.4.8.2 Other Recent Research Syntheses and Reviews

A review of the findings in many short-term mortality studies was published by Gamble and Lewis (1996). A number of methodological and conceptual issues raised by the Gamble review were evaluated in U.S. Environmental Protection Agency (1997). A critique of the findings in the prospective cohort studies was also published in (Gamble, 1998). Earlier integrative syntheses for mortality were published in Lipfert and Wyzga (1995) and Moolgavkar and Luebeck (1996), and for all health endpoints by Vedal (1997), but these syntheses did not include quantitative meta-analyses. A large-scale meta-analysis was published by Zmirou et al. (1997), mostly involving older studies reviewed in U.S. Environmental Protection Agency (1996). Some investigators such as Schwartz (1999a) have assessed multiple sites in a single publication, looking at hospital admissions in eight cities. Meta-analyses for the APHEA study included Anderson et al. (1997), Katsouyanni et al. (1997), Spix et al. (1998), and Zmirou et al. (1998). Results from 14 cities in the PEACE study are given by Roemer et al. (1998).

6.5 THE USE OF EPIDEMIOLOGY STUDIES FOR CAUSAL INFERENCES ABOUT PM HEALTH EFFECTS

6.5.1 Causal Inference and Preventive Intervention

Causal inference methodology should play an important role in evaluating the effectiveness of proposed interventions, such as the effects of changes in regulatory standards for ambient PM. Little research has so far been done, and perhaps little can be done using the regression methods that are found in most published papers, that would clarify the predicted effect of reductions in ambient PM on public health. There is an implicit steady-state assumption that if the PM

concentrations in two communities differ by a certain amount, reducing the ambient PM in the community with the higher level to that in the community with the lower level would – sooner or later – reduce the excess of ambient-PM-attributable health effects in the higher community to that in the lower. One of the strongest empirical bases for this expectation is provided by the natural experiment that was carried out in the Utah Valley, UT, where it was shown that there were substantial reductions in a wide range of adverse health effects associated with the 13-month closure of a major PM-emitting source, with consequent reductions in ambient PM concentrations (Pope, 1996).

PM concentrations have decreased greatly in many cities in the preceding decades. In cities such as London that have virtually eliminated coal smoke as an air pollutant, there have not been any recurrences of smog episodes, such as those of December, 1952 or December, 1962. However, concentrations of many other air pollutants have also decreased during that period of time, so that the effect of banning coal in smoke-free zones can be reasonably, but not wholly, attributed to this intervention. Other major changes have occurred in the population demographics, health care system, transportation, industry, and housing of Greater London. There have even been increases in some sources of air pollution, such as diesel trucks and buses. It is therefore difficult to compare the effects of banning coal in smoke-free zones with the effects of not doing so, "everything else being equal". However, the matter of "absolute proof" notwithstanding, it would be also unreasonable to assume that banning coal smoke had nothing to do with the virtual elimination of "black smoke" health episodes, and consequent reduction of adverse health effects at lower concentrations, no matter that lower current ambient PM concentrations make it much more difficult to detect relationships between ambient PM excess mortality or morbidity.

Technical methods for dealing with these issues may require further development. It would be necessary to evaluate joint exposure-age-time relationships in order to understand the change in death rates in London and other cities where changes in PM took place. It is also possible that susceptibility to ambient PM increases with age, so the appropriate model for RR may not be a constant-hazard-rate log-linear model where the predictor of effect is the mean ambient PM concentration over the last X years, as in the prospective cohort studies of Dockery et al. (1993), Pope et al. (1995), Beeson et al. (1998), Abbey et al. (1999). An age-weighted cumulative exposure index would likely be more appropriate, and could (in principle) be constructed for

Harvard Six Cities and AHSMOG cohorts, if not for London. This would allow assessment of alternative hypotheses about increased RR in the elderly, for example, increasing cumulative ambient PM exposure with age versus increasing sensitivity or susceptibility with age. Some approaches are described by Thomas (1988), and Thomas et al. (1992) for other applications in environmental epidemiology.

It is important to note that "natural experiments" differ from planned experiments in that it may not be possible to control all of the relevant factors. Some factors were probably not affected by the shut-down of the steel mill, such as the range of meteorological conditions during the duration of the shut-down. Other factors, such as the levels of some co-pollutants produced by the plant, probably changed in a manner correlated with the changes in emitted PM levels. However, the study was carried out in a single community, with both baseline pre-shutdown and post-shutdown information available. The evidence must therefore be regarded as providing stronger information about the causal role of ambient PM reductions than do most observational studies.

In order for regression models to capture the effect of reducing ambient PM when other air pollutants also play a role in human health, it would be necessary to model and characterize the reductions (or possibly increases) in all other pollutants attendant to a reduction in ambient PM, including PM precursors that could form secondary particles (see Chapter 3). There is a theoretical basis for such modeling (Pearl, 1995). The underlying concept is that it is necessary to evaluate the consequences of not only setting ambient PM to a specific level, but also modifying the values or distribution of values of all of the PM causal ancestors or predecessors that are implied by specifying the ambient PM value. This has so far received scant attention in discussions of ambient PM by forced changes or interventions. Weed (1995) summarizes grade-of-evidence criteria used in preventive inference. He points out that data-and-judgment based causal inferences need not necessarily govern judgment-based preventive inferences. Other applications, such as regulatory decision making, bear the same relation to causal inference for ambient PM health effects that medical decision-making in clinical practice bears to causal inference in medical science. The scientific search for valid causal inferences are expected to help to inform the preventive (public health) inferences. The concern of this document is scientific causal inference, where evidence exists to carry it out.

6.5.2 Biological Plausibility in Causal Inference

The notion of "biological plausibility" is important for several reasons. The first is that it clearly affects the likelihood of publication of an epidemiology study For example, an editor of the *New England Journal of Medicine* recently wrote that publication may be warranted for large effects that "do not make biologic sense" (Angell, 1990, p. 824). PM-related health effects are clearly do make "sense", in view of the relationship between excess deaths and respiratory illness in the historic London, Donora, and Meuse Valley episodes. The issue now is whether reasonable analogues of the illnesses and causes of sudden death observed during these episodes can be expected to occur when ambient PM concentrations and related exposures to PM are more than an order of magnitude lower. The publication of a large number of PM epidemiology studies suggest that this remains a subject of concern, even when no specific biologic mechanism is identified with the putative ambient PM-attributable deaths or illnesses.

Weed and Hursting (1998, p. 416) discuss three commonly held viewpoints about what constitutes biological plausibility:

(1) Viewpoint 1 – "*a biologically plausible association is one for which a reasonable mechanism can be hypothesized, but for which no biologic evidence may exist;"*

(2) Viewpoint 2 – "*simply suggesting a mechanism for a factor-cancer association is insufficient. Evidence supporting the proposed mechanism is also necessary;*"

(3) Viewpoint 3 – "*an association is considered biologically plausible if there is sufficient evidence to show how the factor influences a known disease mechanism*". (p. 416; authors' italics). The factor in this instance is the concentration of PM of ambient origin in the community.

An example of the first viewpoint might be to hypothesize that airborne particles cause inflammatory reactions in the lungs, exacerbating susceptibility to respiratory diseases. A much more extensive discussion of this hypothesis and others was given by Seaton (1996), who cited studies in laboratory animals as supportive of this hypothesis. Some scientists might require proof beyond the animal experiments, which involved artificial particles such as Teflon microspheres, and require evidence of analogous effects using actual particles recovered from the ambient air. An extensive discussion of biological plausibility at this secondary level is given by Schwartz et al. (1999), who argues that differences in PM effects in eight U.S. counties may be

attributable to cardiovascular effects of PM and CO in animals and in humans. This also illustrates the second viewpoint about biological plausibility.

The presence of urban air particles or other biological, physical, or molecular markers in human tissue, along with *in vivo* damage of the tissue, is likely to be necessary for scientists who hold the third point of view. This might be provided by specimens of diseased tissue with airborne particles present in proximity to sites of damage, or by DNA adducts of components of airborne particles in conjunction with DNA damage. A recent study provides such evidence for polycyclic aromatic hydrocarbons (Whyatt et al., 1998) in mothers and newborns in Poland.

In our opinion, biological plausibility plays an important role in the acceptance of epidemiology data as providing causal evidence. The studies themselves may or may not provide proof of causality because some other criterion (for example, only modest strength of association) is not satisfied in the mind of the reviewer. We tend to agree with Hill (1965) that biological plausibility is not required in order to accept the results of a consistent set of epidemiology studies, provided that the findings do not strongly disagree with commonly (currently) held beliefs about biological mechanisms. Specific causal mechanisms are discussed in Chapter 7.

6.5.3 Natural Experiments, Quasi-Experiments, and Causal Inference

Most scientists would hold that experimental evidence is the most definitive of all scientific methods. This requires direct intervention in the system being studied, varying the factor of interest, and holding all other factors constant, so that conclusions may be drawn about the experimental factor "everything else being equal".

The closest example of this is in the observations in Utah Valley, UT, during the 1986-1989 period, when the main source of PM was shut down for 13 months during that period. This constitutes a "natural experiment" rather than a planned intervention, but certain aspects of the Utah Valley studies allow fairly strong conclusions to be drawn. A comprehensive summary of earlier studies is given by Pope (1996). The most difficult issues arise in connection with time-dependent confounders or covariates associated with ambient PM: everything else rarely is "equal", and one would expect that other pollutants with which emitted PM is associated (SO_2, NO_x, and other combustion products) would also change in a corresponding manner. The Utah Valley studies were evaluated by U.S. Environmental Protection Agency (1996) as showing

likely particle effects in the presence of low concentrations of other co-pollutants. Also, Vedal (1997) writes, "The Utah Valley, for example, experiences only very low concentrations of SO_2, and because the particle concentrations occur mainly in the winter, as opposed to the East where the high particle concentrations are largely a summer-time phenomenon, also very low O_3 concentrations (Pope, 1996). Very low concentrations of acid aerosol in the Utah Valley have also been documented. ... Because the effects are related to particle increases in the wintertime, rather than during the summertime as in the East, it has also been reasonably argued that it is unlikely some effect of meteorology not adequately accounted for in the analyses is responsible for what appears to be the effect of particles." Possible effects of CO, which also tends to be elevated during the winter, were not explicitly evaluated.

Other explanations have been advanced for the Utah Valley findings, such as two-year cycles in the rate of respiratory syncytial virus (Lyon et al., 1996), or other short-term variations in respiratory illness (Lamm et al., 1994). Another possibility is that the Utah Valley population changed during the steel mill strike, but there is little evidence of this. However, these arguments have been refuted by comparisons with nearby locations (Pope et al., 1991; Pope, 1996). On the whole, the Utah Valley studies may be interpreted as a natural experiment in which other causes of adverse health effects with cardiopulmonary symptoms were effectively "controlled" by the context, and the largest source of variation was in the large changes in ambient PM levels during the interval.

6.6 CONCLUSIONS AND DISCUSSION

6.6.1 Conclusions

The epidemiology evidence about the health effects of ambient PM has expanded greatly since the 1996 PM AQCD. The major enhancements in information cover the following areas:

(1) Additional studies of health endpoints using ambient PM_{10} and closely related mass concentration indices such as PM_{13} and PM_7;

(2) New studies on a variety of health endpoints for which information on the ambient coarse PM fraction ($PM_{10-2.5}$), the ambient fine particle fraction ($PM_{2.5}$), and even

ambient ultrafine particle mass concentrations (PM1 and smaller) were observed or estimated from site-specific calibrations;

(3) New studies on some health endpoints in which the relationship of health endpoints to ambient particle number concentrations were evaluated;

(4) Additional studies which evaluated the sensitivity of estimated PM effects to the inclusion of gaseous co-pollutants in the model;

(5) Preliminary attempts to evaluate the effects of air pollutant combinations or mixtures including PM components, based on empirical combinations (factor analysis) or source profiles;

(6) New studies of infants and children as a potentially susceptible population;

(7) Additional studies on cardiovascular endpoints associated with PM exposures.

(8) Studies on asthma and other respiratory conditions exacerbated by PM exposure.

This additional information has not yet resolved some of the key issues in PM air pollution epidemiology. Within each group of health effects studies relating to short-term and long-term PM exposure, the findings of statistically significant associations of ambient PM concentrations with mortality or morbidity in some studies are often accompanied by other studies finding PM-health effects associations that are not statistically significant (these should not be inaccurately characterized as 'negative' findings). In fact, reported results are rarely "negative" (indicating a beneficial affect associated with PM exposure), and the negative results reported are very rarely statistically significant. This does not appear simply to reflect any bias in favor of publication of only positive and significant results in peer-reviewed journals. In order to try to capture the flavor of the full range of newly emerging information, some papers have been included here in this PM AQCD draft review based on published abstracts or non-peer-reviewed conference proceedings when the information presented (whether 'positive' or 'negative') is particularly relevant to inference about the role of PM in producing adverse health effects.

Overall, based on the information thus far reviewed in this draft document, it appears warranted to conclude that the multiplicity of findings about PM health effects suggest that exposure to ambient PM at current concentrations may cause serious adverse health effects, but that the quantitative magnitude of the effects depends on several environmental and biological factors whose role is not yet known. That is, current levels of ambient PM may be harmful to

human health, but not necessarily equally harmful everywhere or at all times. The most important factors are discussed in the following sections.

6.6.2 PM Health Effects May Occur In Any Size Fraction; Some Health Effects May Also Be Absent From Some Mass Fractions Under Some Circumstances

There are some studies in which health effects were estimated in a large number of locations, using generally very similar data bases and ambient PM exposure indices, including the APHEA studies in 12 European cities, Canadian studies in 13 or 16 cities, the Six (U.S.) Cities studies, and the HEI-sponsored NMMAPS studies in 8-, 20-, and 100 U.S. cities. Results of the NMMAPS studies are still pending. Results of the studies in the other cities have been discussed herein. Interpretations of the relatively modest effect sizes reported (odds ratio or relative risk < 2, often < 1.2) are subject to the possibility that differences may be due to small biases from confounding, from model mis-specification and measurement error, or model selection strategy.

The APHEA studies suffer from the use of different PM indices in different locations. The most nearly comparable findings use: (a) PM_{10} in London (Anderson et al., 1996; Ponce de Leon et al., 1996); (b) PM_{7} in Lyon (Zmirou et al., 1996); and (c) PM_{13} in Paris (Dab et al., 1996). Time-series mortality studies found large PM effects for Lyon, much smaller effects for Paris and Cologne. Most other APHEA studies used BS as the PM index. PM effects indexed by BS were much lower in Central-Eastern European cities than in many of the Western European cities, as shown in Section 6.3.2. Various hypotheses have been proposed for this, such as demographic differences in susceptibility, and inadequate adjustments for weather and seasonality. However, the modeling strategy was the same for all the cities, so if inadequate in one region, may be inadequate in all. Perhaps most importantly, it is not clear to what extent the subject BS measurements can be credibly interpreted as mass concentration estimates, given the lack of any documented necessary site-specific calibrations of BS reflectance readings versus co-located gravimetric measurements (see discussion of the need for this in previous U.S. EPA PM AQCDs). Even the comparison across the three western European cities with measurements nominally comparable to PM_{10} are difficult, with the extent to which estimates of PM-related

total mortality may differ across all three not being clear, especially given mortality differences attributed to different co-pollutant mixtures or climate (as discussed below).

Differences across the Harvard Six (eastern and mid-western U.S.) Cities are also of interest in evaluating excess mortality attributable to fine and coarse fractions of PM_{10}. Even though Topeka, KS had a relatively high mean concentration of $PM_{10-2.5}$, there was little evidence of excess mortality associated with either the coarse or fine fractions of PM_{10}. It is likely that the coarse fraction is usually dominated by crustal particles in Topeka, and even the fine fraction (from a high concentration of crustal particles smaller than 2.5 μg), to a larger extent than in the other cities.

Supporting evidence for the hypothesis that there is relatively little excess mortality associated with coarse particles of crustal origin is provided by recent studies in the Wasatch Front (Salt Lake City, Ogden, and Utah Valley, UT) by Pope et al. (1999b), in Spokane, WA, by Schwartz et al. (1999), and in the Coachella Valley of California (Ostro et al., 1999). These Western U.S. studies show that, by removing from the analyses days in which PM_{10} concentrations appear to be dominated by wind-blown dust of presumably crustal origin, there appears to be a stronger association between PM_{10} and mortality during normal wind conditions when air pollution in these metropolitan areas is dominated by urban sources. The excess mortality for the Utah Valley (Provo-Orem) was about 8% per 50 mcg/m^3 PM_{10}, compared with 5% for Ogden and 4% for Salt Lake City. These findings were somewhat higher than earlier studies for Salt Lake City (Styer et al., 1995) and Utah Valley (Pope et al., 1992; Pope, 1996). The local particle sources in the Utah Valley are likely to be enriched in transition metals such as iron, especially during the operation of the steel mill there, possibly accounting for the greater excess mortality attributed to PM_{10} in Utah Valley. A similar assessment for Topeka would also be of interest.

Conversely, Steubenville, OH showed the strongest relationship between $PM_{10-2.5}$ and mortality among the Harvard Six Cities (Schwartz et al., 1996). Steubenville had a very high mean $PM_{2.5}$ concentration and a very high correlation between the fine and coarse fractions (0.69). It is therefore possible that some of the excess mortality attributed to the coarse fraction in Steubenville may be due to 'large small particles', i.e., accumulation-mode or fine-mode particles larger than 2.5 μg. Other time series studies find some association between coarse particles and excess total mortality in the Coachella Valley of California (Ostro et al., 1999), and

between excess hospital admissions and mortality in Toronto (Burnett et al., 1998, 1999), although it is possible that the ambient coarse PM fraction in these locations may include a high concentration of coarse particles of non-crustal origin (such as agriculture and wood-burning) that cause adverse health effects. That is, there may well be circumstances in which coarse particles at current concentrations can be harmful to humans. There is some evidence that this may not always apply to coarse particles (or possibly even smaller particles) of crustal origin.

Section 6.4.6.2 discusses evidence suggesting that fine particles contribute to excess mortality in infants as well as in adults in Mexico City (Borja-Abuto et al., 1998; Loomis et al., 1999). No comparisons with coarse particles or with PM_{10} have been published. There is also some indication that $PM_{2.5}$ is associated with hospital admissions in Toronto (Burnett et al., 1997b, 1998), and with excess mortality (Burnett et al., 1998) even after adjusting for CO. Other indices such as CoH (elemental carbon particles) and CO may be more strongly related to adverse health effects, but $PM_{2.5}$ (and to a lesser extent, $PM_{10-2.5}$) appear to retain their significance even when CO is included as a co-pollutant. A seasonal decomposition of fine versus coarse particle effects would be of interest.

Recent European studies (Peters et al., 1998) also suggest that ultrafine particles are also significantly associated with adverse health effects in humans. Although the number concentration of ultrafine particles appears to be a better predictor than the mass concentration in their studies, the latter is also associated with health effects.

Finally, size-differentiated health effects of particles may also be associated with chemical components or physical properties of the particles, possibly related to their sources. The role of acidity, sulfates, metals, or other components (alone or in conjunction) in causing human health effects remains to be better clarified. The relationship of both sulfate and non-sulfate components of fine particles to excess mortality in the Harvard Six Cities long-term cohort mortality study (Dockery et al., 1993) was shown in the prior PM AQCD (U.S. Environmental Protection Agency, 1996) to be roughly similar. Comparison of sulfate and non-sulfate FP effects, and crustal versus non-crustal FP effects, would be useful in time series studies as well as cohort studies in which both pollutants were available.

6.6.3 PM Health Effects at Different Time Scales

Recently published studies (Schwartz 1999b; Zeger et al., 1999) suggest that a substantial part of excess mortality attributable to ambient PM in Boston and Philadelphia may be found in responses that occur from ambient PM concentrations averaged over intervals of about 30 to 120 days. These so-called "mid-term" effects may occur in addition to the wide variety of responses that occur on the same day as the ambient PM exposure, or within a few days thereafter. Schwartz (1999b) finds ambient $PM_{2.5}$ effects increase RR nearly two-fold for pneumonia and total mortality when a 60-day window is used, compared to a 0-day window at lags 0 to 3 days. This may explain part of the larger RR in the prospective cohort studies of Dockery et al. (1993) and Pope et al. (1995) compared to the daily time-series mortality studies.

The recent reanalyses of the AHSMOG cohort by Beeson et al. (1998) and Abbey et al. (1999) find significant effects of PM_{10} on total mortality, mortality with any contributing non-malignant respiratory causes (CRC), or lung cancer incidence and mortality associated with long exposure to PM_{10} in males, but not in females. There are also no significant effects associated with long-term $_{SO4}^{=}$ or SO_2 exposure, which was probably very low in California during most of this time frame, but some relationships with ozone. The most significant PM_{10} associations are found with the average number of days per year in which PM_{10} exceeded a specific cut-point, such as 100 $\mu g/m^3$, not with the long-term mean PM_{10} concentration for each individual. No significant excess mortality was found for cardiopulmonary effects. These findings tend to support the conclusion of the U.S. Environmental Protection Agency (1996) PM AQCD that long-term PM exposures can also be harmful, but with some noteworthy differences about gender and diagnosis of death cause that remain to be resolved. Reanalyses of the Harvard Six Cities and ACS cohort data commissioned by HEI may also modify conclusions about the earlier studies.

Key issues in the interpretation of the prospective cohort studies are:

(a) Effects of spatial confounding for $_{SO4}^{=}$, and possibly even $PM_{2.5}$, due to local variation;

(b) Lack of assessment of co-pollutant models for comparison;

(c) Lack of consideration of longer-term exposures preceding the study interval, or of alternative exposure metrics over different time periods preceding and during the study period;

(d) Lack of evaluation of non-linear relationships with PM_{10} (although the results from use of exceedance indicators in the AHSMOG study suggests these may exist);

(e) The absence of exposure-time-age studies that would better link short-term, mid-term, and long-term PM exposures to specific health endpoints, or to the progression of endpoints from less adverse to more adverse, with numeric estimates of disability and life-shortening;
(f) Potential confounding associated with personal or demographic risk factors;

6.6.4 Alternative Hypotheses for Adverse Health Effects

In Section 6.1, some alternative hypotheses for PM health effects were proposed. The foregoing evaluation of recent PM epidemiology studies has allowed some tentative conclusions to be drawn about the plausibility of various alternatives expressed in Table 6.1. These tentative conclusions are shown in Table 6-57. The foregoing discussion suggests a somewhat pessimistic prognosis for meaningful large-scale formal (mathematical) synthesis of PM epidemiology studies, except possibly in sub-categories with similar health endpoints, similar PM characterization, and similar environmental co-factors. There is clear evidence that some categories of PM such as ambient $PM_{2.5}$ and PM_{10} may be associated with a number of health effects outcomes under some conditions (perhaps many); that health effects may be associated with the ambient PM coarse fraction under some (but not all) conditions; and that these health effects may vary from place to place and from time to time, depending on a variety of incompletely identified factors. It is further possible that indoor-source particles have different potential for causing health effects than particles from ambient PM exposure. The overall picture is somewhat more diverse than in the previous PM AQCD (in spite of the considerable quantity of new information), because the range of outcomes has expanded considerably. However, a sufficiently large number of additional new findings of health effects being associated with exposure to ambient PM and other atmospheric pollutants (in competently executed independent studies carried out by a large number of investigators around the world) have been reported to justify public health concern that ambient PM exposure at current levels may be a health hazard to susceptible individuals and to at least provisionally conclude that the newer studies support the 1996 PM AQCD key judgement that the observed PM-morbidity/mortality associations likely represent causal relationships.

Of particular interest are new findings and insights derived from new hospital admission studies using various PM mass metrics (PM_{10}, $PM_{2.5}$, etc.) The results of the new PM mass studies are generally consistent with and supportive of the studies presented in the 1996 PM

TABLE 6-57. TENTATIVE CONCLUSIONS ABOUT ALTERNATIVE HYPOTHESES THAT MAY AFFECT THE SYNTHESIS OF EPIDEMIOLOGY STUDIES

Alternative Hypotheses	Adverse Health Effects Depend Only on Ambient PM, Independent of Co-Factors	Adverse Health Effects Depend on Ambient PM as well as Co-factors
Adverse health effects depend only on ambient PM size range	Not likely. Adverse health effects from coarse particles may occur at some sites, not others.	Possible. Adverse health effects from ambient PM are different in sites where ambient PM has different co-factors with same PM range.
Adverse health effects depend on ambient PM with specific physical properties or composition	Possible. Adverse health effects from ambient PM of a given size may be different in sites where PM has different physical properties or composition with same PM size range.	Probable. Adverse health effects from ambient PM are different in sites where PM has different physical properties, composition, or co-factors, even in the same ambient PM size range

AQCD (U. S. Environmental Protection Agency, 1996). Moreover, mathematical syntheses of multiple hospital admissions studies for the various age and disease categories (including relevant studies from the previous AQCD conducted as part of this new review) generally found overall significant and reasonably consistent RR effect sizes (i.e., within their respective confidence intervals) across admissions categories for both PM_{10} and $SO_4^{=}$. As discussed by Hill (1965), such coherence across outcomes and among multiple studies conducted in different places by different investigators are supportive of the conclusion that these associations are caused by PM mass or a closely related pollutant correlate. Hospital admissions studies considering multiple PM components were also evaluated in order to assess the relative roles of the various components in the reported PM-health effects associations (in those studies where multiple PM components were considered). These results indicated that sulfates and acidic aerosols are often among the PM metrics most strongly associated with respiratory morbidity.

Studies of doctors' visits in some cities indicate that the use of hospital admissions alone can understate the total severe morbidity effects of air pollution. For example, in both Paris and London, the number of doctors' visits amount to many times the number of hospital admissions.

Moreover, the Paris Black Smoke RR for asthma doctors visits was actually much higher than that for asthma hospital admissions (doctors' visits RR=1.74 for 100 $\mu g/m^3$, versus hospital admissions RR=1.04). These results suggest that considering only hospital admissions and emergency hospital visit effects may greatly underestimate the numbers of medical visits occurring in a population due to acute particulate matter air pollution exposure.

Also of much interest are new panel studies that report associations between ambient PM concentrations and worsening of asthma conditions. Most studies reported PM_{10} results, and $PM_{2.5}$ was evaluated in two studies (none used $PM_{10-2.5}$ measures of the coarse fraction PM_{10}). Some employed symptoms-scoring approaches and/or asthma medication usage as indicators of asthma exacerbations. A qualitative summary of those studies examining ambient PM_{10} exposure on asthmatic health outcomes indicate that, as a group, the majority of studies report a positive odds ratio for the relationship, with almost half having 95% CI above 1.00, looking at the endpoints one at a time. Viewing all the indicators together within a study may be a better test of the relationship for an asthma attack. Examining all the studies as a group quantitatively describes a stronger relationship. One study examining both PM_{10} and $PM_{2.5}$ reported that $PM_{2.5}$ had a larger effect. Another unique study, which (1) evaluated the size distribution of particles in the range 0.001 to 2.5 μm and (2) examined the number of particles, found that the health effects of 5 day means of the number of ultrafine particles were larger than those for the mass of the fine particles. In contrast, another study also examined a range of PM sizes but found PM_{10} to be more consistently associated with PEF changes, and another study reported that 1-hr and 8-hr maximum PM_{10} had larger effects than the 24 hr mean. Other newer studies also report significant associations of increased emergency room visits or hospital admissions for asthma with various ambient PM indices. Collectively, these studies point toward exacerbation of asthma likely being related to ambient PM exposures; but they do not yet allow for clear-cut attribution of such effects being more closely related to specific PM size fractions or composition or for clear delineation of quantitative contributions of ambient PM acting along versus in combination with ozone (at least in some studies where significant ozone associations with asthma-related health outcomes were also found). Lastly, it should be noted that, overall, the newer epidemiologic analyses of PM-cardiovascular effect relationships also appear to be generally supportive of previous conclusions in the 1996 PM AQCD highlighting such relationships as likely being causative and of likely public health concern. Again, however, it is

still difficult to delineate quantitatively the proportion of risk attributable to: ambient PM acting alone; PM acting in combination with other co-pollutants; other specific co-pollutants, *per se*; or overall ambient mix of pollutants.

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7. DOSIMETRY AND TOXICOLOGY OF PARTICULATE MATTER

7.1 INTRODUCTION

Epidemiological studies strongly implicate respirable particles in increased morbidity and mortality in the general population. The mechanisms by which particulate matter (PM) may cause adverse responses leading to severe health consequences is a matter of extensive investigation. This chapter summarizes recent literature examining particle dosimetry; the toxicological responses of susceptible animal models; pulmonary and systemic responses of healthy and susceptible humans; and the effects of particles on ex vivo systems of cells and/or cellular constituents. This chapter focuses primarily on material published since 1995. Earlier published studies have been summarized in U. S. Environmental Protection Agency (1996a). The reader should refer to chapters 10 and 11 of the 1996 document for more information.

The first section of the chapter deals with human and animal particle dosimetry - the study of the deposition, translocation, clearance, and retention of particles within the respiratory tract and adjacent tissues. Although the physical principles governing deposition of particles have not changed since the publication of the previous Air Quality Criteria for Particulate Matter (U.S. Environmental Protection Agency, 1996a), there is an improved understanding of the role of certain biological determinants of the deposition/clearance process, including body size (especially in relation to respiratory tract dimensions), respiratory flow and volume, and nose versus mouth breathing. In addition, the understanding of regional dosimetry has expanded.

Studies addressing the toxicology of particles or their constituent chemicals on humans, animals, and ex vivo systems is covered in the next major section of the chapter. There are extensive new toxicological studies on combustion particles, such as oil fly ash. Of particular interest are a small, but growing, number of new studies on the toxicology of concentrated ambient air particles (CAPS) (Sioutas et al., 1995; Gordon et al., 1998), especially in susceptible animal models. The aim of these studies is not only to understand the responses to CAPS but also to provide potentially useful dose-response information for risk assessment.

Because the primary purpose of this document is to assess the health effects of particles in humans, human controlled exposure and dosimetry studies are extremely valuable. Such studies avoid uncertainties associated with extrapolation of biochemical, dosimetric, and physiological responses from animals to humans and extrapolating target tissue doses from animals to humans. Both animal and human controlled exposures avoid the uncertainties associated with exposure assessment in field and epidemiological studies. Furthermore, sensitive humans, such as those with cardiovascular or respiratory disease, can also be directly studied. Nevertheless, the number and types of responses that can ethically be evaluated in human volunteers is limited. Such studies are generally limited to acute or very short term exposure scenarios.

Animal toxicology studies are particularly useful for long term or chronic exposures and for the invasive examination of response mechanisms. Animal models of disease can be useful in providing information about responses of sensitive humans. Even though animal models cannot duplicate human disease, certain features of human diseases can be simulated, providing valuable insight into mechanisms of response. Several new studies have examined the effects of inhaled or instilled particles on cardiovascular responses, a potentially important pathway for acute effects. When only small amounts of PM test material are available, intratracheal instillation studies can be useful to examine mechanisms of response. In in vitro studies, animal and human cells and cellular components can be exposed to particles, soluble extracts of particles, or individual chemical constituents of particles. Such studies are often useful in examining cellular and biochemical mechanisms of action within specific cell types, with the recognition that cells may behave differently in tissues or within the whole organism, especially at dose levels that occur with actual ambient inhalation exposures.

7.2 PARTICLE DOSIMETRY

7.2.1 Introduction

A basic tenet of toxicology is that the dose delivered to the target site, rather than the external exposure, is the proximal cause of any biological response. Characterization of the exposure-dose-response continuum for PM requires the elucidation and understanding of the mechanistic determinants of inhaled particle dose, which is dependent initially upon the

deposition of particles within the airways of the respiratory tract. Particle deposition refers to the removal of particles from their airborne state due to their aerodynamic and thermodynamic behavior in air. Once particles have deposited onto the surfaces of the respiratory tract, some may undergo various transformations and others will not, but subsequently all will be subjected to either absorptive or non-absorptive particulate removal processes. This may result in their removal from airway surfaces as well as their removal to a greater or lesser degree from the respiratory tract as a whole. Particulate matter translocated from initial deposition sites is said to have undergone clearance. Clearance of deposited particles depends on the initial deposition site, physicochemical properties of the particles, and on translocation mechanisms. Retained particle burdens are determined by the dynamic relationship between deposition and clearance mechanisms.

This section is concerned with important particle characteristics related to dosimetric considerations and with mechanisms of particle deposition, clearance and retention in the respiratory tract. It summarizes basic concepts as presented in the 1996 Air Quality Criteria Document on Particulate Matter (U.S. Environmental Protection Agency, 1996a) and updates the state of the science based upon new literature on particle deposition, clearance and retention appearing since the publication of the 1996 document.

The dose of inhaled particles deposited and retained in the respiratory tract is governed by the exposure concentration, by respiratory tract anatomy and physiology, and by physicochemical properties of the particle (e.g., initial inhaled particle size, distribution, hygroscopicity, solubility). Anatomic and physiologic factors influencing particle deposition and retention are discussed in depth in the 1996 Criteria Document. Anatomical factors include: nasal, oral and pharyngeal anatomy; size and shape of laryngeal opening; tracheal anatomy; bronchial anatomy; mucus distribution; alveolar anatomy. Physiological factors include breathing pattern characteristics such as respiratory rate; air flow velocities, breathing volumes; air distribution among and within lobes; air-mixing characteristics; breath holding. The physicochemical properties of particles as they relate to dosimetry are summarized in Section 7.2.1.1, while concepts related to specific deposition and clearance mechanisms are presented in subsequent sections.

7.2.1.1 Size Characterization of Inhaled Particles

Information about particle size distribution is important in the evaluation of effective inhaled dose. This section summarizes particle attributes requiring characterization and provides general definitions important in understanding particle fate within the respiratory tract.

Particles exist in the atmosphere as aerosols, which are suspensions of finely dispersed solid or liquid particles in the air. Because aerosols can consist of almost any material, their description in simple geometric terms can be misleading unless important factors relating to constituent particle size, shape, and density are considered. While the size of particles within aerosols can be described based upon actual physical measurements, such as obtained with a microscope, in many cases it is better to use some equivalent diameter in place of the physical diameter. The most commonly used metric is aerodynamic equivalent diameter (AED), whereby particles of differing geometric size, shape and density are compared aerodynamically with the instability behavior of particles that are unit density (1 gm/cm^3) spheres. The aerodynamic behavior of unit density spherical particles constitutes a useful standard by which many types of particles can be compared in terms of certain deposition mechanisms.

It is important to note that aerosols present in natural and work environments have polydisperse size distributions. This means that the constituent particles within an aerosol have a range of sizes, and are more appropriately described in terms of a size distribution parameter. The lognormal distribution, i.e., the logarithms of particle diameter are normally distributed, can be used for describing size distributions of most aerosols. In linear form, the logarithmic mean is the median of the distribution, and the metric of variability around this central tendency is the geometric standard deviation, σg. The σg, a dimensionless term, is the ratio of the 84th (or 16th) percentile particle size to the 50th percentile size. Thus, the only two parameters needed to describe a log normal distribution of aerosol particle sizes are the median diameter and the geometric standard deviation. However, the actual size distribution may be obtained in various ways. For example, when a distribution is described by counting particles, the median is called the count median diameter (CMD). On the other hand, the median of a distribution based upon particle mass in an aerosol is the mass median diameter (MMD). When using aerodynamic diameters, a term that is frequently encountered is mass median aerodynamic diameter (MMAD), which refers to the median of the distribution of mass with respect to aerodynamic equivalent diameter. Most of the discussion in this chapter will focus on MMAD because it is the most

commonly used measure of aerosol distribution. However, alternative size distributions should be used for particles below a certain size, namely ~0.5 μm, which should be based upon actual size, since aerodynamic properties become less important. One such metric is thermodynamic-equivalent size, which is the diameter of a spherical particle that has the same diffusion coefficient in air as the particle of interest.

7.2.1.2 Structure of the Respiratory Tract

Details of respiratory tract structure are provided in the previous Criteria Document (U.S. Environmental Protection Agency, 1996a), and only a brief synopsis is presented here. For dosimetry purposes, the respiratory tract can be divided into three regions on the basis of structure, size, and function: extrathoracic (ET), tracheobronchial (TB) and alveolar (A).

The ET region consists of head airways (i.e., nasal or oral passages) through the larynx, and represents the areas through which inhaled air first passes. In humans, inhalation can occur through the nose or mouth (or both, known as oronasal breathing). However, most animals commonly used in respiratory toxicological studies are obligate nose breathers.

From the ET region, inspired air enters the TB region at the trachea. From the level of the trachea, the conducting airways then undergo branching for a number of generations. The terminal bronchiole is the most peripheral of the distal conducting airways and these lead, in humans, to the respiratory bronchioles, alveolar ducts, alveolar sacs and alveoli, all of which comprise the A region. All of the conducting airways, except the trachea and portions of the mainstem bronchi, are surrounded by parenchymal tissue. This is composed primarily of the alveolated structures of the A region and associated blood and lymphatic vessels. It should be noted that these respiratory tract regions are comprised of various cell types, and that there are distinct differences in the cellular composition of the ET, TB and A regions. While a discussion of cellular structure of the respiratory tract is beyond the scope of this section, details may be found in a number of sources (e.g., Crystal et al., 1997).

7.2.2 Factors Controlling Dose

Characterization of the exposure-dose-response continuum is the fundamental objective of any dose-response assessment. This section reviews the major factors controlling the fate of inhaled particles as discussed in detail in the previous Criteria Document (U.S. Environmental

Protection Agency, 1996a), and provides an update as new information on particle fate has become available. It must be emphasized that dissection of the factors that control inhaled dose into discrete topics masks the dynamic and interdependent nature of the intact respiratory system. For example, although deposition is discussed separately from clearance mechanisms, retention (i.e., the actual amount of particles found in the respiratory tract at any point in time) is determined by the relative rates of deposition and clearance. Retention and the toxicologic properties of the inhaled agent are related to the magnitude of the pharmacologic, physiologic, or pathologic response. Therefore, assessment of the overall dosimetry and toxic response requires integration of these various factors.

Inasmuch as particles which are too massive to be inhaled occur in the environmental air, the description "inhalability" is used to denote the overall spectrum of particle sizes which are potentially capable of entering the respiratory tract. Inhalability can be defined as the ratio of the number concentration of particles of a certain aerodynamic diameter that are inspired through the nose or mouth to the number concentration of the same diameter particle present in an inspired volume of ambient air (International Commission on Radiological Protection, 1994). In general, for humans, unit density particles >100 μm diameter have a low probability of entering the mouth or nose in still air. However, there is no sharp cutoff to zero probability. Furthermore, there is no lower limit to inhalability as long as the particle exceeds a critical size where the aggregation of atomic or molecular units is stable enough to endow it with "particulate" properties, in contrast to those of free ions or gas molecules.

7.2.3 Particle Deposition

7.2.3.1 Mechanisms of Deposition

Particles may deposit within the respiratory tract by five mechanisms: inertial impaction, sedimentation, diffusion, electrostatic precipitation and interception.

Sudden changes in airstream direction and velocity cause particles to fail to follow the streamlines of airflow. As a consequence, the particles contact, or impact, onto airway surfaces. The ET and upper TB airways are characterized by high air velocities and sharp directional changes and, thus, dominate as sites of inertial impaction. Impaction is a significant deposition mechanism for particles larger than 1 μm AED.

All aerosol particles are continuously influenced by gravity, but particles with an AED > 0.5 μm are affected to the greatest extent. A particle will acquire a terminal settling velocity when a balance is achieved between the acceleration of gravity acting on the particle and the viscous resistance of the air, and it is this settling which takes it into contact with airway surfaces. Both sedimentation and inertial impaction can influence the deposition of particles within the same size range. These deposition processes act together in the ET and TB regions, with inertial impaction dominating in the upper airways and gravitational settling becoming increasingly dominant in the lower conducting airways, especially for the largest particles which can penetrate into the smaller bronchial airways.

As particle diameters become <1 μm, the particles are increasingly subjected to diffusive deposition due to random bombardment by air molecules, which results in contact with airway surfaces. The root mean square displacement that a particle experiences in a unit of time along a given cartesian coordinate is a measure of its diffusivity. The density of a particle is unimportant in determining particle diffusivity. Thus, instead of having an aerodynamic equivalent size, diffusive particles of different shapes can be related to the diffusivity of a thermodynamic equivalent size based on spherical particles.

The particle size region around 0.3-0.5 μm is frequently described as consisting of particles which are small enough to be minimally influenced by impaction or sedimentation and large enough to be minimally influenced by diffusion. Such particles are the most persistent in inhaled air and undergo the lowest extent of deposition in the respiratory tract.

Interception is deposition by physical contact with airway surfaces. The interception potential of any particle depends on its physical size, and fibers are the chief concern in relation to the interception process. Their aerodynamic size is determined predominantly by their diameter, rather than their length.

Electrostatic precipitation is deposition related to particle charge. The minimum charge an aerosol particle can have is zero, when it is electrically neutral. This condition is rarely achieved because of the random charging of aerosol particles by air ions. Aerosol particles will acquire charges from these ions by collisions with them due to their random thermal motion. Furthermore, many laboratory generated aerosols are charged. Such aerosols will lose their charge slowly as they attract oppositely charged ions. An equilibrium state of these competing processes is eventually achieved. This Boltzmann equilibrium represents the charge distribution

of an aerosol in charge equilibrium with bipolar ions. The minimum amount of charge is very small, with a statistical probability that some particles within the aerosol will have no charge and others will have one or more charges.

The electrical charge on some particles may result in an enhanced deposition over what would be expected from size alone. This is due to image charges induced on the surface of the airway by these particles or to space-charge effects whereby repulsion of particles containing like charges results in increased migration toward the airway wall. The effect of charge on deposition is inversely proportional to particle size and airflow rate. This type of deposition is probably small compared to the effects of turbulence and other deposition mechanisms, and has generally been considered to be a minor contributor to overall particle deposition. However, a recent study employing hollow airway casts of the human tracheobronchial tree assessed deposition of ultrafine (0.02 μm) and fine (0.125 μm) particles; the deposition of singly charged particles was found to be 5-6 times that of particles having no charge, and 2-3 times that of particles at Boltzmann equilibrium (Cohen et al., 1998). This suggests that electrostatic precipitation may, in fact, be a significant deposition mechanism for ultrafine, and some fine, particles within the TB region.

7.2.3.2 Deposition Patterns in the Human Respiratory Tract

Knowledge of sites where particles of different sizes deposit in the respiratory tract and the amount of deposition is necessary for understanding and interpreting the health effects associated with exposure to particles. Particles deposited in the various regions are subjected to large differences in clearance mechanisms and pathways and, consequently, retention times. This section summarizes concepts of particle deposition in humans and laboratory animals as reported in U.S. Environmental Protection Agency (1996a), and provides additional information based upon studies published since the release of this document.

Total Respiratory Tract Deposition

Total human respiratory tract deposition, as a function of particle size, is depicted in Figure 7-1. These data were obtained by various investigators using different sizes of spherical test particles in healthy male adults under different ventilation conditions; the large standard deviations reflect interindividual viability of deposition efficiencies. Deposition with nose

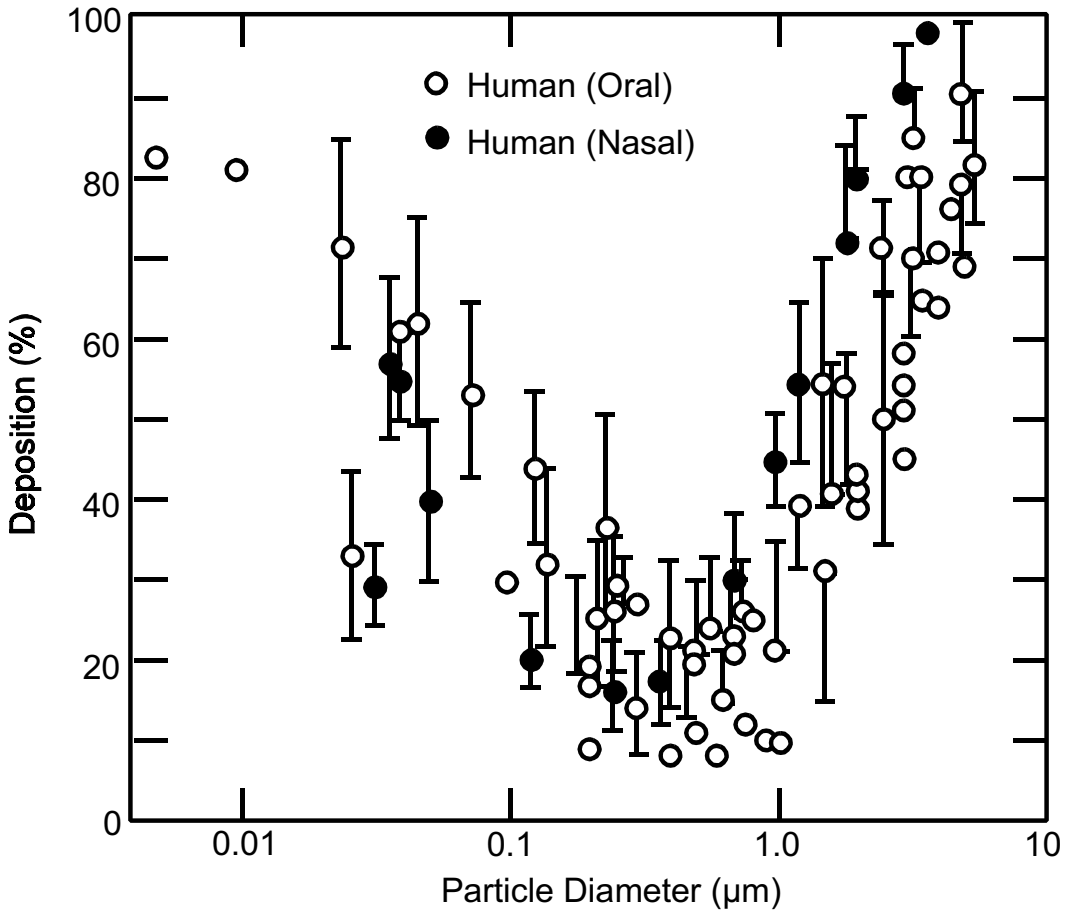

Figure 7-1. Total deposition data (percentage deposition of amount inhaled) in humans as a function of particle size. All values are means with standard deviations when available. Particle diameters are aerodynamic (MMAD) for those ≥ 0.5 μm.

Source: Schlesinger (1988).

breathing is generally higher than that with mouth breathing due to the superior filtration capabilities of the nasal passages. For particles with aerodynamic diameters greater than 1 μm, deposition is governed by impaction and sedimentation and it increases with increasing AED. When AED is >10 μm, almost all inhaled particles are deposited. As the particle size decreases from ~0.5 μm, diffusional deposition becomes dominant and total deposition depends more upon the actual physical diameter of the particle, with decreasing particle diameter leading to an increase in total deposition. Total deposition shows a minimum for particle diameters in the

range of 0.3 - 0.5 μm, where, as noted above, neither sedimentation, impaction or diffusion deposition are very effective.

A property of some ambient particulate species that affects deposition is hygroscopicity, the propensity of a material for taking up and retaining moisture under certain conditions of humidity and temperature. Such particles can increase in size in the humid air within the respiratory tract and when inhaled will deposit according to their hydrated size rather than their initial size. The implications of hygroscopic growth upon deposition has been extensively reviewed 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 upon the initial size. Thus, for particles with initial sizes larger than ~ 0.5 μm, the influence of hygroscopicity is to increase total deposition, whereas for smaller ones total deposition is decreased.

ET Region

The fraction of inhaled particles depositing in the ET region is quite variable, depending on particle size, flow rate, breathing frequency and whether breathing is through the nose or the mouth. Mouth breathing bypasses much of the filtration capabilities of the nasal airways, leading to increased deposition in the lungs (TB and A regions). The ET region is clearly the site of first contact with particles in the inhaled air, and acts as a "prefilter" for the lungs.

Since release of the previous Criteria Document, a number of studies have explored ET deposition with in vivo studies, as well as in both physical and mathematical model systems. In one new study, the relative distribution of particle deposition between the oral and nasal passages was assessed during inhalation by use of a physical model (silicone rubber) of the human upper respiratory system, extending from the nostrils and mouth through the main bronchi (Lennon et al., 1998). Monodisperse particles ranging in size from 0.3 - 2.5 μm were used at various flow rates ranging from 15 - 50 l/min. Total deposition was assessed, as was regional deposition in the oral passages, lower oropharynx-trachea, nasal passages, and nasopharynx-trachea. Deposition within the nasal passages was found to agree with available data obtained from a human inhalation study (Heyder and Rudolf, 1977), being proportional to particle size, density and inspiratory flow rate. It was also found that for oral inhalation, the relative distribution between the oral cavity and the oropharynx-trachea was similar, while for

nasal inhalation, the nasal passages contained most of the particles deposited in the model, with only about 10% depositing in the nasopharynx-trachea section. Furthermore, the deposition efficiency of the nasopharynx-trachea region was greater than that of the oropharynx-trachea region. For simulated oronasal breathing, deposition in the ET region depended primarily upon particle size rather than flowrate. For all flows and for all breathing modes, total deposition in the ET region increased as particle diameter increased. Such information on deposition patterns in the ET region is useful in refining empirical deposition models.

Deposition within the nasal passages was further evaluated by Kesavanathan and Swift (1998), who examined the deposition of 1-10 μm particles in the nasal passages of normal adults under an inhalation regime in which the particles were drawn through the nose and out through the mouth at flow rates ranging from 15 - 35 l/min. At any particle size, deposition increased with increasing flow rate, while at any flow rate, deposition increased with increasing particle size. In addition, as was shown experimentally by Lennon et al. (1998) under oronasal breathing conditions, deposition of 0.3 to 2.5 μm particles within the nasal passages was significantly greater than within the oral passages, and nasal inhalation resulted in greater total deposition in the model than did oral inhalation. These results are consistent with other studies discussed in the previous Criteria Document and with the dominance of impaction deposition within the ET region.

For ultrafine particles ($d < 0.1$ μm), deposition in the ET region is controlled by diffusion, which depends only on the particle's geometric diameter. Prior to 1996, ET deposition for this particle size range had not been studied extensively in humans, and this remains the case. In the earlier document, the only data available for ET deposition of ultrafine particles were from cast studies. More recently, deposition in the ET was examined using mathematical modeling. Three dimensional numerical simulations of flow and particle diffusion in the human upper respiratory tract, which included the nasal region, oral region, larynx and first two generations of bronchi, were performed by Yu et al. (1998). Deposition of particles ranging from 0.001 - 0.1 μm in these different regions was calculated under inspiratory and expiratory flow conditions. Deposition efficiencies in the total model were lower on expiration than inspiration, although the former were quite high. Nasal deposition of ultrafine particles can be quite high. For example, it accounted for up to 54% of total deposition in the model system for 0.001 μm particles (total deposition efficiency in the mathematical model was 75% [of amount entering] for this size

particle). With oral breathing, deposition efficiency was estimated at 48% (of amount entering) (Yu et al., 1998).

Swift and Strong (1996) examined the deposition of ultrafine particles, ranging in size from 0.053-0.062 μm, in the nasal passages of normal adults during constant inspiratory flows of 6 - 22 l/min. The results are consistent with results noted in studies above, namely that the nasal passages are highly efficient collectors for ultrafine particles. In this case, fractional deposition ranged from 94 - 99% (of amount inhaled). There was found to be only a weak dependence of deposition on flow rate, which contrasts with results noted above (Lennon et al., 1998) for particles >0.3 μm but is consistent with diffusion as the deposition mechanism for ultrafines.

Cheng et al. (1997) examined oral airway deposition in a replicate cast of the human nasal cavity, oral cavity and laryngeal-tracheal sections. Particle sizes ranged from 0.005 - 0.150 μm, and constant inspiratory and expiratory flow rates of 7.5 - 30 l/min were used. They noted that the deposition fractions within the oral cavity were essentially the same as that in the laryngeal-tracheal sections for all particle sizes and flowrates. They ascribed this to the balance between flow turbulence and residence time in these two regions. Svartengren et al. (1995) examined the effect of changes in external resistance on oropharyngeal particle deposition in asthmatics. Under control mouthpiece breathing conditions, the median deposition as a percentage of inhaled particles in the mouth and throat was 20% (mean = 33%; range 12-84%). Although the mean deposition fell to 22% with added resistance, the median value remained at 20% (range 13-47%). Fiberoptic examination of the larynx revealed that there was a trend for increased mouth and throat deposition associated with laryngeal narrowing. Katz et al. (1999) suggest, on the basis of mathematical model calculations, that turbulence may play a key role in enhancing particle deposition in the larynx and trachea.

The results of all of the above studies support the previously known ability of the ET region, and especially the nasal passages, to act as an efficient filter for inhaled particles. Ultrafine particles <0.01 μm also have significant deposition within the ET region and this region, therefore, serves as an important filter for these particles as well as for larger ones, potentially reducing the amount of particles within some size ranges which are available for deposition in the TB and A regions.

TB and A Regions

Particles which do not deposit in the ET region enter the lung, but their regional deposition in the lung cannot be precisely measured. Much of the available regional deposition data have been obtained from experiments with radioactive labeled poorly soluble particles. These have been described in U.S. Environmental Protection Agency (1996a) and there are no new regional data available since the publication of this document which would amend the descriptions of regional deposition patterns as presented in that document.

Local Distribution of Deposition

Airway structure and its associated air flow patterns are exceedingly complex and ventilation distribution of air in different parts of the lung is uneven. Thus, it is expected that particle deposition patterns within the ET, TB, and A regions would be highly nonuniform. This was discussed in detail. Basically, using deposition data from living subjects as well as from mathematical and physical models, enhanced deposition has been shown to occur in the nasal passages, trachea and at branching points in the TB and A regions. Recently, Churg and Vedal (1996) examined retention of particles on carinal ridges and tubular sections of airways from lungs obtained at necropsy. Results indicated significant enhancement of particle deposits on carinal ridges through the segmental bronchi; the ratios were similar in all airway generations examined.

Deposition "hot spots" at airway bifurcations have undergone additional analyses using mathematical modeling techniques. Using calculated deposition sites, a number of studies showed a strong correlation between secondary flow patterns and deposition sites and density for large (10 μm) particles, as well as for ultrafine particles (0.01 μm) (Heistracher and Hofmann, 1997; Hofmann et al., 1996). This supports experimental work, noted in U.S. Environmental Protection Agency (1996a) indicating that, like larger particles, ultrafine particles also show enhanced deposition at airway branch points, even in the upper tracheobronchial tree.

7.2.3.3 Biological Factors Modifying Deposition

Experimental deposition data in humans are commonly derived using healthy adult Caucasian males. Various factors can act to alter deposition patterns from those obtained in this group. Evaluation of these factors is important to help understand potentially susceptible

subpopulations, since differences in response may be due to dosimetry differences as well as to differences in sensitivity to a pollutant. The effects of different biological factors on deposition were discussed in U.S. Environmental Protection Agency (1996a) and are summarized below with additional information obtained from more recent studies.

Gender

Males and females differ in body size and ventilatory parameters, so it is expected that there would be gender differences in deposition. Using particles in the 2.5 to 7.5 μm size range Pritchard et al. (1986) indicated that, for comparable particle sizes and inspiratory flow rates, females had higher ET and TB deposition and smaller A deposition than did males. The ratio of A deposition to total thoracic deposition in females was also found to be smaller. These differences were attributed to gender differences in airway size.

In a recent study (Bennett et al., 1996), the total respiratory tract deposition of 2 μm particles was examined in adult males and females aged 18 - 80 years who breathed with a normal resting pattern. Deposition was assessed in terms of a deposition fraction, which was the difference between the amount of particles inhaled and exhaled during oral breathing. While there was a tendency for a greater deposition fraction in females compared to males, because males had greater minute ventilation, the deposition rate (i.e., deposition per unit time) was greater in males than in females.

Kim and Hu (1998) assessed regional deposition patterns in healthy adult males and females using sebacate aerosols with median aerodynamic sizes of 1, 3 and 5 μm and a bolus delivery technique, which involved controlled breathing. The total deposition in the lungs was similar for both genders with the smaller particle, but was greater in women for the 3 and 5 μm particles regardless of the inhalation flow rate used; this difference ranged from 9 - 31%, with higher values associated with higher flow rates. The pattern of deposition was similar for both genders, although females showed enhanced deposition peaks for all three particle sizes. The volumetric depth location of these peaks was similar in both genders, but was found to shift from peripheral (increased volumetric depth) to proximal (shallow volumetric depth) regions of the lung with increasing particle size. Thus, deposition appeared to be more localized in the lungs of females compared to those of males. Local deposition of 1 μm particles was somewhat flow

dependent, but for larger (5 μm) particles was largely independent of flow (flows did not include those that would be typical of exercise).

Age

Airway structure and respiratory conditions vary with age, and these variations may alter the deposition pattern of inhaled particles. The limited experimental studies reported in the earlier Criteria Document indicated results ranging from no clear dependence of total deposition on age to slightly higher deposition in children than adults. Potential deposition differences between children and adults were assessed to a greater extent using mathematical models. These indicated that if the entire respiratory tract and a complete breathing cycle at normal rate are considered, that ET deposition in children would generally be higher than that in adults, but that TB and A regional deposition in children may be either higher or lower than the adult, depending upon particle size (Xu and Yu, 1986). Enhanced deposition in the TB region would occur for particles <5 μm in children (Xu and Yu, 1986; Hofmann et al., 1989a).

Cheng et al. (1995) examined deposition of ultrafine particles in replica casts of the nasal airways of children aged 1.5 to 4 yrs. Particle sizes ranged from 0.0046 to 0.2 μm, and both inspiratory and expiratory flowrates were used (3-16 l/min). Deposition efficiency was found to decrease with increasing age for a given particle size and flowrate.

Oldham et al. (1997) examined the deposition of monodisperse particles having diameters of 1, 5, 10 and 15 μm in hollow airway models which were designed to represent the trachea and the first few bronchial airway generations of an adult, a 7 yr old child and a 4 yr old child. They noted that in most cases, the total deposition efficiency was greater in the child-size models than in the adult model.

Bennett et al. (1997a) analyzed the regional deposition of 4.5 μm, poorly soluble (Fe_2O_3) particles in children and in adults with mild cystic fibrosis (CF), but who likely had normal upper airway anatomy, such that intra- and extra- thoracic deposition would be similar to that in healthy adults. The mean age of the children was 13.8 yr and adults were 29.1 yr. ET deposition, as a percentage of total respiratory tract deposition, was higher by about 50% in children compared to CF and healthy adults (30.7% vs 20.1% vs 16.0% respectively). There was an age dependence of ET deposition in the children, in that the percentage ET deposition tended to be higher at a younger age; the younger group (<14 yr) had almost twice the percentage ET deposition of the

older group (>14 yr). Additional analyses showed an inverse correlation of extrathoracic deposition with body height (Bennett et al., 1997a). There was no significant difference in lung or total respiratory tract deposition between the children and adults. Since ET deposition was age-dependent and total deposition was not, this suggests that the ET region does a more effective job in children of filtering out the particles that would otherwise reach the TB region. However, since the lungs of children are smaller than those of adults, children may still have comparable deposition per unit surface area as would adults.

Bennett and Zeman (1998) measured the deposition of monodisperse 2 μm (MMAD) wax particles in children aged 7-14 yr and adolescents aged 14-18 yr for comparison to that in adults (19-35 yr). Each subject inhaled the particles by following their previously determined individual spontaneous resting breathing pattern. Deposition was assessed by measuring the amount of particles inhaled and exhaled. There was no age-related difference in deposition within the children group. There was also no significant difference in deposition between the children and adolescents, between the children and adults, or between the adolescents and adults. However, the investigators noted that since the children had smaller lungs and higher minute volumes relative to lung size, they would likely receive greater doses of particles per lung surface area compared to adults. Furthermore, deposition in children did vary with tidal volume, increasing with increasing volume to a greater extent than was seen in adults. These additional studies still do not provide unequivocal evidence for significant differences in deposition between adults and children, even when considering differences in lung surface area. However, it should be noted that differences in levels of activity between adults and children are likely to play a fairly large role in age-related differences in deposition patterns of ambient particles. Children generally have higher activity levels during the day, and higher associated minute ventilation per lung size. This will contribute to a greater inhaled dose of particles. Activity levels in relationship to exposure are discussed more fully in Chapter 5.

Another subpopulation of potential concern related to susceptibility to inhaled particles is the elderly. In the study of Bennett et al. (1996) described above, in which the total respiratory tract deposition of 2 μm particles was examined in people aged 18 to 80, the deposition fraction in the lungs in people with normal lung function was found to be independent of age, depending solely upon breathing pattern and airway resistance.

Respiratory Tract Disease

The presence of respiratory tract disease can affect airway structure and ventilatory parameters, thus altering deposition compared to that in healthy individuals. The effect of airway diseases on deposition has been studied extensively (U.S. Environmental Protection Agency, 1996a). Studies described therein had shown that people with chronic obstructive pulmonary disease (COPD) had deposition patterns that were very heterogeneous with differences in regional deposition compared to normals. People with asthma and obstructive pulmonary disease tended to have greater TB deposition than did healthy people. Furthermore, there tended to be an inverse relationship between bronchconstriction and the extent of deposition in the A region, while total respiratory tract deposition generally increased with increasing level of airway obstruction. The described studies were performed during controlled breathing, where all subjects breathed with the same tidal volume and respiratory rate. However, while resting tidal volume is similar or elevated in people with COPD compared to normals, the former tend to breathe at a faster rate, resulting in higher than normal tidal peak flow and resting minute ventilation. Thus, some of the reported differences in the deposition of particles could have been due to increased fractional deposition with each breath. While the extent to which lung deposition may change with respect to particle size, breathing pattern, and disease status in people with COPD is still unclear, some recent studies have attempted to provide additional insight into this issue.

Bennett et al. (1997b) measured the fractional deposition of insoluble 2 μm particles in people with severe to moderate COPD (mix of emphysema and chronic bronchitis, mean age 62 yr) and compared this to healthy older adults (mean age 67 yr) under conditions where the subjects breathed using their individual resting breathing pattern as well as a controlled breathing pattern. People with COPD tended to breathe with elevated tidal volume and at a faster rate than people with healthy lungs, resulting in about 50% higher resting minute ventilation. Total respiratory tract deposition was assessed in terms of deposition fraction, a measure of the amount deposited based upon measures of aerosol inhaled and amount exhaled, and deposition rate, the particles deposited per unit time. Under typical breathing conditions, people with COPD had about 50% greater deposition fraction than did age-matched healthy adults. Due to the elevation in minute ventilation, people with COPD had average deposition rates about 2.5 times that of healthy adults. Similar to previously reviewed studies (U.S. Environmental Protection Agency,

1996a), these investigators observed an increase in deposition with an increase in airway resistance, suggesting that, at rest, COPD resulted in increased deposition of fine particles in proportion to the severity of airway disease. The investigators also reported a decrease in deposition with increasing mean effective airspace diameter; this suggested that the enhanced deposition was associated more with the chronic bronchitic component of COPD than with the emphysematous component of the disease. Greater deposition was noted with the natural breathing compared to the fixed pattern.

Kim and Kang (1997) measured lung deposition of 1 μm particles inhaled via the mouth by healthy adults (mean age 27 yr) and by those with various degrees of airway obstruction, namely smokers (mean age 27 yr), smokers with small airway disease (SAD; mean age 37 yr), asthmatics (mean age 48 yr) and patients with COPD (mean age 61 yr) breathing under the same controlled pattern. Deposition fraction was obtained as in the study of Bennett et al. (1997b), described above. There was a marked increase in deposition in people with COPD. Deposition was 16%, 49%, 59% and 103% greater in smokers, smokers with SAD, asthmatics and people with COPD, respectively, than healthy adults. Deposition in COPD patients was significantly greater than that associated with either SAD or asthma; there was no significant difference in deposition between people with SAD and asthma. Deposition fraction was found to be correlated with percent predicted forced expiratory volume (FEV_1) and forced expiratory flow (FEF25-75%). Kohlhäufl et al. (1999) also showed increased deposition of fine particles (0.9 μm) in women with bronchial hyperresponsiveness.

Thus, the data base related to particle deposition and lung disease suggests that total lung deposition is generally increased with obstructed airways, regardless of deposition distribution between the TB and A regions. Airflow distribution is very uneven in COPD due to the irregular pattern of obstruction, and there can be closure of small airways. In this situation, a part of the lung is inaccessible and particles can penetrate deeper into other ventilated regions. Thus, deposition can be enhanced locally in regions of active ventilation, particularly in the A region.

Anatomical Variability

As indicated above, variations in anatomical parameters between genders and between healthy people and those with obstructive lung disease can affect deposition patterns. However, previous analyses have generally overlooked the effect upon deposition of normal interindividual

variability in airway structure in healthy individuals. This is an important consideration in dosimetry modeling, which is often based upon a single idealized structure. Studies available since 1996 have attempted to assess the influence of such variation in respiratory tract structure upon deposition patterns.

The ET region is the first to contact inhaled particles, and therefore deposition within this region would reduce the amount of particles available for deposition in the lungs. Variations in relative deposition within the ET region will, therefore, propagate through the rest of the respiratory tract, creating differences in calculated doses from individual to individual. A number of studies have examined the influence of variations in airway geometry upon deposition in the ET region.

Cheng et al. (1996) examined nasal airway deposition in healthy adults using particles ranging in size from 0.004-0.15 μm at two constant inspiratory flow rates, 167 and 33 ml/sec. Deposition was evaluated in relation to measures of nasal geometry as determined by magnetic resonance imaging and acoustic rhinometry. They noted that interindividual variability in deposition was correlated with the wide variation of nasal dimensions, in that greater surface area, smaller cross-sectional area and increasing complexity of airway shape were all associated with enhanced deposition.

Using a regression analysis of data on nasal airway deposition derived from Cheng et al. (1996), Guilmette et al. (1997) noted that the deposition efficiency within this region was highly correlated with both nasal airway surface area and volume; this indicated that airway size and shape factors were important in explaining the intraindividual variability noted in experimental studies of human nasal airway aerosol deposition. Thus, much of the variability in measured deposition among people was due to differences in the size and shape of airway regions.

Kesavanathan and Swift (1998) also evaluated the influence of geometry in affecting deposition in the nasal passages of normal adults from two ethnic groups. Mathematical modeling of the results indicated that the shape of the nostril affected particle deposition in the nasal passages, but that there still remained large intersubject variations in deposition when this was accounted for, and which was likely due to geometric variability in the mid and posterior regions of the nasal passages.

Bennett et al. (1998) studied the role of anatomic dead space (ADS) in particle deposition and retention in bronchial airways using an aerosol bolus technique. They found that the

fractional deposition was dependant on the subject's ADS and that a significant number of particles were retained beyond 24 h. This finding of prolonged retention of insoluble particles in the airways substantiates the findings of Scheuch et al. (1995) and Stahlhofen et al. (1986a). Bennett et al. (1999) also found a lung volume-dependant asymmetric distribution of particles between the left and right lung; the left:right ratio was increased at increased percent of total lung capacity (at 70% TLC, L:R was 1.60).

7.2.3.4 Interspecies Patterns of Deposition

The various species used in inhalation toxicology studies that serve as the basis for dose-response assessment may not receive identical doses in a comparable respiratory tract region (i.e., ET, TB, or A) when exposed to the same aerosol at the same inhaled concentration. Such interspecies differences are important because the adverse toxic effect is often related to the quantitative pattern of deposition within the respiratory tract as well as to the exposure concentration; this pattern determines not only the initial respiratory tract tissue dose but also the specific pathways by which deposited material is cleared and redistributed (Schlesinger, 1985). Differences in patterns of deposition between humans and animals have been summarized (U.S. Environmental Protection Agency, 1996a; Schlesinger et al., 1997). Such differences in initial deposition must be considered when relating biological responses obtained in laboratory animal studies to effects in humans.

Some recent studies have addressed various aspects of interspecies differences in deposition using mathematical modeling approaches. Hofmann et al. (1996) compared deposition between rat and human lungs using three-dimensional asymmetric bifurcation models and mathematical procedures for obtaining air flow and particle trajectories. Deposition in segmental bronchi and terminal bronchioles was evaluated under both inspiration and expiration, at particle sizes of 0.01, 1 and 10 μm (which covered the range of deposition mechanisms from diffusion to impaction). Total deposition efficiencies of all particles in the upper and lower airway bifurcations were comparable in magnitude for both rat and human. However, the investigators noted that penetration probabilities from preceding airways must be considered. When considering the higher penetration probability in the human lung, the resulting bronchial deposition fractions were generally higher in human than rat. For all particle sizes, deposition at

rat bronchial bifurcations was less enhanced on the carinas compared to that found in human airways.

Hofmann et al. (1996) attempted to account for interspecies differences in branching patterns in deposition analyses. Numerical simulations of three-dimensional particle deposition patterns within selected (species-specific) bronchial bifurcations indicated that morphologic asymmetry was a major determinant of the heterogeneity of local deposition patterns. They noted that many interspecies deposition calculations used morphometry which was described by deterministic lung models, i.e., the number of airways in each airway generation adopts a constant value and all airways in a given generation have identical lengths and diameters. Such models cannot account for variability and branching asymmetry of airways in the lungs. Thus, their study employed computations which used stochastic morphometric models of human and rat lungs (Koblinger and Hofmann, 1985, 1988; Hofmann et al., 1989b) and evaluated regional and local particle deposition. Stochastic models of lung structure describe, in mathematical terms, the inherent asymmetry and variability of the airway system, including diameter, length and angle. They are based upon statistical analyses of actual morphometric analyses of lungs. The model also incorporated breathing patterns for humans and rats. The dependence of deposition on particle size was found to be similar in both rats and humans, with a deposition minima in the size range of 0.1 to 1 μm for both total deposition and deposition within the TB region. This was not found to occur in the A region, where a deposition maximum occurred at about 0.02-0.03 μm in both species followed by a decline, and then another maximum between 3 and 5 μm. The deposition decrease in the A region at the smallest and largest sizes was due to the filtering efficiency of upstream airways. While deposition patterns were qualitatively similar in rat and human, total respiratory tract and TB deposition in the human lung appeared to be consistently higher than in the rat. Alveolar region deposition fraction in humans was lower than in the rat over the size range of 0.001 to 10 μm. Furthermore, both species showed a similar pattern of dependence of deposition on flow rate.

The above model also assessed local deposition. In both human and rat, deposition of 0.001 μm and 10 μm particles was highest in the upper bronchial airways, while 0.1 and 1 μm particles showed higher deposition in more peripheral airways, namely the bronchiolar airways in rat and the respiratory bronchioles in humans. Deposition was variable within any branching generation due to differences in airway dimensions, and regional and total deposition also

exhibited intrasubject variations. Airway geometric differences between rats and humans were reflected in deposition. Due to the greater branching asymmetry in rats, prior to about generation 12, each generation showed deposition maxima at two particle sizes, reflecting deposition in major and minor daughters. These geometric differences became reduced with depth into the lung; beyond generation 12, these two maxima were no longer seen.

The probability of any biological effect in humans or animals depends on deposition and retention of particles as well as the underlying dose-response relationship. Interspecies dosimetric extrapolation must consider differences in deposition, clearance and dose response. Thus, even similar deposition patterns may not result in similar effects in different species, since dose is also affected by clearance mechanisms and species sensitivity. In addition, the total number of particles deposited in the lung may not be the most relevant dose metric to compare species. For example, it may be the number of deposited particles per unit surface area that determines response. More specifically, even if deposition is similar in rat and human, there would be a higher deposition density in the rat due to the smaller surface area of rat lung. Thus, species specific differences in deposition density should be considered when health effects observed in laboratory animals are being evaluated in terms of the human situation.

7.2.4 Particle Clearance and Translocation

7.2.4.1 Mechanisms and Pathways of Clearance

Particles that deposit upon airway surfaces may be cleared from the respiratory tract completely, or may be translocated to other sites within this system, by various regionally distinct processes. These clearance mechanisms, which are outlined in Table 7-1, can be categorized as either absorptive (i.e., dissolution) or nonabsorptive (i.e., transport of intact particles) and may occur simultaneously or with temporal variations. It should be mentioned that particle solubility in terms of clearance refers to solubility within the respiratory tract fluids and cells. Thus, an "insoluble" particle is considered to be one whose rate of clearance by dissolution is insignificant compared to its rate of clearance as an intact particle. For the most part, all deposited particles are subject to clearance by the same mechanisms, with their ultimate fate a function of deposition site, physicochemical properties (including any toxicity), and sometimes deposited mass or number concentration. Clearance routes from the various regions of the respiratory tract have

TABLE 7-1. OVERVIEW OF RESPIRATORY TRACT PARTICLE CLEARANCE AND TRANSLOCATION MECHANISMS

Extrathoracic region (ET)
Mucociliary transport
Sneezing
Nose wiping and blowing
Dissolution (for "soluble" particles) and absorption into blood
Tracheobronchial region (TB)
Mucociliary transport
Endocytosis by macrophages/epithelial cells
Coughing
Dissolution (for "soluble" particles) and absorption into blood
Alveolar region (A)
Macrophages, epithelial cells
Interstitial
Dissolution for "soluble" and "insoluble" particles (intra-and extracellular) and absorption into blood/lymph

Source: Schlesinger (1995).

been discussed in detail (U.S. Environmental Protection Agency, 1996a; Schlesinger et al., 1997). They are schematically shown in Figure 7-2, and will be reviewed only briefly.

ET Region

The clearance of insoluble particles deposited in the posterior portions of the nasal passages occurs via mucociliary transport, with the general flow of mucus towards the nasopharynx. Mucus flow in the most anterior portion of the nasal passages is forward, clearing deposited particles to the vestibular region where removal is by sneezing, wiping, or blowing.

Soluble material deposited on the nasal epithelium is accessible to underlying cells via diffusion through the mucus. Dissolved substances may be subsequently translocated into the bloodstream. The nasal passages have a rich vasculature, and uptake into the blood from this region may occur rapidly.

Clearance of poorly soluble particles deposited in the oral passages is by coughing and expectoration or by swallowing into the gastrointestinal tract. Soluble particles are likely to be rapidly absorbed after deposition.

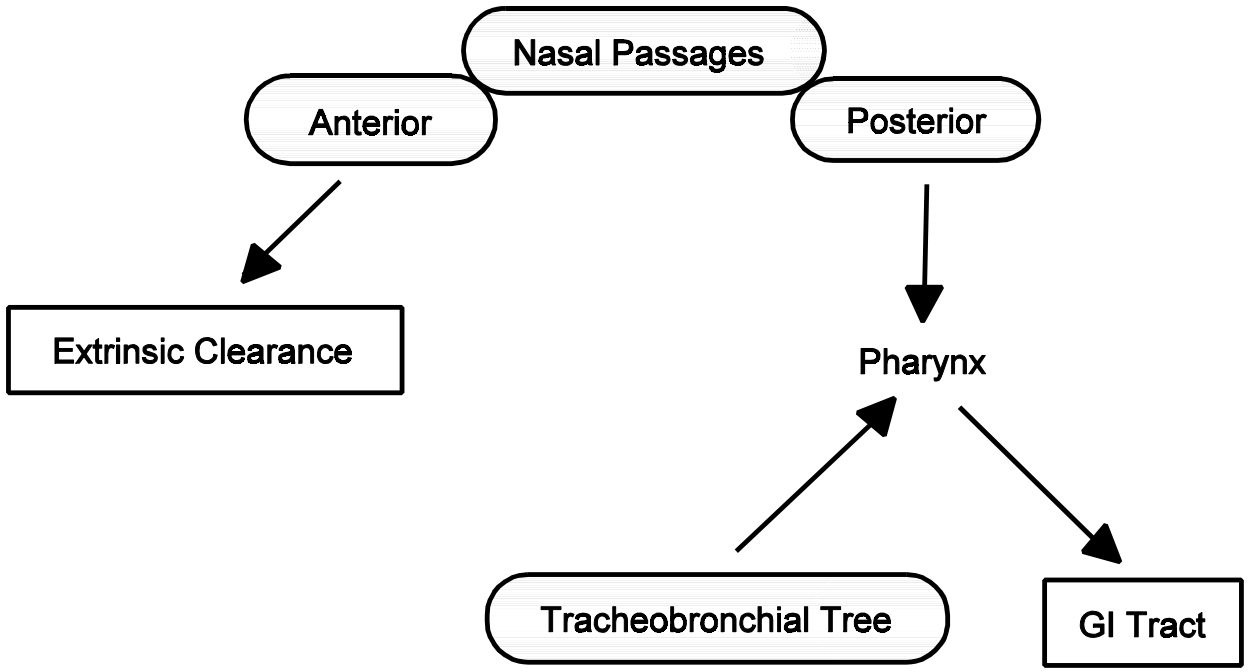

Figure 7-2. Major physical clearance pathways for particles deposited in the extrathoracic region and tracheobronchial tree.

Source: U.S. Environmental Protection Agency (1996a)

TB Region

Poorly soluble particles deposited within the TB region are cleared by mucociliary transport towards the oropharynx, followed by swallowing. Poorly soluble particles may also traverse the epithelium by endocytotic processes, entering the peribronchial region, be engulfed via phagocytosis by airway macrophages, which can then move cephalad on the mucociliary blanket, or enter the airway lumen from the bronchial or bronchiolar mucosa. Soluble particles may be absorbed through the epithelium into the blood. There is, however, evidence that even some soluble particles may be cleared by mucociliary transport (Bennett and Ilowite, 1989; Matsui et al., 1998).

A Region

Clearance from the A region occurs via a number of mechanisms and pathways. Particle removal by macrophages comprises the main nonabsorptive clearance process in this region. These cells, which reside on the epithelium, phagocytize and transport deposited material which they contact by random motion or via directed migration under the influence of chemotactic factors.

While alveolar macrophages normally comprise up to about 5% of the total alveolar cells in healthy, non-smoking humans and other mammals, the actual cell count may be altered by particle loading. The magnitude of any increase in cell number is related to the number of deposited particles rather than to total deposition by weight. Thus, equivalent masses of an identically deposited substance would not produce the same response if particle sizes differed, and the deposition of smaller particles would tend to result in a greater elevation in macrophage number than would deposition of larger particles.

Particle-laden macrophages may be cleared from the A region along a number of pathways. As noted in Figure 7-3, this includes: cephalad transport via the mucociliary system after the cells reach the distal terminus of the mucus blanket; movement within the interstitium to a lymphatic channel; or perhaps traversing of the alveolar-capillary endothelium, directly entering the bloodstream. Particles within the lymphatic system may be translocated to tracheobronchial lymph nodes, which can become reservoirs of retained material. Particles subsequently reaching the post-nodal lymphatic circulation will enter the blood. Once in the systemic circulation, these particles, or transmigrated macrophages, can travel to extrapulmonary organs. Deposited particles which are not ingested by alveolar macrophages may enter the interstitium, where they are subject to phagocytosis by resident interstitial macrophages, and may travel to perivenous, peribronchiolar or subpleural sites, where they become trapped, increasing particle burden. The migration and grouping of particles and macrophages within the lungs can lead to the redistribution of initially diffuse deposits into focal aggregates. Some particles or components can bind to epithelial cell membranes or macromolecules, or other cell components, delaying clearance from the lungs.

Churg and Brauer (1997), examined lung autopsy tissue from 10 never smokers from Vancouver, Canada. They noted that the geometric mean particle diameter (GMPD) in lung parenchymal tissue was 0.38 μm ($\sigma g = 2.4$). Ultrafines were less than 5% of the total retained

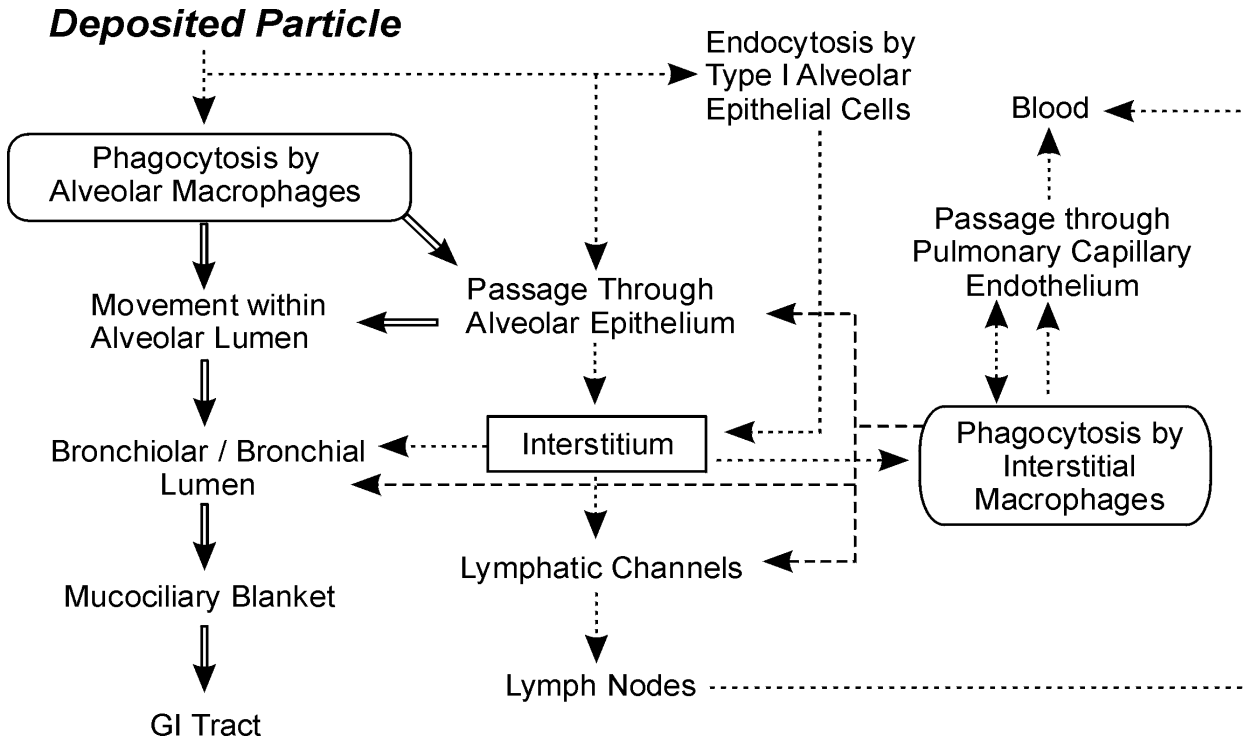

Figure 7-3. Diagram of known and suspected clearance pathways for poorly soluble particles depositing in the alveolar region.

Source: Modified from Schlesinger et al. (1997).

PM. Metal particles had a GMPD of 0.17 μm and silicates 0.49 μm. Ninety-six percent of retained PM was less than 2.5 μm. This observation suggests that PM <2.5 μm may be of appropriate concern for chronic PM effects.

Clearance by the absorptive mechanism involves dissolution in the alveolar surface fluid, followed by transport through the epithelium and into the interstitium, and diffusion into the lymph or blood. Although factors affecting the dissolution of deposited particles are poorly understood, solubility is influenced by the particle's surface to volume ratio and other properties, such as hydrophilicity and lipophilicity (Mercer, 1967; Morrow, 1973; Patten, 1996). Thus, as noted, materials generally considered to be relatively insoluble may still have high dissolution rates and short dissolution half-times if the particle size is small.

Some deposited particles may undergo dissolution in the acidic milieu of the phagolysosomes after ingestion by macrophages, and such intracellular dissolution may be the initial step in translocation from the lungs for these particles and for material associated with these particles (Kreyling, 1992; Lundborg et al., 1985). Following dissolution, the material can be absorbed into the blood. Dissolved materials may then leave the lungs at rates which are more rapid than would be expected based upon an "expected" normal dissolution rate in lung fluid.

7.2.4.2 Clearance Kinetics

The kinetics of clearance has been reviewed in U. S. Environmental Protection Agency (1996a) and in a number of monographs (e.g., Schlesinger et al., 1997). It will be discussed briefly. The actual time frame over which clearance occurs affects the cumulative dose delivered to the respiratory tract, as well as delivered to extrapulmonary organs.

ET Region

Mucus flow rates in the posterior nasal passages are highly nonuniform, but the median rate in a healthy adult human is about 5 mm/min, resulting in a mean anterior to posterior transport time of about 10-20 min for poorly soluble particles (Rutland and Cole, 1981; Stanley et al., 1985). Particles deposited in the anterior portion of the nasal passages are cleared more slowly by mucus transport, and are usually more effectively removed by sneezing, wiping, or nose blowing (Fry and Black, 1973; Morrow, 1977).

TB Region

Mucus transport in the tracheobronchial tree occurs at different rates in different local regions; the velocity of movement is fastest in the trachea, and it becomes progressively slower in more distal airways. In healthy non-smoking humans, using non-invasive procedures and no anesthesia, average tracheal mucus transport rates have been measured at 4.3 to 5.7 mm/min (Yeates et al., 1975, 1981; Foster et al., 1980; Leikauf et al., 1981, 1984), while that in the main bronchi has been measured at ≈2.4 mm/min (Foster et al., 1980). Estimates for human medium bronchi range between 0.2-1.3 mm/min, while those in the most distal ciliated airways range down to 0.001 mm/min (Morrow et al., 1967; Cuddihy and Yeh, 1988; Yeates and Aspin, 1978).

The total duration of bronchial clearance, or some other time parameter, is often used as an index of mucociliary kinetics. While clearance from the TB region is generally rapid, there is experimental evidence, discussed in U.S. Environmental Protection Agency (1996a) that a fraction of material deposited in the TB region is retained much longer than the 24 h commonly used as the outer range of clearance time for particles within this region (Stahlhofen et al., 1986a,b; Scheuch and Stahlhofen, 1988; Smaldone et al., 1988). Some recent studies (Bennett et al., 1998) described below continue to support the concept that TB regional clearance consists of both a fast and a slow component.

Falk et al. (1997) studied clearance in healthy adults using monodisperse Teflon particles (6.2 μm) inhaled at two flow rates. A considerable fraction (about 50%) of particles deposited in small airways had not cleared within 24 h following exposure. These particles cleared with a half time of 50 days. While the deposition sites of the particles were not confirmed experimentally, calculations suggested these to be in the smaller ciliated airways. Camner et al. (1997) also noted that clearance from the TB region was incomplete by 24 h post exposure, and suggested that this may be due to incomplete clearance from bronchioles. Healthy adults inhaled teflon particles (6, 8 and 10 μm) under low flow rates to maximize deposition in the small ciliated airways. The investigators noted a decrease in 24 h retention with increasing particle size, indicating a shift with increasing size toward either a smaller retained fraction, deposition more proximally in the respiratory tract, or both. They calculated that a large fraction, perhaps as high as 75%, of particles depositing in generations 12-16 was still retained at 24 h post-exposure.

The underlying sites and mechanisms of long-term TB retention in the smaller airways are not known. Some proposals were presented in U.S. Environmental Protection Agency (1996a). This slow clearing tracheobronchial compartment may be associated with those bronchioles <1 mm in diameter (Lay et al., 1995). Based upon a study in which an adrenergic agonist was used to stimulate mucus transport, so as to examine the role of mucociliary transport in the bronchioles, it was found that clearance from the smaller airways was not influenced by the drug, suggesting to the investigators that mechanisms other than mucociliary transport contributed to clearance from this region (Svartengren et al., 1998). However, the issue of retention of large fractions of tracheobronchial deposit is not resolved.

Long-term TB retention patterns are not uniform. There is an enhancement at bifurcation regions (Radford and Martell, 1977; Henshaw and Fews, 1984; Cohen et al., 1988), the likely

result of both greater deposition and less effective mucus clearance within these areas. Thus, doses calculated based upon uniform surface retention density may be misleading, especially if the material is, toxicologically, slow acting.

A Region

Particles deposited in the A region generally are retained longer than those deposited in airways cleared by mucociliary transport. There are limited data on alveolar clearance rates in humans. Within any species, reported clearance rates vary widely due, in part, to different properties of the particles used in the various studies. Furthermore, some chronic experimental studies have employed high concentrations of poorly soluble particles, which may have interfered with normal clearance mechanisms, resulting in clearance rates different from those that would typically occur at lower exposure levels. Prolonged exposure to high particle concentrations is associated with what is termed particle "overload". This is discussed in greater detail in Section 7.2.5.

There are numerous pathways of A region clearance, and the utilization of these may depend upon the nature of the particles being cleared. Little is known concerning relative rates along specific pathways. Thus, generalizations about clearance kinetics are difficult to make. Nevertheless, A region clearance is usually described as a multiphasic process, each phase considered to represent removal by a different mechanism or pathway, and often characterized by increased retention half-times following exposure.

The initial uptake of deposited particles by alveolar macrophages is very rapid, and generally occurs within 24 h of deposition (Lehnert and Morrow, 1985; Naumann and Schlesinger, 1986; Lay et al., 1998). The time for clearance of particle-laden alveolar macrophages via the mucociliary system depends upon the site of uptake relative to the distal terminus of the mucus blanket at the bronchiolar level. Furthermore, clearance pathways, and subsequent kinetics, may depend to some extent upon particle size. For example, some smaller ultrafine particles (perhaps $< 0.02\ \mu$m) may be less effectively phagocytosed than are larger ones (Oberdörster, 1993).

Uningested particles may penetrate into the interstitium within a few hours following deposition. This transepithelial passage seems to increase as particle loading increases, especially to a level above the "overload" point for increasing macrophage number (Ferin, 1977;

Adamson and Bowden, 1981). It may also be particle size dependent, since insoluble ultrafine particles (<0.1 μm diameter) of low intrinsic toxicity show increased access to and greater lymphatic uptake than do larger ones of the same material (Oberdörster et al., 1992). However, ultrafine particles of different materials may not enter the interstitium to the same extent. Similarly, a depression of phagocytic activity, a reduction in macrophage ability to migrate to sites of deposition (Madl et al., 1998), or the deposition of large numbers of ultrafine particles may increase the number of free particles in the alveoli, perhaps enhancing removal by other routes. In any case, free particles may reach the lymph nodes, perhaps within a few days after deposition (Lehnert et al., 1988; Harmsen et al., 1985), although this route is not certain and may be species dependent. Furthermore, the extent of lymphatic uptake of particles may depend upon the effectiveness of other clearance pathways, in that lymphatic translocation probably increases when phagocytic activity of alveolar macrophages is decreased. This may be a factor in lung overload. However, it seems that the deposited mass or number of particles must exceed some threshold below which increases in loading do not affect translocation rate to the lymph nodes (Ferin and Feldstein, 1978; LaBelle and Brieger, 1961). In addition, the rate of translocation to the lymphatic system may be somewhat particle size dependent. Although no human data are available, translocation of latex particles to the lymph nodes of rats was greater for 0.5 to 2 μm particles than for 5 and 9 μm particles (Takahashi et al., 1992), and smaller particles within the 3 to 15 μm size range were found to be translocated at faster rates than were larger sizes (Snipes and Clem, 1981). On the other hand, translocation to the lymph nodes was similar for both 0.4 μm barium sulfate or 0.02 μm gold colloid particles (Takahashi et al., 1987). It seems that particles $\leq$ 2 μm clear to the lymphatic system at a rate independent of size, and it is particles of this size, rather than those $\geq$ 5 μm, that would have significant deposition within the A region following inhalation. In any case, the normal rate of translocation to the lymphatic system is quite slow and elimination from the lymph nodes is even slower, with half-times estimated in tens of years (Roy, 1989).

Soluble particles depositing in the A region may be rapidly cleared via absorption through the epithelial surface into the blood. Actual rates depend upon the size of the particle (i.e., solute size), with smaller molecular weight solutes clearing faster than larger ones. Absorption may be considered as a two stage process, with the first stage dissociation of the deposited particles into material that can be absorbed into the circulation (dissolution) and the second stage the uptake of

this material. Each of these stages may be time-dependent. The rate of dissolution depends upon a number of factors, including particle surface area and chemical structure. A portion of the dissolved material may be absorbed more slowly due to binding to respiratory tract components. Accordingly, there is a very wide range for absorption rates depending upon the physicochemical properties of the material deposited.

7.2.4.3 Interspecies Patterns of Clearance

The inability to study the retention of certain materials in humans for direct risk assessment requires use of laboratory animals. Since dosimetry depends upon clearance rates and routes, adequate toxicologic assessment necessitates that clearance kinetics in these animals be related to those in humans. The basic mechanisms and overall patterns of clearance from the respiratory tract are similar in humans and most other mammals. However, regional clearance rates can show substantial variation between species, even for similar particles deposited under comparable exposure conditions. This has been extensively reviewed (U.S. Environmental Protection Agency, 1996a; Schlesinger et al., 1997; Snipes et al., 1989).

In general, there are species-dependent rate constants for various clearance pathways. Differences in regional and total clearance rates between some species are a reflection of differences in mechanical clearance processes. For example, the relative proportion of particles cleared from the A region in the short and longer term phases differs between laboratory rodents and larger mammals, with a greater percentage cleared in the faster phase in rodents. A recent study (Oberdörster et al., 1997) showed interstrain differences in mice and rats in the handling of particles by alveolar macrophages. Macrophages of B6C3F1 mice could not phagocytize 10 μm particles, but those of C57 black/6Jmice did. In addition, the nonphagocytized 10 μm particles were efficiently eliminated from the alveolar region, while previous work in rats found that these large particles, after uptake by macrophages, were persistently retained (Snipes and Clem, 1981; Oberdörster et al., 1992). The end result of interspecies differences in clearance for consideration in assessing particle dosimetry is that the retention of deposited particles can differ between species, and this may result in differences in response to similar particulate exposure atmospheres.

Hsieh and Yu (1998) summarized the existing data on pulmonary clearance of inhaled, poorly soluble particles in the rat, mouse, guinea pig, dog, monkey and human. Clearance at

different initial lung burdens, ranging from 0.001 - 10 mg particles/g lung, was analyzed using a two phase exponential decay function. Two clearance phases in the alveolar region, namely fast and slow, were associated with mechanical clearance along two pathways, the former with the mucociliary system and the latter with the lymph nodes. Rats and mice were noted to be fast clearers compared to the other species. Increasing the initial lung burden resulted in an increasing mass fraction of particles cleared by the slower phase. As lung burden increased beyond 1 mg particles/g lung, the fraction cleared by the slow phase increased to almost 100% for all species. However, the rate for the fast phase was similar in all species and did not change with increasing lung burden of particles, while the rate for the slow phase decreased with increasing lung burden. At elevated burdens, the "overload" effect on clearance rate was greater in rats than in humans, an observation consistent with previous findings (Snipes, 1989).

7.2.4.4 Biological Factors Modifying Clearance

A number of factors have been assessed in terms of modulation of normal clearance patterns. These include aging, gender, workload, disease and irritant inhalation, and have been discussed in detail previously (U.S. Environmental Protection Agency, 1996a).

Age

Studies previously described (U.S. Environmental Protection Agency, 1996a) indicated there appeared to be no clear evidence for any age-related differences in clearance from the respiratory tract, either from child to adult or adult to elderly. Studies of mucociliary function have shown either no changes or some slowing in mucous clearance function with age after maturity, but at a rate which would be unlikely to significantly affect overall clearance kinetics.

Gender

Previous studies (U.S. Environmental Protection Agency, 1996a) indicated no gender related differences in nasal mucociliary clearance rates in children (Passali and Bianchini Ciampoli, 1985) nor in tracheal transport rates in adults (Yeates et al., 1975).

Physical Activity

The effect of increased physical activity upon mucociliary clearance is unresolved, with previously discussed studies (U.S. Environmental Protection Agency, 1996a) indicating either no effect or an increased clearance rate with exercise. There are no data concerning changes in A region clearance with increased activity levels. Breathing with an increased tidal volume was noted to increase the rate of particle clearance from the A region, and this was suggested to be due to distension related evacuation of surfactant into proximal airways, resulting in a facilitated movement of particle-laden macrophages or uningested particles due to the accelerated motion of the alveolar fluid film (John et al., 1994).

Respiratory Tract Disease

Various respiratory tract diseases are associated with clearance alterations. The examination of clearance in individuals with lung disease requires careful interpretation of results, since differences in deposition of particles used to assess clearance function may occur between normal individuals and those with respiratory disease; this would directly impact upon the measured clearance rates, especially in the tracheobronchial tree. Earlier studies reported in U.S. Environmental Protection Agency (1996a) noted findings of slower nasal mucociliary clearance in humans with chronic sinusitis, bronchiectasis, rhinitis, or cystic fibrosis, and slowed bronchial mucus transport associated with bronchial carcinoma, chronic bronchitis, asthma and various acute respiratory infections. However, a recent study by Svartengren et al. (1996a) concluded, based upon deposition and clearance patterns, that particles cleared equally effectively from the small ciliated airways of healthy humans and those with mild to moderate asthma. However, this similarity was ascribed to effective therapy for the asthmatics.

In another study, Svartengren et al. (1996b) examined clearance from the TB region in adults with chronic bronchitis who inhaled 6 μm Teflon particles. Based upon calculations, particle deposition was assumed to be in small ciliated airways at low flow and in larger airways at higher flow. The results were compared to that obtained in healthy subjects from other studies. At low flow (resulting in small airway deposition), a larger fraction of particles was retained over 72 h in people with chronic bronchitis compared to healthy subjects, indicating that clearance due to spontaneous cough could not fully compensate for impaired mucociliary transport in small airways. For larger airways, patients with chronic bronchitis cleared a larger

fraction of the deposited particles over 72 h than did healthy subjects, but this was reportedly due to differences in deposition resulting from airway obstruction.

An important method of clearance from the tracheobronchial region, under some circumstances, is cough. While cough is generally a reaction to an inhaled stimulus, in some individuals with respiratory disease, spontaneous coughing also serves to clear the upper bronchial airways of deposited substances by dislodging mucus from the airway surface. Recent studies confirm that this mechanism likely plays a significant role in clearance for people with mucus hypersecretion, at least for the region of the upper bronchial tree affected by cough, and for a wide range of deposited particle sizes (0.5 - 5 μm) (Toms et al., 1997; Groth et al., 1997). There appears to be a general trend towards an association between the extent, i.e., number, of spontaneous coughs and the rate of particle clearance, with faster clearance associated with a greater number of coughs (Groth et al., 1997). Thus, recent evidence continues to support cough as an adjunct to mucociliary movement in the removal of particles from the lungs of individuals with COPD. However, some recent evidence suggests that, like mucociliary function, cough clearance may become depressed with worsening airway disease. Noone et al. (1999) found that the efficacy of clearance via cough in patients with primary ciliary dyskinesia, who rely on coughing for clearance due to immotile cilia, correlated with lung function (FEV1), in that decreased cough clearance was associated with decreased percentage of predicted FEV1.

Earlier reported studies (U.S. Environmental Protection Agency, 1996a) indicated that rates of A region particle clearance were reduced in humans with chronic obstructive lung disease and in laboratory animals with viral infections, while the viability and functional activity of macrophages was impaired in human asthmatics and in animals with viral induced lung infections. However, any modification of functional properties of macrophages appears to be injury specific, in that they reflect the nature and anatomic pattern of disease.

A factor which may affect clearance of particles is the integrity of the epithelial surface lining of the lungs. Damage or injury to the epithelium may result from disease or from the inhalation of chemical irritants. Earlier studies performed with particle instillation had shown that alveolar epithelial damage at the time of deposition in mice resulted in increased translocation of inert carbon to pulmonary interstitial macrophages (Adamson and Hedgecock, 1995). A similar response was observed in a recent assessment (Adamson and Prieditis, 1998), whereby silica (<0.3 μm) was instilled into a lung having alveolar epithelial damage, as

evidenced by increased permeability; retained particles were noted to reach the interstitium and lymph nodes, thus increasing the translocation to the interstitium and increasing the extent of activation of interstitial macrophages.

7.2.5 Particle Overload

Experimental studies using some laboratory rodents have employed high exposure concentrations of relatively nontoxic, poorly soluble particles. These particle loads interfered with normal clearance mechanisms, producing clearance rates different from those that would occur at lower exposure levels. Prolonged exposure to high particle concentrations is associated with a phenomenon that has been termed particle "overload", defined as the overwhelming of macrophage-mediated clearance by the deposition of particles at a rate that exceeds the capacity of that clearance pathway. It has been hypothesized that in the rat, overload will begin when deposition approaches 1 mg particles/g lung tissue (Morrow, 1988). Overload is a nonspecific effect noted in experimental studies using many different kinds of poorly soluble particles and results in A region clearance slowing or stasis, with an associated chronic inflammation and aggregation of macrophages in the lungs and increased translocation of particles into the interstitium.

The relevance of lung overload to humans, and even to species other than laboratory rats, remains unclear. While it is likely to be of little relevance for most "real world" ambient exposures of humans, it may be of concern in interpreting some long-term experimental exposure data and, perhaps, also for human occupational exposures. In addition, the relevance to humans is clouded by the suggestion that macrophage-mediated clearance is normally slower and perhaps of less relative importance in overall clearance in humans than in rats (Morrow, 1994), and that there can be significant differences in macrophage loading between species.

7.2.6 Comparison of Deposition and Clearance Patterns of Particles Administered by Inhalation and Intratracheal Instillation

The most relevant exposure route to evaluate the toxicity of particulate matter is inhalation. However, many studies delivered particles by intratracheal instillation. This latter technique has been used since it is easy to perform, and requires significantly less effort, cost and amount of test material than does inhalation and can deliver a known, exact dose of a toxicant to the lungs.

Since particle disposition is a determinant of dose, it is important to compare deposition and clearance of particles delivered by these two routes. However, in most instillation studies, the effect of this route of administration upon particle deposition and clearance *per se* was not examined. While these parameters were evaluated in some studies, it is very difficult to compare particle deposition/clearance between different inhalation and instillation studies due to differences in experimental procedures and in the manner by which particle deposition/clearance was quantitated. Nevertheless, a few studies directly compared the two exposure techniques upon deposition/clearance, and the results are summarized in this section.

The pattern of initial regional deposition is strongly influenced by the exposure technique used. Furthermore, the patterns within specific respiratory tract regions are also influenced in this regard. Depending upon particle size, inhalation results in varying degrees of deposition within the upper respiratory tract, a region which is completely bypassed by instillation. Thus, differences in amount of particles deposited in the lower airways will occur between the two procedures (Leong et al., 1986; Oberdörster et al., 1980). Furthermore, inhalation tends to result in greater variability in particle burden among animals than does instillation (Dorries and Valberg, 1992).

The specific exposure procedure also influences the intrapulmonary distribution of particles. This would potentially affect routes and rates of ultimate clearance from the lungs and dose delivered to specific sites within the respiratory tract or to extrapulmonary organs. Intratracheal instillation tends to disperse particles fairly evenly within the tracheobronchial tree, but can result in inhomogeneous distribution in the alveolar region, while inhalation tends to produce a more homogeneous distribution throughout the major conducting airways as well as the alveolar region (Leong et al., 1986, 1998). In addition, inhalation produced more uniform distribution of particles within a specific lobe than did instillation which produced focally increased particle burdens compared to inhalation (Pritchard et al., 1985; Driscoll et al., 1990, 1991). In one study, the intralobular distribution (i.e., homogeneity of distribution) with instillation was about four fold less homogeneous than with inhalation (Pritchard et al., 1985). Thus, inhalation results in a randomized distribution of particles within the lungs, while intratracheal instillation produces an inhomogeneous distribution within the lungs. The periphery of the lung receives little particle load and most of the particles are found in regions that have a short path length from the major airways. Furthermore, inhalation results in greater

deposition in apical areas of the lungs and less in basal areas, while intratracheal instillation results in less apical than basal deposition (Brain et al., 1976). Some of the differences between these two exposure techniques may be due to the positioning of the animal during the instillation process, which was not the same as that during inhalation exposure. But, in general, instillation produces less uniform deposition than inhalation, although the inhomogeneity of distribution of a single instillation exposure could be reduced by multiple instillation exposures. Instillation results in heavier and more centralized particle deposition, while particles delivered by inhalation are more evenly and more widely distributed throughout the lungs.

Comparison of the kinetics of clearance of particles administered by instillation or inhalation have shown similarities (Oberdörster et al., 1980, 1997; Dahl et al., 1983; Drew et al., 1987), as well as differences (Pritchard et al., 1985; Müller et al., 1989), in rates for different clearance phases, dependent upon the exposure technique used. However, some of the differences in kinetics may be explained by differences in the initial sites of deposition (Driscoll et al., 1990, 1991).

There are some data to allow assessment of differences in the pathways by which particles delivered by different techniques may be cleared. For example, while particles delivered via either intratracheal instillation or inhalation were transported via peribronchial lymphatics to bronchus-associated lymphoid tissue (BALT), only those delivered by inhalation reached the pleura (likely via pleural lymphatics) in sufficient amounts to produce a biological response (granuloma) (Henderson et al., 1995). Furthermore, particles depositing within the lungs may be subject to systemic absorption, the extent of which may depend upon the clearance rates and routes. Thus, Chui et al. (1988) noted that the systemic absorption of particles delivered via inhalation was somewhat greater than that for particles delivered by intratracheal instillation; the half-time for elimination from blood was over twice as long for instillation as for inhalation, suggesting that the route of administration can affect the rate and extent of systemic bioavailability of inhaled particles.

One of the major pathways of clearance involves particle uptake and removal via pulmonary macrophages. Dorries and Valberg (1992) noted that inhalation resulted in a lower percentage of particles recovered in lavaged cells and a more even distribution of particles among macrophages. More individual cells received measurable amounts of particles via inhalation than via intratracheal instillation, whereas with the latter, many cells received little or no particles

while others received very high burdens. The distribution among macrophages was more homogeneous with inhalation than with instillation. Furthermore, with intratracheal instillation, macrophages at the lung periphery contained few if any particles, while cells in the regions of highest deposition were overloaded, reflecting the inhomogeneity of particle distribution when particles are administered via instillation (Pritchard et al., 1985). Thus, the route of exposure influenced the particle distribution in the macrophage population and could, by assumption, influence clearance pathways and clearance kinetics.

In conclusion, inhalation may result in deposition within the upper respiratory tract, the extent of which depends upon the size of the particles used. Of course, intratracheal instillation bypasses this portion of the respiratory tract and delivers particles directly to the tracheobronchial tree. While some studies indicate that short (0-2d) and long (100 - 300 d post exposure) phases of clearance of insoluble particles delivered either by inhalation or intratracheal instillation are similar, other studies indicate that the percentage retention of particles delivered by instillation is greater than that for inhalation, at least up to 30d post exposure. Thus, there is some inconsistency in this regard. Perhaps the most consistent conclusion regarding differences between inhalation and intratracheal instillation is related to the intrapulmonary distribution of particles. Inhalation generally results in a fairly homogeneous distribution of particles throughout the lungs. On the other hand, instillation results in an inhomogeneous distribution, especially within the alveolar region, and focally high concentrations of particles. The bulk of instilled material penetrates beyond the major tracheobronchial airways, but the lung periphery is often virtually devoid of particles. This difference is reflected in particle burdens within macrophages, with those from animals inhaling particles being burdened more homogeneously and those from animals with instilled particles showing some populations of cells with no particles and others with heavy burdens. This difference reflects upon clearance pathways, dose to cells and tissues and systemic absorption. Exposure method, thus, clearly influences dose distribution.

7.2.7 Modeling the Disposition of Particles in the Respiratory Tract

7.2.7.1 Modeling Deposition and Clearance

The biologic effects of inhaled particles are a function of their disposition. This, in turn, depends on their patterns of both deposition and clearance. Removal of deposited materials

involves the competing processes of macrophage - mediated clearance and dissolution-absorption. Over the years, mathematical models for predicting deposition, clearance and, ultimately, retention of particles in the respiratory tract have been developed. Such models help interpret experimental data and can be used to make predictions of deposition for cases where data are not available.

A review of various mathematical deposition models was given by Morrow and Yu (1993) and in U.S. Environmental Protection Agency (1996a). There are three major elements involved in mathematical modeling. First, a structural model of the airways must be specified in mathematical terms. Second, deposition efficiency in each airway must be derived for each of the various deposition mechanisms. Finally, a computational procedure must be developed to account for the transport and deposition of the particles in the airways. As noted earlier, most models are deterministic, in that particle deposition probabilities are calculated using anatomical and airflow information on an airway generation by airway generation basis. Other models are stochastic, whereby modeling is performed using individual particle trajectories and finite element simulations of airflow.

Recent reports involve modeling the deposition of ultrafine particles and deposition at airway bifurcations. Zhang and Martonen (1997) used a mathematical model to simulate diffusion deposition of ultrafine particles in the human upper tracheobronchial tree, and compared the results to those in a hollow cast obtained by Cohen et al. (1990). The model was in good agreement with experimental data. Zhang and Martonen (1997) studied the inertial deposition of particles in symmetric three-dimensional models of airway bifurcations, mathematically examining effects of geometry and flow. They developed equations for use in predicting deposition based upon Stokes numbers, Reynolds numbers and bifurcation angles for specific inflows.

Models for deposition, clearance, and dosimetry of the respiratory tract of humans have been available for the past four decades. The International Commission on Radiological Protection (ICRP) has recommended three different mathematical models during this time period (International Commission on Radiological Protection, 1960, 1979, 1994). These models make it possible to calculate the mass deposition and retention in different parts of the respiratory tract and provide, if needed, mathematical descriptions of the translocation of portions of the deposited material to other organs and tissues beyond the respiratory tract.

Another respiratory tract dosimetry model was developed, concurrently with the new ICRP model, by the National Council on Radiation Protection and Measurements (NCRP) (1997). As with the ICRP model (International Commission on Radiological Protection, 1994), the new NCRP model addresses (1) inhalability of particles, (2) revised sub-regions of the respiratory tract, (3) dissolution-absorption as an important aspect of the model, and (4) body size and age. The NCRP model defines the respiratory tract in terms of a naso-oro-pharyngo-laryngeal (NOPL) region, a tracheobronchial (TB) region, a pulmonary (P) region, and lung-associated lymph nodes (LN). Deposition and clearance are calculated separately for each of these regions. As with the 1994 ICRP model, inhalability of aerosol particles is considered, and deposition in the various regions of the respiratory tract is modeled using methods that relate to mechanisms of inertial impaction, sedimentation, and diffusion.

Fractional deposition in the NOPL region was developed from empirical relationships between particle diameter and air flow rate. Deposition in the TB and P regions were projected from model calculations based upon geometric or aerodynamic particle diameter and physical deposition mechanisms such as impaction, sedimentation, diffusion and interception. Deposition in the TB and P regions used the lung model of Yeh and Schum (1980), with a method of calculation similar to that of Findeisen (1935) and Landahl (1950). This method was modified so as to be able to accomodate an adjustment of lung volume and substitution of realistic deposition equations. These calculations were based upon air flow information and idealized morphometry, using a typical pathway model. (Comparison of regional deposition fraction predictions between the NCRP and ICRP models was given in U.S. Environmental Protection Agency [1996a]). Inhalability was defined as per the American Conference of Governmental Industrial Hygenists (1985) definition. Breathing frequency, tidal volume and functional residual capacity are the ventilatory factors used to model deposition. These were related to body weight and to three levels of physical activity, namely low activity, light exertion and heavy exertion.

Clearance from all regions of the respiratory tract was considered to result from competitive mechanical and absorptive mechanisms. Mechanical clearance in the NOPL and TB regions was considered to result from mucociliary transport. This was represented in the model as a series of escalators moving towards the glottis and where each airway had an effective clearance velocity. Clearance from the P region was represented by fractional daily clearance rates to the TB region, the pulmonary LN region and the blood. A fundamental assumption in

the model was that the rates for absorption into blood were the same in all regions of the respiratory tract; the rates of dissolution-absorption of particles and their constituents were derived from clearance data primarily from laboratory animals. The effect of body growth on particle deposition was also considered in the model, but particle clearance rates were assumed to be independent of age. Some consideration for compromised individuals was incorporated into the model by altering rates (compared to normal) for the NOPL and TB regions.

Mathematical deposition models for deposition in a number of nonhuman species have been developed and discussed previously (U.S. Environmental Protection Agency, 1996a). Despite difficulties, modeling studies in laboratory animals remain a useful step in extrapolating exposure-dose-response relationships from laboratory animals to human. Some additional work on modeling deposition in animals has been reported, but it merely expands upon work and approaches already reported (U.S. Environmental Protection Agency, 1996a).

Respiratory-tract clearance begins immediately upon deposition of inhaled particles. Given sufficient time, the deposited particles may be completely removed by these clearance processes. However, single inhalation exposures may be the exception rather than the rule. It is generally accepted that repeated or chronic exposures are common for environmental aerosols. As a result of such exposures, accumulation of particles may occur. Chronic exposures produce respiratory tract burdens of inhaled particles that continue to increase with time until the rate of deposition is balanced by the rate of clearance. This is defined as the "equilibrium respiratory tract burden".

It is important to evaluate these accumulation patterns, especially when assessing ambient chronic exposures, because they dictate what the equilibrium respiratory tract burdens of inhaled particles will be for a specified exposure atmosphere. Equivalent concentrations can be defined as "species-dependent concentrations of airborne particles which, when chronically inhaled, produce equal lung deposits of inhaled particles per gram of lung during a specified exposure period" (Schlesinger et al., 1997). Available data and approaches to evaluate exposure atmospheres that produce similar respiratory tract burdens in laboratory animals and humans have been discussed in detail in the previous criteria document.

Several laboratory animal models have been developed to help interpret results from specific studies that involved chronic inhalation exposures to non-radioactive particles (Wolff et al., 1987; Strom et al., 1988; Stöber et al., 1994). These models were adapted to data from studies involving high level chronic inhalation exposures in which massive lung burdens of low

toxicity, poorly soluble particles were accumulated but the models have not been adapted to chronic exposures to low concentrations of aerosols in which particle overload does not occur.

7.2.7.2 Models To Estimate Retained Dose

Models have routinely been used to express retained dose in terms of temporal patterns for alveolar retention of acutely inhaled materials. Available information for a variety of mammalian species and humans can be used to predict deposition patterns in the respiratory tract for inhalable aerosols with reasonable degrees of accuracy. Additionally, alveolar clearance data for mammalian species commonly used in inhalation studies are available from numerous experiments that involved small amounts of inhaled radioactive particles.

A very important factor in using models to predict retention patterns in laboratory animals or humans is the dissolution-absorption rate of the inhaled material. Factors that affect the dissolution of materials or the leaching of their constituents in physiological fluids, and the subsequent absorption of these constituents, are not fully understood. Solubility is known to be influenced by the surface-to-volume ratio and other surface properties of particles (Mercer, 1967; Morrow, 1973). The rates at which dissolution and absorption processes occur are influenced by factors that include the chemical composition of the material. Temperature history of materials is an important consideration for some metal oxides. For example, in controlled laboratory environments, the solubility of oxides usually decreases when the oxides are produced at high temperatures, which generally results in compact particles having small surface-to-volume ratios. It is sometimes possible to accurately predict dissolution-absorption characteristics of materials based on physical/chemical considerations. However, predictions for in vivo dissolution-absorption rates for most materials, especially if they contain multivalent cations or anions, should be confirmed experimentally.

Phagocytic cells, primarily macrophages, clearly play a role in dissolution-absorption of particles retained in the respiratory tract (Kreyling, 1992). Some particles dissolve within the phagosomes due to the acidic milieu in those organelles (Lundborg et al., 1984, 1985), but the dissolved material may remain associated with the phagosomes or other organelles in the macrophage rather than diffuse out of the macrophage to be absorbed and transported elsewhere (Cuddihy, 1984). This same phenomenon has been reported for organic materials. For example, covalent binding of benzo(a)pyrene or metabolites to cellular macromolecules resulted in an

increased alveolar retention time for that compound after inhalation exposures of rats (Medinsky and Kampcik, 1985). Understanding these phenomena and recognizing species similarities and differences are important for evaluating alveolar retention and clearance processes and interpreting results of inhalation studies.

Dissolution-absorption of materials in the respiratory tract is clearly dependent on the chemical and physical attributes of the material. While it is possible to predict rates of dissolution-absorption, it is prudent to experimentally determine this important clearance parameter. It is important to understand the impact of this clearance process for the lung, TLNs, and other body organs that might receive particles, or their constituents that enter the circulatory system from the lung.

Insufficient data were available to adequately model long-term retention of particles deposited in the conducting airways of any mammalian species at the time of the previous document, and this remains the case. Additional research must be done to provide the information needed to properly evaluate retention of particles in conducting airways.

However, a number of earlier studies discussed in the previous document and in Section 7.2.2.2 herein noted that some particles were retained for relatively long times in the upper respiratory tract and tracheobronchial regions, effectively contradicting the general conclusion that almost all inhaled particles that deposit in the TB region clear within hours or days. These studies have demonstrated that variable portions of the particles that deposit in, or are cleared through, the TB region are retained with half-times on the order of weeks or months. Long-term retention and clearance patterns for particles that deposit in the head airways and TB region must continue to be thoroughly evaluated because of the implications of this information for respiratory tract dosimetry and risk assessment.

Model projections are possible for the A region using the cumulative information in the scientific literature relevant to deposition, retention, and clearance of inhaled particles. Clearance parameters for six laboratory animal species were summarized in U.S. Environmental Protection Agency (1996a). Recently, Nikula et al. (1997) evaluated results when rats were exposed to high levels of either diesel soot or coal dust. While the amount of retained material was similar in both species, the rats retained a greater portion in the lumens of the alveolar ducts and alveoli than did monkeys, while the monkeys retained a greater portion of the material in the interstitium than did rats. The investigators concluded that intrapulmonary retention patterns in

one species may not be predictive of those in another species at high levels of exposure, but this may not be the case at lower levels.

7.3 TOXICOLOGY OF PARTICULATE MATTER

Due to the lack of data on actual ambient PM toxicology at the time the previous CD was compiled, the respiratory effects of PM were organized into specific chemical components of ambient PM or model "surrogate" particles, e.g. acid aerosols, metals, ultrafine particles, bioaerosols, and "other particle matter". The following section summarizes the conclusions of the 1996 CD for each of these components.

There are many new studies of combustion related particles. The reasons for this increased interest in combustion particles are that these particles are typically the dominant sources represented in the fine fraction of PM. The combined evaluation of the health effects and the physico-chemical properties of combustion PM will be useful in relating emission sources with health effects.

7.3.1 Summary of Previous Criteria Document

7.3.1.1 Acid Aerosols

EPA previously concluded that healthy subjects experienced no decrements in lung function and only mild lower respiratory symptoms following single exposures to sulfuric acid aerosol at exposure concentrations in the mg/m^3 range, even with exercise and the use of acidic oral rinses to minimize neutralization by oral ammonia (U.S. Environmental Protection Agency, 1996a). Acid aerosols do alter mucociliary clearance in healthy subjects at lower concentrations, with effects dependent on exposure concentration and the region of the lung being studied.

Asthmatic subjects appear to be more sensitive than healthy subjects to the effects of acid aerosols on lung function, but the effective concentration differs widely among studies. Adolescent asthmatics may be more sensitive than adults, and may experience small decrements in lung function in response to H_2SO_4 at exposure levels only slightly above peak ambient levels. In a very limited number of studies, the elderly and individuals with chronic obstructive

pulmonary disease do not appear to be particularly susceptible to the effects of acid aerosols on lung function.

The adverse respiratory effects of acid aerosols in humans were supported by laboratory animal studies of H_2SO_4 and other acidic sulfates. The available evidence indicates that the observed responses to these are likely due to H^+ rather than to $SO_4^=$. Acidic sulfates exert their action throughout the respiratory tract, with the response and location of effect dependent upon particle size and mass and number concentration.

Both acute and chronic exposure to H_2SO_4 at well below lethal levels can produce functional changes in the respiratory tract of animals. Acute exposure will alter pulmonary function, largely due to bronchoconstrictive action. However, attempts to produce changes in airway resistance in healthy animals at levels below 1,000 $\mu g/m^3$ have been largely unsuccessful, except in the guinea pig. In general, the smaller size droplets (submicron) were more effective in altering pulmonary function, especially at low concentrations. Very low concentrations (< 100 $\mu g/m^3$) of acid-coated ultrafine particles are associated with lung function and diffusion decrements, as well as changes in airway responsiveness. Chronic exposure to H_2SO_4 is also associated with alterations in pulmonary function (e.g., changes in the distribution of ventilation and in respiratory rate in monkeys). But, in these cases, the effective concentrations are ≥ 500 $\mu g/m^3$. Airway hyperresponsiveness has been induced with repeated exposures to 250 $\mu g/m^3$ H_2SO_4 in rabbits, and has been suggested to occur following single exposures at 75 $\mu g/m^3$.

Lung defenses, such as resistance to bacterial infection, may be altered by acute exposure to concentrations of H_2SO_4 around 1,000 $\mu g/m^3$. However, the bronchial mucociliary clearance system is very sensitive to inhaled acids; fairly low levels of H_2SO_4 produce alterations in mucociliary transport rates in healthy animals. The lowest level shown to have such an effect, 100 $\mu g/m^3$ with repeated exposures in rabbits, is well below that which results in other physiological changes in most experimental animals. Furthermore, exposures to somewhat higher levels that also alter clearance have been associated with various morphometric changes in the bronchial tree that are suggestive of hypersecretion.

Limited data also suggest that exposure to acid aerosols may affect the functioning of AMs. The lowest level examined in this regard to date is 500 $\mu g/m^3$ H_2SO_4. Alveolar region particle clearance is affected by repeated H_2SO_4 exposures to as low as 125 $\mu g/m^3$.

U.S. Environmental Protection Agency (1996a) also reported results of studies which examined potential interactions of acid sulfates with other air pollutants. Such interactions may be antagonistic, additive, or synergistic. Evidence for interactive effects may depend upon the sequence of exposure as well as on the endpoint examined. Low levels of H_2SO_4 (100 $\mu g/m^3$) have been shown to react synergistically with O_3 in simultaneous exposures using biochemical endpoints. In this case, the H_2SO_4 enhanced the damage due to the O_3. The most realistic exposures were to multicomponent atmospheres, but the results of these studies are often difficult to assess due to chemical interactions of components and a resultant lack of precise control over the composition of the exposure environment.

7.3.1.2 Metals

Data from occupational studies and laboratory animal studies indicate that acute exposures to very high levels (hundreds of $\mu g/m^3$ or more) or chronic exposures to lower levels (up to 15 $\mu g/m^3$ albeit high compared to ambient levels) of metallic particulates can have an effect on the respiratory tract. However, it was concluded that the metals at concentrations present in the ambient atmosphere (1 to 14 $\mu g/m^3$) were not likely to have a significant acute effect in healthy individuals. These metals include arsenic, cadmium, copper, vanadium, iron, and zinc. Other metals found at concentrations less than 0.5 $\mu g/m^3$ were not reviewed in the previous CD.

7.3.1.3 Ultrafine Particles

There were only limited data available from human studies or laboratory animal studies on ultrafine aerosols at the time of the release of the previous CD. In vitro studies have shown that ultrafine particles have the capacity to cause injury to cells of the respiratory tract. High levels of ultrafine particles, as metal or polymer "fume," are associated with toxic respiratory responses in humans and other mammals. Such exposures are associated with cough, dyspnea, pulmonary edema, and acute inflammation. At concentrations less than 50 $\mu g/m^3$, freshly generated insoluble ultrafine teflon polymer fume particles can be severely toxic to the lung. However it was not clear what role in the observed effects was played by fume gases which adhered to the particles. Thus it was not clear at the time of the previous review (U.S. Environmental Protection Agency, 1996a) what role, if any, ambient ultrafine particles may play in PM-induced mortality/morbidity.

7.3.1.4 Bioaerosols

Ambient bioaerosols include fungal spores, pollen, bacteria, viruses, endotoxins, and plant and animal debris. Such biological aerosols can produce various health effects including: infections, hypersensitivity, and toxicoses. Bioaerosols present in the ambient environment have the potential to cause disease in humans under certain conditions. However, it was concluded that bioaerosols, at the concentrations present in the ambient environment, would not account for the observed effects of particulate matter on human mortality and morbidity reported in PM epidemiological studies. Moreover, bioaerosols generally represent a rather small fraction of the measured urban ambient PM mass and are typically present even at lower concentrations during the winter months when notable ambient PM effects have been demonstrated. Bioaerosols tend to be in the coarse fraction of PM, but some bioaerosols are found in the fine fraction.

7.3.1.5 "Other Particulate Matter"

Toxicologic studies of other particulate matter species were discussed in the previous CD. These studies included exposures to fly ash, volcanic ash, coal dust, carbon black, TiO_2, and miscellaneous other particles, either alone or in mixture. Some of the particles discussed were considered to be models of "nuisance" or "inert" dusts (i.e., those having low intrinsic toxicity) and were used in instillation studies to delineate nonspecific particle effects from effects of known toxicants. A number of studies on "Other PM" examined effects of up to 50,000 $\mu g/m^3$ of respirable particles with inherently low toxicity. While there was no mortality, some mild pulmonary function changes after exposure to 5,000 to 10,000 $\mu g/m^3$ of inert particles were observed in rats and guinea pigs. Lung morphology studies revealed focal inflammatory responses, some epithelial hyperplasia, and fibrotic responses after exposure to >5,000 $\mu g/m^3$. Changes in macrophage clearance after exposure to >10,000 $\mu g/m^3$ were equivocal (no infectivity effects). In studies of mixtures of particles and other pollutants, effects were variable depending on the toxicity of the associated pollutant. In humans, co-exposure to carbon particles appeared to increase responses to formaldehyde but not to acid aerosol. None of the "other" particles mentioned above are present in ambient air in more than trace quantities. Thus, it was concluded that the relevance of any of these studies to ambient particulate standard setting may be extremely limited.

7.3.2 Respiratory Effects of Particles

The following section (7.3.3) assesses results of exposure to various types of PM in humans. Section 7.3.4 discusses controlled animal toxicology studies as well as *in vitro* studies using animal or human respiratory cells. It focuses on those studies published since the 1996 Air Quality Criteria Document for Particulate Matter (U.S. Environmental Protection Agency, 1996a).

The biological responses occurring in the respiratory tract following controlled PM inhalation encompass a continuum of changes, including changes in pulmonary function, pulmonary inflammation, and systemic effects. The observed responses are dependent on the physicochemical characteristics of the PM, the total exposure and the health status of the host. However, many of the responses are usually seen only at higher level exposures characteristic of occupational and laboratory animal studies and not at (typically much lower) ambient particle concentrations.

Particulate matter is a broad term that encompasses thousands of chemical species, many of which have not been investigated in controlled laboratory animal or human studies. However, a full discussion of all types of particles that have been studied is beyond the scope of this chapter. Thus, specific criteria were used to select topics for presentation. High priority was placed on studies that may: (1) elucidate health effects of major common constituents of ambient PM and/or (2) contribute to enhanced understanding of the epidemiological studies (e.g., use of ambient particles, "surrogate" particles, or particles with low inherent toxicity that may cause effects due to their physicochemical characteristics, such as their size and composition).

Diesel exhaust particles (DPM) generally fit the criteria; but, because they are described elsewhere in great detail (U. S. Environmental Protection Agency, 1999; Health Effects Institute, 1995), they are not covered in this chapter except in the discussions of their immunological effects. Particles with high inherent toxicity, such as silica and asbestos, that are of concern primarily because of occupational exposure, are also excluded from this chapter and are discussed in detail elsewhere (U.S. Environmental Protection Agency, 1996b; Gift and Faust, 1997). Most of the laboratory animal studies summarized here have used high particulate mass concentrations administered by inhalation, compared to ambient levels, even when laboratory animal-to-human dosimetric differences or high doses by intratracheal instillation are considered.

This raises a question about the relevance, for example, of a rat study at 5,000 $\mu g/m^3$ in terms of direct extrapolation to humans in ambient exposure scenarios.

As mentioned earlier, the data available in the previous Criteria Document were from studies that investigated the respiratory effects of specific components of ambient PM or surrogate particles. More recently, pulmonary effects upon controlled exposures to ambient PM have been investigated by the use of aerosol concentrators (Sioutas et al., 1995; Gordon et al., 1998). These concentrators are capable of exposing animals or humans to PM concentrations that are up to 90-fold higher than ambient PM levels and have been used to investigate the effects of ambient PM in normal and compromised animals and humans.

7.3.3 Effects in Healthy Humans

7.3.3.1 Human Acid Aerosol Exposure Studies

There have been extensive studies of the effects of controlled exposures to aqueous acid aerosols on various aspects of lung function in humans. Many of these studies were reviewed in U.S. Environmental Protection Agency (1996a) and in the Acid Aerosol Issue Paper (U.S. Environmental Protection Agency, 1989). Methodology and measurement methods for controlled human exposure studies have been reviewed elsewhere (Folinsbee et al., 1997).

These studies have illustrated that aqueous acidic aerosols have minimal effects on symptoms and mechanical lung function in young healthy adult volunteers at concentrations as high as 2000 $\mu g/m^3$. The findings include minimal changes in lung function accompanied by only mild lower respiratory symptoms. However at concentrations as low as 100 $\mu g/m^3$, acid aerosols can alter mucociliary clearance. Brief exposures ($\leq$1 h) to low concentrations ($\sim$100 $\mu g/m^3$) may accelerate clearance while longer (multihour) exposures to higher concentrations (> 100 $\mu g/m^3$) can cause depression of clearance. Culp et al. (1995) examined the effects of inhaled acid aerosols on mucus secretion and composition; they found no significant changes in mucin glycoproteins, collected via BAL at 18 h postexposure, as a result of an acute 2 h exposure to approximately 1000 $\mu g/m^3$.

Asthmatic subjects appear to be more sensitive to the effects of acidic aerosols on mechanical lung function. Responses have been reported in adolescent asthmatics at concentrations as low as 68 $\mu g/m^3$ and modest bronchoconstriction has been seen in adult asthmatics exposed to concentrations $\geq$400 $\mu g/m^3$. The effects of acidic aerosols are most likely

related to decreases in local airway surface pH as a result of acid deposition. Airway ammonia can neutralize a portion of the inhaled acid aerosol and the airway surface fluids have the capacity to buffer the deposited acid. The variability of the response to acid aerosols among asthmatics is at least partially explained by the variability of the disease itself; variability in acid neutralization by oral/airway ammonia may also be a factor.

The inhalation of submicron acid particles appears to have greater effects on spirometry and airway resistance than does inhalation of large particles characteristic of fog droplets (10-20 μm). Leduc et al. (1995) exposed two groups of asthmatics to acid "fog" droplets (7-9 μm MMAD; sulfuric acid or ammonia sulfate aerosol) and found no evidence of bronchoconstriction or change in airway responsiveness to methacholine. Although there is some evidence of increased airway responsiveness after acid aerosol exposure (Utell et al., 1983a) as well as enhanced responses to ozone after acid aerosol inhalation in asthmatic subjects (Linn et al., 1994; Frampton et al., 1995) the weight of evidence indicates that low concentrations of acid aerosols (<200 $\mu g/m^3$) typically do not tend to change airway responsiveness.

Acid aerosol exposure in humans (1000 $\mu g/m^3$) did not result in airway inflammation (Frampton et al., 1992) and there was no evidence of altered macrophage host defenses. Zelikoff et al. (1997) compared the responses of rabbits and humans exposed to similar concentrations of acid aerosol (~1000 $\mu g/m^3$, 0.8 to 0.9 μm MMAD, 3 h duration). For both rabbits and humans there was no evidence of PMN infiltration into the lung and no change in BAL protein level, although there was an increase in LDH in rabbits but not in humans. Macrophages showed less antimicrobial activity in rabbits; insufficient data were available for humans. Macrophage phagocytic activity was slightly reduced in rabbits but not in humans. Superoxide production by macrophages was somewhat depressed in both species.

Human Exposure to Other Particles

Only limited controlled human exposure studies have been performed with particles other than acid aerosols. Metal fume fever has long been recognized in workers occupationally exposed to metal fume (Mueller and Seger, 1985). The associated fever appears to be related to pulmonary inflammation subsequent to inhalation of metal particles, most commonly zinc oxide. In BAL samples taken from welders, marked elevation of PMNs was noted (Blanc et al., 1991). This inflammation was associated with increased TNF-α and IL-8, which may be responsible for

the chemotaxis for PMNs (Blanc et al., 1993). Controlled exposure studies to high concentrations of two different metal fumes, MgO and ZnO, demonstrate the differences in response based on particle metal composition (Kushner et al., 1997). Up to 6400 mg/m^3• min cumulative dose (100-200 mg/m^3 for 45 min; 99% of particles <1.8 μm and 29% <0.1 μm) of MgO had no effect on lung function (spirometry, $D_{L_{CO}}$), symptoms of metal fume fever, or changes in inflammatory mediators or cells recovered by BAL. However, lower concentrations of ZnO fume (165-1110 mg/m^3• min; 15-120 min at 3-37 mg/m^3; MMD 0.17 μm) induced a neutrophilic inflammatory response in the airways 20 h post-exposure. Lavage fluid PMNs, TNF-α, and IL-8 were increased by ZnO exposure. However, the concentrations used in these exposure studies exceed ambient levels by more than 1000-fold. The absence of a response to an almost 10-fold higher concentration of MgO compared with ZnO indicates that metal composition is an important factor in response to inhaled PM. Fine et al. (1997) have shown elevated body temperature (metal fume fever) and increased levels of plasma IL-6 (from 2.9 to 6.4 pg/ml) in naive subjects exposed to the 8h TLV concentration of ZnO of 5 mg/m^3 for 2 h.

Several metals have been shown to stimulate cytokine release in cultured human pulmonary cells including zinc, chromium, cobalt, and vanadium. Boiler makers, exposed occupationally to approximately 400-500 μg/m^3 of fuel oil ash, showed acute nasal inflammatory responses characterized by increased PMNs and elevated IL-8 which were associated with vanadium levels (increased about 9-fold) in the upper airway (Woodin et al., 1998). Irsigler et al. (1999) reported that V_2O_5 can induce asthma and bronchial hyperreactivity in exposed workers. A comparison of autopsy cases in Mexico City from the 1950s with the 1980s indicated substantially higher levels of (5-20 fold) Cd, Co, Cu, Ni, and Pb in lung tissue from the1980s (Fortoul et al., 1996). Similar studies have examined metal content in human blood and lung tissue (Tsuchiyama et al., 1997; Osman et al., 1998). These data support the hypothesis that certain particulate metals may play a role in the effects of inhaled ambient PM.

Because iron is the most abundant of the elements, which are capable of catalyzing oxidant generation, and present in ambient urban particles, Lay and colleagues examined the cellular and biochemical response of human subjects instilled with iron (III) oxide via the intrapulmonary route (Lay et al., 1998). Subjects underwent bronchoalveolar lavage at 1 to 91 days after instillation of 2.6 μm diameter iron oxide particles. The investigators found the greatest iron oxide-induced inflammatory response in the alveolar fraction of the lavage fluid, although a

significant increase in neutrophils was also observed in the bronchial fraction. The peak response for all cellular and biochemical changes occurred at 1 day post-instillation. The same iron oxide preparation, which contained a small amount of soluble iron, instilled in rats produced similar pulmonary changes. Instillation of rats with 2 iron oxide preparations that contained no soluble iron did not produce injury or inflammation, thus suggesting that soluble iron was responsible for the observed intrapulmonary changes. It is not clear, however, whether the dose of iron oxide delivered acutely to the lingular subsegment of the human subjects (approximately 5 mg or 2.1×10^8 particles) would be relevant to deposition of iron oxide particles at the concentrations of iron present in ambient urban air (generally less than 1 $\mu g/m^3$).

Human Exposures to Endotoxin

Endotoxin exposure in pig farmers is associated with the farmers' large annual decline in FEV_1 (mean of 73 ml/yr), which is about 2-3 times more rapid than in healthy adults (Vogelzang et al., 1998). Michel et al. (1997) examined the dose-response relationship to inhaled lipopolysaccharide (LPS: the purified derivative of endotoxin) in normal healthy volunteers exposed to 0, 0.5, 5, and 50 μg of LPS. Inhalation of 5 or 50 μg of LPS resulted in increased PMNs in blood and sputum samples. At the higher concentration, a slight (3%) but not significant decrease in FEV_1 was observed. Cormier et al. (1998) reported an approximate 10% decline in FEV_1 and an increase in methacholine airway responsiveness after a 5 h exposure inside a swine containment building. This exposure induced significant neutrophilic inflammation in both the nose and the lung. Although these exposures are massive compared to endotoxin levels in ambient PM in U.S. cities, these studies serve to illustrate the effects of endotoxin and associated bioaerosol material in healthy non-sensitized individuals.

Adverse health effects have been observed after occupational exposure to complex aerosols containing endotoxin at concentrations relevant to ambient levels. Zock et al. (1998) reported a decline in FEV_1 (~3%) across a shift in a potato processing plant with up to 56 endotoxin units (EU)/m^3 in the air. Rose et al. (1998) reported a high incidence (65%) of BAL lymphocytes in lifeguards working at a swimming pool where endotoxin levels in the air were on the order of 28 EU/m^3. While these latter two studies may point towards pulmonary changes at low concentrations of airborne endotoxin, it is not possible to rule out the contribution of other agents in these complex organic aerosols.

7.3.4 Effects in Healthy Animals

7.3.4.1 Ambient Particles

The majority of the in vivo exposures to ambient particles have utilized intratracheal instillation techniques. A discussions on the pros and cons of this technique are covered in Section 7.2.6 and these issues have also been reviewed (Oberdörster et al., 1997; Osier and Oberdörster, 1997). The doses used in these instillation studies are generally high relative to ambient concentrations, even when laboratory animal-to-human dosimetric differences are considered. Therefore, in terms of direct extrapolation to humans in ambient exposure scenarios, greater importance should be place on inhalation studies. Table 7-2 outlines studies in which various biological endpoints were measured following intratracheal instillation of ambient PM, complex combustion related PM, as well as laboratory derived surrogate PM.

In most of these studies, PM samples were collected on filters, resuspended in a vehicle (usually saline) and a small volume of the suspension was intratracheally instilled into the animals. Various inflammatory indices were evaluated at several time points post-instillation. In some studies, the responses in animals to the soluble (leachate) or insoluble components were measured. Costa and Dreher (1997) investigated the health effects of PM samples from three emission sources (two oil and one coal fly ash) and four ambient airsheds (St Louis, MO; Washington, D.C.; Dusseldorf, Germany; and Ottawa, Canada). PM was administered to rats by intratracheal instillation in doses that were either equivalent in total mass or in total mass of metal. Increases in neutrophils and eosinophils were noted at 24 h for all types of emission source and for ambient PM. Biomarkers of permeability (total protein, albumin) and cellular injury (LDH) were also increased. The results of this study indicate that the lung dose of bioavailable transition metal, not instilled PM mass, was the primary determinant of the acute inflammatory response. Kennedy et al. (1998) observed a dose-dependent inflammation (i.e., increase in protein and PMN in lavage fluid, proliferation of bronchiolar epithelium, and intra-alveolar hemorrhage) in rats instilled with particles (TSP) collected in Provo, Utah. Treatment with anti-cytokine-induced neutrophil-chemoattractant (CINC) antibody, at the same time as TSP, blocked the airway inflammation suggesting CINC's role in the PMN-induced responses. In addition, by comparing the responses of cultured BEAS-2B cells exposed to Provo particles or its components (copper, lead, zinc and iron), these authors suggested that copper ions may contribute to the biological effects.

TABLE 7-2. RESPIRATORY EFFECTS OF PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size (μm)	Exposure Duration	Effect of Particles	Reference
M Syrian golden hamsters 90-125g.	Kuwaiti Oil Fire particles Urban particles from St. Louis, MO	Intratracheal Instillation	0.15, 0.75, and 3.75 mg/100g	Oil fire particles: <3.5 μm, 10 days of 24 h samples (Apr 30 to May 9, 1991), in Ahmadi, Kuwait	Sacrificed 1 and 7 days post instillation	Increases in PMN, AM, albumin, LDH, myeloperoxidase, and β--N-acetylglucosaminidase; acute toxicity of the particles found in the smoke from the Kuwaiti oil fires is comparable to that of urban particles.	Brain et al. (1998)
NMRI mouse	CFA CMP WC	Intratracheal instillation	CMP: 20 μg arsenic/kg; or CMP 100 mg particles/kg; WC alone (100 mg/kg), CFA alone (100 mg/kg, i.e., 20 μg arsenic/kg), CMP mixed with WC (CMP, 13.6 mg/kg, i.e., 20 μg arsenic/kg; WC, 86.4 mg/kg) and Ca3(AsO4)2 mixed with WC (20 μg arsenic/kg; WC, 100 mg/kg)	N/A	1, 5, 30 days post treatment, lavage for total protein content, inflammatory cell number and type, and TNF-α production particle retention	Mild inflammation for WC; $Ca_3(AsO_4)_2$ caused significant inflammation; CMP caused severe but transient inflammation; CFA caused persistent alveolitis; Cytokine production was upregulated in WC- and $Ca_3(AsO_4)$ treated animals after 6 and 30 d, respectively; A 90% inhibition of TNF-α production was still observed at day 30 after administration of CMP and CFA; a significant fraction persisted (10-15% of the arsenic administered) in the lung of CMP- and CFA-treated mice at day 30. Suppression of TNF-α production is dependent upon the slow elimination of the particles and their metal content from the lung	Broeckaert et al. (1997)
NHBE cells	ROFA	In vitro	0, 50, 200 μg/ml		Analysis at 2 and 24 h post	Increase in expression of the cytokines IL-6, IL-8 and TNF-α; Inhibition by DMTU or deferoxamine	Carter et al. (1997)
Male S-D rats 200-225 g. control and SO_2-treated	Concentrated Ambient Particles (Boston) (CAPS)	Harvard/EPA Fine Particle Concentrator Animals restrained in chamber	206,733, 607 µg/m^3 for days 1-3; 29 °C, 59% RH	0.18 µm δg = 2.9	5h/day for 3 days	PEF and TV increased in CAPS exposed animals. Increased protein and % neutrophils and lymphocytes in lavage fluid after CAPS exposure. Responses were greater in SO_2-bronchitis animals. No changes in LDH. No deaths occurred.	Clarke et al. (1999)

TABLE 7-2 (cont'd). RESPIRATORY EFFECTS OF PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size (μm)	Exposure Duration	Effect of Particles	Reference
Rats, M, SD, 60 days old MCT (60/mg/kg), i.p	Emission source PM Ambient airshed PM ROFA	Intratracheal instillation	Total mass: 2.5 mg/rat Total transition metal: 46 μg/rat	Emission PM: 1.78-4.17 μm Ambient PM: 3.27-4.09 μm	Analysis at 24 & 96 h following instillation.	Increases in PMNs, albumin, LDH, PMN, and eosinophils following exposure to emission and ambient particles; Induction of injury by emission and ambient PM samples is determined primarily by constituent metals and their bioavailability; MCT-ROFA show enhanced neutrophilic inflammation; MCT-ROFA increase in mortality; More and worsened dysrhythmias.	Costa and Dreher (1997)
WISTAR male rats. Bor: WISW strain).	Coal oil Fly Ash	Inhalation (chamber)	0, 11, 32, 103 mg/m^3	1.9-2.6 μm (δg=1.6-1.8)	6h/day, 5d/week, 4 weeks.	At the highest conc., type II cell proliferation and mild fibrosis occurred and increased perivascular lymphocytes were seen. The main changes at the lowest concentration were particle accumulation in AM and mediastinal lymph nodes. Lymphoid hyperplasia observed at all concentrations. Effects increased with exposure duration.	Dormans et al. (1999)
Rat, M, SD, 60 day old	ROFA	Intratracheal instillation	8.33 mg/ml 0.3 ml/rat	1.95 μm MMAD	Analysis at 24 and 96 h	Increased PMNs, protein, LDH at both time points	Dreher et al. (1997)
C57Bl/6J mice	PTFE TiO_2	Inhalation	PTFE: 1.25, 2.5, 5 x 10^5 particles/cc TiO_2-F: 10 mg/m^3 NiO: 5 mg/m^3 Ni_3S_2: 0.5 mg/m^3	PTFE: 18 nm TiO_2-F: 200 nm TiO_2-D: 10 nm	30 min or 6 h/d, 5d/w, 6 months	Effects on the epithelium are due to direct interactions with particles, not a result of macrophage-derived mediators, and suggest a more significant role in the overall pulmonary response than previously suspected; type II cell growth factor production may be significant in the pathogenesis of pulmonary fibrosis	Finkelstein et al. (1997)

TABLE 7-2 (cont'd). RESPIRATORY EFFECTS OF PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size (μm)	Exposure Duration	Effect of Particles	Reference
Rat, M, SD. 60 day old	Two ROFA Samples R1 had 2x saline-leachable sulfate, Ni, and V and 40x Fe as R2; R2 had 31x higher Zn	Intratracheal instillation	2.5 mg in 0.3 ml	R1: 1.88 μm, MMAD R2: 2.03 μm, MMAD	Analysis at 4 days	4 of the 24 animals treated with R2 or R2s (supernatant) died; none in R1s treated animals; more AM, PMN, eosinophils protein, and LDH in R2 and R2s animals; more focal alveolar lesions, thickened alveolar septae, hyperplasia of type II cells, alveolar fibrosis in R2 and R2s animals; Baseline pulmonary function and airway hyperreactivity were worse in R2 and R2s groups	Gavett et al. (1997)
Female Balb/cJ mice 7-15 weeks.	ROFA	Intratracheal instillation	60 μg in 50 μl (dose 3mg/kg)	< 2.5	N/A	ROFA caused increases in eosinophils, IL-4 and IL-5 and airway responsiveness in ovalbumin-sensitized and challenged mice.	Gavett et al. (1999)
Human	Colloidal iron oxide	Bronchial instillation	5 mg in 10 ml.	2.6 μm	1, 2, 4 days after instillation	L-ferritin increased after iron oxide particle exposure; Transferrin was decreased, both lactoferrin and transferrin receptor were increased	Ghio et al. (1998a)
Rat, M, SD	ROFA	Intratracheal instillation	500 μg/animal	3.6 μm	Analyzed 4 and 96 h post exposure	Ferritin and transferrin were elevated; greatest increase in ferritin, lactoferrin, transferrin occurred 24 h post exposure	Ghio et al. (1998b)
S-D rats 60 days	Provo, UT TSP filters (10 yr old) soluble and insoluble extracts.	Intratracheal instillation	100-1000 μg of PM extract m 0.5 ml saline.	N/A	24 h	Inflammation (PMN) and lavage fluid protein was greater with the soluble fraction containing more metal (Zn, Fe, Cu).	Ghio et al. (1999b)
Rats	CAP	nose-only inhalation	110-350 $\mu g/m^3$	N/A	3 h	Increased peripheral blood neutrophils and decreased lymphocytes heart rate increased 10-20 BPM after PM exposure.	Gordon et al. (1998)
Rat	PTFE Fumes	Whole body inhalation	1, 2.5 or 5 x 10^5 particles/cm3	18 nm	15 min analysis 4 h post exposure	Increased PMN, mRNA of MnSOD and MT, IL-1α, IL-1β, IL-6, MIP-2, TNF-α mRNA of MT and IL-6 expressed around all airways and interstitial regions; PMN expressed IL-6, MT, TNF-α; AM and epithelial cells were actively involved	Johnston et al. (1996)

TABLE 7-2 (cont'd). RESPIRATORY EFFECTS OF PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size (μm)	Exposure Duration	Effect of Particles	Reference
Mice,C57BL/6J, 8 wk and 8 mo old	PTFE Fumes	Whole body inhalation	1, 2.5 or 5 x 10^5 particles/cm3	18 nm	30 min exposure Analysis 6 h following exposure	Increased PMN, lymphocytes and protein levels in old mice over young mice; Increased TNF-α mRNA in old mice over young mice; No difference in LDH and β-Glucuronidase	Johnston et al. (1998)
Rat, M, SD, 60 day old	ROFA	Intratracheal instillation	1.0 mg in 0.5 ml saline	1.95 μm	Analysis at 24 h	Increased PMNs, protein	Kadiiska et al. (1997)
SD rats Human Bronchial Epithelial (BEAS-2B) cells	TSP collected in Provo, Utah	Intratracheal instillation	TSP filter samples (36.5 mg/ml) agitated in deionized H_2O_2 for 96 h; centrifuged at 1,200g for 30 min; lyophylized, and resuspended in deionized H_2O_2 or saline	N/A (TSP samples, comprised 50 to 60% PM10)	Sacrificed at 24 h	Provo particles caused cytokine-induced neutrophil chemoattractant-dependent inflammation of rat lungs; Provo particles stimulated IL-6 and IL-8 production, increased IL-8 mRNA and ICAM-1 in BEAS-2B cells, and stimulated IL-8 secretion in primary cultures of BEAS-2B cells; Cytokine secretion was preceded by activation of NF-κB and was reduced by SOD, DEF, or NAC; Quantities of Cu^{2+} found in Provo particles replicated the effects	Kennedy et al. (1998)
Rats, M, SD and F-344 rats (60 days old)	ROFA	Intratracheal instillation	8.3 mg/kg	1.95 μm	Sacrificed at 24 h	increase in neutrophils in both SD and F-344 rats; A time-dependent increase in eosinophils occurred in SD rats but not in F-344 rats.	Kodavanti et al. (1996)
Rats, M, SD, WIS and F-344 rats (60 days old)	ROFA	Intratracheal instillation	8.3 mg/kg	1.95 μm	Sacrificed at 24 h	inflammatory cell infiltration as well as alveolar, airway, and interstitial thickening in all three rat strains; a sporadic incidence of focal alveolar fibrosis in SD rats, but not in WIS and F-344 rats; Fn mRNA isoforms EIIIA(+) were upregulated in SD and WIS rats but not in F-344 rats. Fn mRNA expression by macrophage and alveolar and airway epithelium and within fibrotic areas in SD rats; increased presence of Fn EIIIA(+) protein in the areas of fibrotic injury and basally to the airway epithelium.	Kodavanti et al. (1997)

TABLE 7-2 (cont'd). RESPIRATORY EFFECTS OF PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size (μm)	Exposure Duration	Effect of Particles	Reference
Rats, M, SD and F-344 rats (60 days old)	10 ROFA water and .1 M HCl leachable As, Be, Cd, Co, Cr, Cu, Fe, Mn, Ni, Pb, V, Zn, S	Intratracheal instillation	0.833, 3.33, 8.3 mg/kg	1.99 – 2.59 μm MMAD	Sacrificed at 24 h	ROFA induced increases in BAL protein and LDH, but not PMN were associated with water-leachable total metal, Ni, Fe, and S; PMN was correlated with V; Chemiluminescence signals in vitro (AM) were greatest with ROFA containing soluble V and less with Ni plus V.	Kodavanti et al. (1998a)
60 day male S-D rats treated with monocrotaline 60 mg/kg	ROFA	Intratracheal instillation (IT); Nose-only inhalation (IN)	0, 0.83, 3.3 mg/kg; 15 mg/m^3	Source: 1.95 μm; N/A	24-96 h ; 6h/day for 3 days	Both IT and IN rats showed inflammatory responses (IL-6, MIP-2, inflammatory cells, etc.). 58% of IT rats exposed to ROFA died within 96 h. No mortality occurred in the IN rats. ROFA exacerbated lung lesions (edema, inflammatory cells, alveolar thickening).	Kodavanti et al. (1999)
Brown Norway rat	ROFA	Intratracheal instillation	200 μg 100 μg	N/A	N/A	ROFA enhanced the response to house dust mite (HDM) antigen challenge. Eosinophil numbers, LDH, BAL protein, and IL-10 were increased with ROFA + HDM versus HDM alone.	Lambert et al. (1999)
Human 27M, 7F 20-36 yr.	Fe_20_3	Intrapulmonary instillation	3×10^8 microspheres in 10 ml saline.	2.6 μm	N/A	Transient inflammation induced initially (neutrophils, protein, LDH, IL-8) was resolved by 4 days post-instillation.	Lay et al. (1998)
Fischer 344 rats. (25g)	Fe_20_3	Intratracheal instillation	7.7×10^7 microspheres in 5 ml saline	2.6 μm	N/A	Transient inflammation at 1 day post instillation.	
Rats Wis (HAN strain),	Ambient PM Edinburgh; CB, CB Ultrafine (UCB)	Intratracheal instillation	50-125 μg in 0.2 ml	PM_{10} CB = (200-500 nm) UCB = 20 nm	Sacrificed at 6 h	Increased PMN, protein and LDH following PM_{10}; greater response with ultrafine CB but not CB; decreased GSH level in BAL; free radical activity (deplete supercoil DNA); Leukocytes from treated animals produced greater NO and TNF	Li et al. (1996, 1997)

TABLE 7-2 (cont'd). RESPIRATORY EFFECTS OF PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size (μm)	Exposure Duration	Effect of Particles	Reference
NMRI mice; Mouse peritoneal macrophage	MnO_2	Intratracheal instillation; In vitro	0.037, 0.12, 0.75, 2.5 mg/animal	surface area of 0.16, 0.5; 17, 62 m^2/g	Sacrificed at 5 days	LDH, protein and cellular recruitment increased with increasing surface area; Freshly ground particles had enhanced cytotoxicity	Lison et al. (1997)
60 day S-D rats, male	Florida ROFA; Domestic oil fly ash	Intratracheal instillation	1,000 μ in 0.5 ml		15 min to 24 h	ROFA induced production of acetaldehyde with a peak at about 2 h. No acetaldehyde was seen in plasma at any time. DOFA increased acetaldehyde as did V and Fe.	Madden et al., (1999)
Male SD rat (200g)	Diesel, SiO_2, Carbon black	Intratracheal instillation	1 mg in 0.4 ml.	DEP Collected as TSP - disaggregated in solution by sonication (20 nm); SiO_2 (7 nm); Carbon Black	Sacrificed at 2, 7, 21, 42, and 84 days post-instillation	Amorphous SiO_2 increased permeability, neutrophillic inflammation. Carbon black and DEP translocated to interstitum and lymph nodes by 12 weeks.	Murphy et al., 1998
Rat , M, F344, 175-225g	TiO_2	Intratracheal inhalation and Intratracheal instillation	Inhalation at 125 $\mu g/m^3$ Instillation at: 500 μg for fine 750 μg for ultrafine	Fine: 250 nm Ultrafine: 21 nm	inhalation exposure, 2 h; sacrificed at 0, 1 3, and 7 days postexposure for both techniques	Inflammation produced by intratracheal inhalation (both severity and persistence) was less than that produced by instillation; Ultrafine particles produced greater inflammatory response than fine particles for both dosing methods	Osier and Oberdörster (1997)
Rat, M. F344, 175-225 g	TiO_2	Intratracheal inhalation and Intratracheal instillation	Inhalation at 125 $\mu g/m^3$ Instillation at: 500 μg for fine 750 μg for ultrafine	Fine: 250 nm Ultrafine: 21 nm	inhalation exposure, 2 h; sacrificed at 0, 1 3, and 7 days postexposure for both techniques	MIP-2 increased in lavage cells but not in supernatant in those groups with increased PMN (more in instillation than in inhalation; more in ultrafine than in fine); TNF-α levels had no correlation with either particle size or dosing methods	Osier et al. (1997)

TABLE 7-2 (cont'd). RESPIRATORY EFFECTS OF PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size (μm)	Exposure Duration	Effect of Particles	Reference
Rats	$NaVO_3$ $VOSO_4$ V_2O_5	Intratracheal instillation	21 or 210 μg V/kg ($NaVO_3$, $VOSO_4$ soluble) 42 or 420 μg V/kg (V_2O_s) less soluble	N/A	1 h or 10 days following instillation	PMN influx was greatest following $VOSO_4$, lowest for V_2O_5; $VOSO_4$ induced inflammation persisted longest; MIP-2 and KC (CXC chemokines) were rapidly induced as early as 1 h post instillation and persisted for 48 h; Soluble V induced greater chemokines mRNA expression than insoluble V AM have the highest expression level;	Pierce et al. (1996)

AM - Alveolar Macrophage
CAP - Concentrated Ambient Particles
CB - Carbon Black
CFA - Coal Fly Ash
CMP - Copper Smelter Dust
DEF - Deferoxamine or Desferrioxamine
DMTU - Dimethylthiourea
DNA - Deoxyribonucleic Acid
DPM - Diesel Particulate Matter
ERK - Extracellular Receptor Kinases
F-344 - Fischer 344
Fe_2O_3 - Iron Oxide
Fn - Fibronectin
G-6-PDH - Glucose-6-Phosphate Dehydrogenase
IL-6; Il-8 - Interleukin 6,8
JNK - Jun H_2-Terminal Kinases
LCL - Luminol Enhanced Chemiluminescence
LDH - Lactate Dehydrogenase
LPS - Liopopolysaccharide (Endotoxin)
MAPK - Mitogen-Activated Protein Kinases
MCT - Monocrotaline
MMAD - Mass Median Aerodynamic Diameter
mRNA - Messenger Ribonucleic Acid
NF-κB - Nuclear factor-kappa B
NHBE - Normal Human Broncial Epithelial Cells
PHS - Prostaglandin H Synthetase
PMA - Phorbol Myristate Acetate
PMN - Neutrophil
PTFE - Polytetrafluoroethylene
ROFA - Residual Oil Fly Ash
RTE - Rat Tracheal Epithelial Cells
SD - Sprague Dawley
SiO_2 - Silicon Dioxide
SOD - Superoxide Dismutase
SR - Scavenger-Type Receptors
Ti O_2 - Titanuim Dioxide
TNF - Tumor Necrosis Factor
TSP - Total Suspended Paticles
UAP - Urban Air Particles
UF - Ultrafine
WC - Tungsten Carbide
Wis - Wistar

Instillation of ambient PM_{10} collected in Edinburgh, Scotland, also caused pulmonary injury and inflammation in rats (Li et al., 1996, 1997). Six hours after intratracheal instillation of PM_{10} (in 0.2 ml saline containing 50 to 125μg of particles), an influx of PMN, and increased epithelial permeability, total protein, and LDH in BAL were observed. An even greater inflammatory response was observed after instillation of ultrafine carbon black (125μg, 20 nm) but not after fine carbon black (200-250 nm) particles. A decrease in reduced glutathione (GSH) in the BAL suggested that PM_{10} is capable of inducing the production of oxidants. In addition, BAL leukocytes recovered from rats treated with PM_{10} produced greater amounts of nitric oxide and tumor necrosis factor alpha (TNF-α) than control animals. These data provide evidence that instillation of PM_{10} causes lung injury, which may be mediated through oxidant generation and cytokines.

Brain et al. (1998) examined the effects of particles that resulted from the Kuwaiti oil fires in 1991. Hamsters were intratracheally instilled with particles (0.15, 0.75, and 3.75 mg per 100 g animal) collected in Ahmadi, a residential area of Kuwait. The response of hamsters instilled with particles from Ahmadi was compared to the response of hamsters instilled with particles collected in St. Louis, MO. When compared to hamsters instilled with St. Louis particles, hamsters instilled with Ahmadi particles had between 1.4 and 2.2-fold more neutrophils in their BAL fluid. However, Ahmadi-treated hamsters had a lesser decrease in macrophage number and a smaller increase in LDH activity. There were no significant differences in albumin and β-N-acetylglucosaminidase levels (the latter indicative of damage to macrophages or neutrophils). These results showed that on an equal mass basis, the acute toxicity of the Ahmadi combustion particles was similar to that of urban particles collected in the United States.

In summary, intratracheal instillation of ambient particles induced an inflammatory response in the lungs, perhaps mediated through cytokines, and the responses appears to be dependent on the bioavailable transition metals and subsequent oxidant production, rather than on instilled PM mass.

7.3.4.2 Coal Fly Ash or Residual Oil Fly Ash (ROFA)

Many studies investigating the response of animals to particle exposures have used ROFA as a surrogate for ambient particles. ROFA has a high content of water soluble sulfate and metals. As described previously (U.S. Environmental Protection Agency, 1996a), intratracheal

instillation of high doses of ROFA suspension generally produced severe inflammation, an indicator of pulmonary injury which included recruitment of neutrophils, eosinophils, and monocytes into the airway. The biological effects of ROFA have been shown to depend on aqueous leachable chemical constituents of the particles. Dreher et al. (1997) have shown that a leachate prepared from ROFA, containing predominantly Fe, Ni, V, Ca, Mg, and sulfate, produced similar lung injury to that induced by the complete ROFA suspension. Depletion of Fe, Ni, and V from the ROFA leachate eliminated its pulmonary toxicity. Correspondingly, minimal lung injury was observed in animals exposed to saline-washed ROFA particles. A surrogate transition metal sulfate solution containing Fe, V, and Ni largely reproduced the lung injury induced by ROFA. Interestingly, ferric sulfate and vanadium sulfate antogonized the pulmonary toxicity of nickel sulfate. Interactions between different metals and the acidity of PM were found to influence the severity and kinetics of lung injury induced by ROFA and its soluble transition metals.

To further confirm the role of soluble metal components in the toxicity of emission source particles, Gavett et al. (1997) investigated the effects of two ROFA samples of equivalent diameters, but having different metal and sulfate content, on pulmonary responses in Sprague-Dawley rats. ROFA sample 1 (R1) (the same emission particles used by Dreher et al. [1997]) had approximately twice as much saline-leachable sulfate, nickel, and vanadium, and 40 times as much iron as ROFA sample 2 (R2); while R2 had a 31-fold higher zinc content. Four groups of rats received intratracheal instillations with suspensions of 2.5 mg R2 in 0.3 ml saline, the supernatant of R2 (R2s), the supernatant of 2.5 mg R1 (R1s), or saline only. By 4 days after instillation, 4 of 24 rats treated with R2s or R2 had died. None of those treated with R1s or saline died. Pathological indices such as alveolitis, early fibrotic changes and perivascular edema, were greater in both R2 groups. In surviving rats, baseline pulmonary function parameters and airway hyperreactivity to acetylcholine were significantly worse in R2 and R2s groups than in the R1s groups. Other than BAL neutrophils, which were significantly higher in the R2 and R2s groups, no other inflammatory cells (macrophages, eosinophils, or lymphocytes) or biochemical parameters of lung injury were significantly different between the R2 and R2s groups and the R1s group. They also observed an increase in focal alveolar lesions, thickened alveolar septae, hyperplasia of type II cells and fibrosis in rats instilled with ROFA (2.5 mg) and examined 4 days later. Although soluble forms of zinc had been found in guinea pigs to produce

a greater pulmonary response than other sulfated metals (Amdur et al., 1978), and although the level of zinc was 30 fold greater in R2 than R1, the precise mechanisms by which zinc may induce such responses are unknown. Nevertheless, these results show that the composition of soluble metals and sulfate leached from ROFA, a type of emission source particle, is critical in the development of airway hyperractivity and lung injury.

In an effort to determine the role of reactive oxygen species in the *in vivo* toxicity of ROFA, Dye et al. (1997) treated rats with an intraperitoneal injection of saline or dimethylthiourea (DMTU) (500 mg/kg), followed 30 min later by intratracheal instillation of either acidic saline (pH = 3.3) or an acidified suspension of ROFA (500 μg/0.3 ml). The systemic administration of DMTU impeded development of the cellular inflammatory response to ROFA, but did not ameliorate biochemical alterations in BAL fluid. In addition, it is suggested that systemic administration of DMTU resulted either in scavenging or diminished production of key reactive oxygen species. This in turn ameliorated cellular redox changes and thus diminished the "effector cell" response to ROFA (i.e., decreased cytokine production by airway epithelial cells, alveolar macrophages, or lymphocytes).

The response of different strains of rats to ROFA instillation was investigated by Kodavanti et al. (1996). Male Sprague Dawley (SD) and Fischer-344 (F-344) rats were intratracheally instilled with saline or ROFA particles. ROFA exposure produced an increase in BAL neutrophils in both SD and F-344 rats. A time-dependent increase in eosinophils occurred in SD rats but not in F-344 rats. In a subsequent study (Kodavanti et al., 1997a), male SD, Wistar (WIS), and F-344 rats (60 days old) were exposed to saline or ROFA (8.3 mg/kg) by intratracheal instillation and examined for up to 12 wk. Histology indicated focal areas of lung damage showing inflammatory cell infiltration as well as alveolar, airway, and interstitial thickening in all three rat strains during the week following exposure. Trichrome staining of the lung sections indicated a sporadic incidence of focal alveolar fibrosis at 1, 3, and 12 wk in SD rats, whereas WIS and F-344 rats showed only a modest increase in trichrome staining in the septal areas. One of the isoforms of fibronectin (Fn) mRNA was upregulated in ROFA-exposed SD and WIS rats but not in F-344 rats. These studies indicate that there is a rat strain variation in ROFA-induced fibrosis and associated Fn expression.

To determine which of the three dominant metals of ROFA were associated with the development of lung lesions and how it related to the kind of inflammatory response and

proinflammatory cytokine expression, SD rats were intratracheally instilled with either ROFA or metal sulfates (iron sulfate, vanadium sulfate, and nickel sulfate), individually or in combination of all three (at a dose equivalent to one ROFA instillate) Kodavanti et al., 1997b). Kinetics of pulmonary injury and cytokine expression profile over 96 h indicated that injury induced by Ni was greater, had a delayed onset and was persistent over 96 h. However, V caused less injury and early (3 h) cytokine gene expression. Iron was associated with mild lung lesions and early cytokine gene expression. Within 96 hours lung lesions consolidated to fibrosis in the case of V, the metal mixture, and ROFA (ROFA>metal mixture>V). In the case of Ni, lesions were associated with continued alveolar edema, hemorrhage, and inflammatory cell influx but did not consolidate to fibrosis in 96 h. Thus, of all three predominant metals, Ni accounted for the majority of the ROFA toxicity.

To further investigate the response to ROFA with differing metal and sulfate composition, male SD rats (60 days old) were exposed to ten different ROFA samples collected at various sites within a power plant (Kodavanti et al., 1998a). Animals received intratracheal instillations of either saline or a saline suspension of whole ROFA (< 3.0 μm MMAD) at three concentrations (0.833, 3.33, or 8.33 mg/kg). ROFA-induced increases in BAL fluid protein and LDH, but not neutrophilic inflammation, were associated with its water-leachable total metal, Ni, Fe, and sulfate content. However, the neutrophilic response following ROFA exposure was positively correlated with its water-leachable V content. Modest lung injury was observed with ROFA samples that contained the smallest amounts of water-leachable metals. The ability of ROFA to induce oxidative burst in AM was determined in vitro using a chemiluminescence (CL) assay. Alveolar macrophage CL signals in vitro were greatest with ROFA containing primarily soluble V and were less with ROFA containing Ni plus V. These results showed that ROFA-induced PMN influx appeared to be associated with its water-leachable V content; however, protein leakage appeared to be associated with water-leachable Ni content. ROFA-induced in vitro activation of AM was highest with ROFA containing leachable V but not with Ni plus V, suggesting that the potency and the mechanism of pulmonary injury may differ between emissions containing V and Ni.

Kadiiska et al. (1997) instilled rats with either saline or 500 μg of ROFA in saline. Neutrophils accounted for the majority of cells recovered by lavage 24 h following instillation of ROFA. An increased BAL fluid protein concentration was indicative of increased epithelial

permeability subsequent to injury. Both the influx of neutrophils and the increase in lavage protein concentration were associated with the soluble, rather than insoluble component of the ROFA. Twenty-four hours following instillation, rats were intraperitoneally injected with an aqueous solution of α-(4-pyridyl 1-oxide)-N-*tert*-butylnitrone (POBN). One hour later, the Electron Spin Resonance (ESR) spectrum of POBN radical adducts was determined in lung lipid extracts. Relative to the ESR spectrum after saline instillation, there were significant increases in the intensities of the signals after exposure to total ROFA, the soluble component of ROFA, the synthetic ROFA (a mixture of vanadyl, nickel and ferric sulfate, reflecting their concentrations in the ROFA), vanadyl sulfate ($VOSO_4$), and ferric sulfate ($Fe_2(SO_4)_3$). However, there were no significant differences in the signal intensities of the spectra associated with exposure to the insoluble component of the ROFA and nickel sulfate ($NiSO_4$). The authors concluded that ESR analysis of lung tissue demonstrates *in vivo* free radical production and that the generation of free radicals appears to be associated with soluble metals in the oil fly ash.

Broeckaert et al. (1997) investigated the effect of intratracheally instilled coal fly ash (CFA) and copper smelter dust (CMP) on the lung integrity and on the ex vivo release of TNF-α by alveolar phagocytes. Female Naval Medical Research Institute (NMRI) mice were instilled with different particles normalized for the arsenic content (20 μg/kg body weight, i.e., 600 ng arsenic/mouse) and the particle load (100 mg/kg body weight, i.e., 3 mg/mouse). Mice received tungsten carbide (WC) alone (100 mg/kg), CFA alone (100 mg/kg, i.e., 20 μg arsenic/kg), CMP mixed with WC (CMP, 13.6 mg/kg, i.e., 20 μg arsenic/kg; WC, 86.4 mg/kg) and $Ca_3(AsO_4)_2$ mixed with WC (20 μg arsenic/kg; WC, 100 mg/kg). Additional mice were studied to evaluate particle retention by measuring total arsenic retention in the lung over time. Instillation of WC induced a mild and transient (day 1) inflammatory reaction characterized by an increase of BAL fluid protein and an influx of PMNs into the alveolar compartment. Compared to WC, $Ca_3(AsO_4)_2$ produced a significant increase of BAL protein. CMP particles caused a severe but transient inflammatory reaction, while a persisting alveolitis (30 d) was observed after treatment with CFA. Compared to control saline, a marked inhibition of TNF-α release in AMs ex vivo was observed in response to lipopolysaccharide (LPS) in all groups at day 1. Cytokine production was upregulated in WC- and $Ca_3(AsO_4)_{2-}$ treated animals after 6 and 30 d, respectively. However, a 90% inhibition of TNF-α production was still observed at 30 d after administration of CMP and CFA. Although arsenic was cleared from the lung tissue 6 d after

$Ca_3(AsO_4)_2$ administration, a significant fraction persisted (10-15% of the arsenic administered) in the lung of CMP- and CFA-treated mice at day 30. It is possible that suppression of TNF-α production is dependent upon the slow elimination of the particles and their metal content from the lung.

In summary, intratracheally injected ROFA produced similar or greater inflammatory response than that produced by ambient particles at similar high doses. Although the water soluble metals in ROFA appear to play a role in the inflammatory response, the precise mechanisms of their effect and the complex interactions are not yet clear.

7.3.4.3 In Vitro Exposures

In vitro exposure is a useful technique when only limited quantities of the test material are available. Exposing respiratory cells to particles in vitro not only reduces the amount of material needed for the experiments but also provides an opportunity to investigate the mechanisms of particle toxicity. In addition, in vitro exposure allows the examination of the response to particles in only one or two cell types. Limitations of in vitro studies include difficulty in dose-response and mechanistic extrapolation. Furthermore, use of "non-cytotoxic" doses in in vitro studies does not necessarily imply that the doses are relevant to in vivo exposure situations. However, in vitro studies do not provide an approach to identify potential cellular and molecular mechanisms by which PM mediates health effects. These mechanisms can then be evaluated in vivo. In vitro/ex vivo studies are summarized in Table 7-3.

Ambient Particles

To investigate the mechanisms of the in vivo effects of PM, Kennedy et al. (1998) used cultured BEAS-2B cells to study the effect of ambient particles (TSP) collected in Provo, Utah. Similar to ROFA, Provo particles stimulated IL-6 and IL-8 production as well as increased IL-8 mRNA and enhanced expression of intercellular adhesion molecule-1 (ICAM-1) in these cells. Provo particles also stimulated IL-8 secretion in primary cultures of human bronchial epithelial cells. Cytokine secretion was preceded by activation of nuclear factor kappa B (NF-κB) and was reduced by treatment with superoxide dismutase (SOD), Deferoxamine (DEF), or N-acetylcysteine. The addition of similar quantities of Cu^{2+} as found in the Provo extract

TABLE 7-3. EFFECTS OF PARTICULATE MATTER EX VIVO

Species, Cell type, etc.	Particle or Constituent	Exposure Technique	Concentration	Particle Size (μm)	Exposure Duration	Effect of Particles	Reference
Human bronchial epithelial cells Asthmatic (ASTH) Nonasthmatic (NONA)	Diesel Exhaust Particles	In vitro	10-100 µg/ml	0.4 µm	2, 4, 6, 24 h	DEP caused no gross cellular damage. Ciliary beat frequency was attentuated at all doses. DEP caused IL-8 release at lower dose in ASTH than NONA. Higher concentrations of DEP suppressed IL-8, GM-CSF, RANTES in ASTH cells.	Bayram et al. (1998a)
Human bronchial epithelial cells (smokers)	DEP	In vitro	10-100 µg/ml	0.4 µm	24 h	DEP attenuated ciliary beating. Release of IL-8, protein, GM-CSF, SICAM-1 increased after DEP exposure.	Bayram et al. (1998b)
Human and rat alveolar macrophages	4 Urban air particles ROFA Diesel Volcanic ash Silica	In vitro exposure; 2 x 10^5 cells exposed for 2 h	Urban and diesel: 12, 27, 111, 333, 1000 μg/ml SiO_2 and TiO_2: 4, 12, 35, 167 μg/ml Fe_2O_3: 1:1, 3:1; 10:1 particles/cell ratio	Urban particles: 0.3-0.4 μm Diesel: 0.3 μm ROFA: 0.5 μm Volcanic ash: 1.8 μm Silica: 05-10 μm TiO_2: <5 μm Latex: 3.8 μm	2 h for cytotoxicity 16-18 h for cytokine assay Chemiluminescence at 30 minutes	UAP-induced cytokine production (TNF, IL-6) in AM of both species and is not related to respiratory burst or transition metals; but may be related to LPS (blocked by polymyxin B but not DEF) ROFA induced strong chemiluminescence but had weak effects on TNF production.	Becker et al. (1996)
Human AM and blood monocytes	urban air particles; St Louis SRM 1648; Washington, DC SRM 1649; Ottawa, Canada EHC-93	In vitro	33 or 100 μg/ml	0.2 to 0.7 μm	3 h, 6 h, or 18-20 h	Phagocytosis was inhibited by UAP at 18 h. UAP caused decreased expression of β_2-integrins involved in antigen presentation and phagocytosis.	Becker and Soukup (1998)
Rat alveolar macrophages	PM_{10} Mexico City 1993; voleanic ash. (MSHA)	In vitro	1-100 μg/ml	<10 μm	24 h	PM_{10} stimulated alveolar macrophages to induce upregulation of PDGF ∝ receptor on myofiboroblasts. Endotioxin and metal components of PM_{10} stimulate release of IL-β. This is a possible mechanism for PM_{10}-induced airway remodeling.	Bonner et al. (1998)

TABLE 7-3 (cont'd). EFFECTS OF PARTICULATE MATTER EX VIVO

Species, Cell type, etc.	Particle or Constituent	Exposure Technique	Concentration	Particle Size (μm)	Exposure Duration	Effect of Particles	Reference
Supercoiled DNA	PM_{10} from Edinburgh, Scotland	In vitro	996.2±181.8 μg/filter in 100 μl	PM_{10}	8 h	PM_{10} caused damage to DNA; mediated by hydroxyl radicals (inhibited by mannitol) and iron (DEF); Clear supernatant has all of the suspension activity; Free radical activity is derived either from a fraction that is not centrifugeable on a bench centrifuge or that the radical generating system is released into solution	Donaldson et al. (1997)
Rat AM	UAP DPM	In vitro	50 to 200 μg/ml	DPM: 1.1 – 1.3 μm UAP: St Louis, MO between 1974 and 1976 in a baghouse, sieved through 200-mesh (125 μm)	2 h exposure; supernatant collected 18 h post	Dose dependent increase in TNF-α, IL-6, CINC, MIP-2 gene expression by urban particles but not with DPM; Cytokine production were not related to ROS; Cytokine production can be inhibited by polymyxin B; LPS was detected on UAP but not DPM; Endotoxin is responsible for the cytokine gene expression induced by UAP in AM	Dong et al. (1996)
Primary cultures of RTE	ROFA	In vitro	5, 10, 20 $\mu g/cm^2$	Same as Dreher et al. (1997)	Analysis at 6 and 24 hours	Particle induced epithelial-cell detachment and lytic cell injury; alterations in the permeability of the cultured RTE cell layer; Increase in LDH, G-6-PDH, gluathione reductase, glutathione S-transferase; Mechanism of ROFA-induced RTE cytotoxicity involves the development of an oxidative burden.	Dye et al. (1997)
Peripheral blood monocytes	Organic extract of TSP, Italy	In vitro	42.5 μg extract/m^3 (acetone)	N/A, Collected from high volume sampler (60 m^3/h)	2 h	Superoxide anion generation was inhibited at a particulate concentration of 0.17 mg/ml when stimulated with PMA; 50% increase in LDH; disintegration of plasma membrane	Fabiani et al. (1997)
Rat AM	ROFA, iron sulfate, nickel sulfate, vanadyl sulfate Latex particles with metal complexed on the surface	In vitro (0.7 x 10^6 cells/ml)	0.01 – 1.0 mg/ml	3.6 μm MMAD	Up to 400 minutes	Increase chemiluminescence, inhibited by DEF and hydroxyl radical scavengers; solutions of metal sulfates and metal-complexed latex particles similarly elevated chemiluminescence in a dose-and time-dependent manner.	Ghio et al. (1997a)
NHBE BEAS-2B	ROFA	In vitro	5 – 200 μg/ml	3.6 μm	2 and 24 h	mRNA for ferritin did not change; ferritin protein increase; mRNA for transferrin receptor decreased, mRNA for lactoferrin increased; Transferrin decreased whereas lactoferrin increased; Deferoxamine alone increased lactoferrin mRNA	Ghio et al. (1998c)

TABLE 7-3 (cont'd). EFFECTS OF PARTICULATE MATTER EX VIVO

Species, Cell type, etc.	Particle or Constituent	Exposure Technique	Concentration	Particle Size (μm)	Exposure Duration	Effect of Particles	Reference
BEAS-2B respiratory epithelial cells.	oil fly ash	In vitro	100 μg/ml	N/A	~1h	Lactoferrin binding with PM metal occurred within 5 min. V and Fe $^{(III)}$ but not Ni bound to the lactoferrin receptor.	Ghio et al. (1999a)
BEAS-2B	Provo, UT TSP soluble and insoluble extract	In vitro	500 μg/ml	TSP	24 h	Water soluble fraction caused greater release of IL-8 than insoluble fraction. The effect was blocked by deferoxamine and presumably due to metals (Fe, Cu, Zn, Pb).	Ghio et al. (1999b)
ØX174 RF1 DNA	PM_{10} from Edinburgh, Scotland	In vitro	3.7, 7.5 μg/ml	PM_{10}	8 h	Significant free radical activity on degrading supercoiled DNA; Mainly due to hydroxyl radicals (inhibited by mannitol); Fe involvement (DEF-B conferred protection); More Fe^{3+} was released compared to Fe^{2+}, especially at pH 4.6 than at 7.2	Gilmour et al. (1996)
Hamster AM	ROFA or CAP	In vitro	0, 25, 50, 100, 200 μg/ml	CAP: 0.1 – 2.5 μm (from Harvard concentrator) TiO_2: 1 μm	30 min incubation; Analysis immediately following	Dose dependent increase in AM oxidant stress with both ROFA and CAP Increase in particle uptake; Mac-type SR mediate a substantial proportion of AM binding; particle-associated components (e.g., transition metals) are likely to mediate intracellular oxidant stress and proinflammatory activation	Goldsmith et al. (1997)
Hamster AM	CAP, ROFA, and their water-soluble and particulate fractions	In vitro	0-200 mg/ml	CAP = 0.125 ROFA = 1.0	30 min	ROFA and CAPs (water soluble components) caused increases in DCFH oxidation; CAPs samples and components showed substantial day-to-day variability in their oxidant effects; ROFA increased MIP-2 and TNF-α production in AM and can be inhibitable by NAC.	Goldsmith et al. (1998)
AM's from female CD rats.	vanadyl chloride sodium metavanadate	In vitro	10-1000 μm metavanadate	N/A	30 min	Metavanadate caused increased production of ROS. The LOEL was 50 μM	Grabowski et al. (1999)
Human PMN	Aqueous and organic extracts of TSP in Dusseldorf and Duisburg, Germany	In vitro	0.42 – 0.78 mg dust/ml	Collected by high volume sampler, 90% < 5 μm, 50% < 1μm, maximum at 0.3 – 0.45 μm Extracted using water and then dichloromethane to yield aqueous and organic extracts	Up to 35 min	PM extract alone significantly stimulated the production and release of ROS in resting but not in zymosan-stimulated PMN. The effects of the PM extracts were inhibited by SOD, catalase and sodium azide (NaN_3); Zymosan-induced LCL is inhibited by both types of extracts, but aqueous extracts have a stronger inhibitory effect.	Hitzfeld et al. (1997)

TABLE 7-3 (cont'd). EFFECTS OF PARTICULATE MATTER EX VIVO

Species, Cell type, etc.	Particle or Constituent	Exposure Technique	Concentration	Particle Size (μm)	Exposure Duration	Effect of Particles	Reference
Human AM	UAP (#1648, 1649) Volcanic ash ROFA	In vitro	0, 25, 100 200 μg/ml	Volume median diameter: ROFA 1.1 μm #1648: 1.4 μm #1649: 1.1 volcanic ash 2.3 μm	24 h	ROFA highly toxic; Urban PM toxic at 200μg/ml; ROFA produced significant apoptosis as low as 25 μg/ml; UAP produced apoptosis at 100 μg/ml; UAP and ROFA also affect AM phenotype: increase immune stimulatory while decrease immune suppressor phenotype	Holian et al. (1998)
BEAS-2B, airway epithelial cells	ROFA	In vitro	0, 0.5, 2.0 mg in 10 ml	N/A	1 h	ROFA induced production of acetaldehyde in dose-dependant fashion	Madden et al. (1999)
Male (Wistar) Rat lung macrophages	urban dust SRM 1649, TiO_2, Quartz	In vitro	0-100 μg in 1 ml	N/A	18 h	Cytotoxicity ranking was quartz > SRM 1649 > TiO_2, based on cellular ATP decrease and LDH, acid phosphatase, and β-glucuronidase release	Nadeau et al. (1996)
Human blood monocytes and neutrophils (PMN)	ambient air particles, carbon black; oil fly ash, coal fly ash	In vitro	100 μg in 0.2 ml	N/A	40 min.	ROS generation measured by LCL increased in PMN, was correlated with Si, Fe, Mn, Ti, Co content by not V, Cr, Ni, and Cu. Deferoxamine did not affect LCL suggesting that transition metals are not related to LCL.	Prahalad et al. (1999)
Human airway epithelium derived cell lines BEAS-2B (S6-subclone)	ROFA	In vitro	0, 6, 12, 25 50 μg/ml	1.96 μm	1 and 24 h	Activation of IL-6 gene by NF-κB activation and binding to specific sequences in promoter of IL-6 gene; Inhibition of NF-κB activation by DEF and NAC; Increase in PGE_2, IL-6, TNF, and IL-8; Activation NF-κB may be a critical first step in the inflammatory cascade following exposure to ROFA particles.	Quay et al. (1998)
Human airway epithelium derived cell line BEAS 2B	ROFA	In vitro	2, 20, 60 μg/cm^2	1.96 μm	24 h exposure	Epithelial cells exposed to ROFA for 24 h secreted substantially increased amounts of the PHS products prostaglandins E_2 and $F_{2\alpha}$; ROFA-induced increase in prostaglandin synthesis was correlated with a marked increase in PHS activity	Samet et al. (1996)
Human airway epithelium derived cell line BEAS	ROFA Synthetic ROFA (soluble Ni, Fe, and V)	In vitro	ROFA: 0 – 200 μg/ml Synthetic ROFA (100μg/ml): Ni, 64 μM Fe, 63 μM V, 370 μM	ROFA: 1.96 μm Synthetic ROFA: N/A (soluble)	Up to 24 h	Tyrosine phosphatase activity, which was known to be inhibited by vanadium ions, was markedly diminished after ROFA treatment; ROFA exposure induces vanadium ion-mediated inhibition of tyrosine phosphatase activity, leading to accumulation of protein phosphotyrosines in BEAS cells.	Samet et al. (1997)

TABLE 7-3 (cont'd). EFFECTS OF PARTICULATE MATTER EX VIVO

Species, Cell type, etc.	Particle or Constituent	Exposure Technique	Concentration	Particle Size (μm)	Exposure Duration	Effect of Particles	Reference
Human airway epithelium derived cell lines BEAS-2B	Particle components As, Cr, Cu, Fe, Ni, V, and Zn	In vitro	500 μM of As, F, Cr (III), Cu, V, Zn	N/A (soluble)	20 min 6 and 24 h	Noncytotoxic concentrations of As, V, and Zn induced a rapid phosphorylation of MAPK in BEAS cells; activity assays confirmed marked activation of ERK, JNK, and P38 in BEAS cells exposed to As, V, and Zn. Cr and Cu exposure resulted in a relatively small activation of MAPK, whereas Fe and Ni did not activate MAPK under these conditions; the transcription factors c-Jun and ATF-2, substrates of JNK and P38, respectively, were markedly phosphorylated in BEAS cells treated with As, Cr, Cu, V, and Zn; acute exposure to As, V, or Zn that activated MAPK was sufficient to induce a subsequent increase in IL-8 protein expression in BEAS cells.	Samet et al. (1998)
A549 ØX174 RFI DNA	Urban particles: SRM 1648, St. Louis, MO SRM 1649, Washington, DC	In vitro	1 mg/ml for Fe mobilization assay	SRM 1648: 50% < 10 μm SRM 1649: 30% < 10 μm	Up to 25 h	Single-strand breaks in DNA were induced by PM only in the presence of ascorbate, and correlated with amount of Fe that can be mobilized; Ferritin in A549 cells was increased with treatment of PM suggesting mobilization of Fe in the cultured cells.	Smith and Aust (1997)
Rat (Wistar) AM RAM cells (a rat AM cell line)	TiO_2	In vitro	20, 50, 80 μg/ml	N/A	4 h	Opsonization of TiO_2 with surfactant components resulted in a modest increase in AM uptake compared with that of unopsonized TiO_2; surfactant components increase AM phagocytosis of particles	Stringer and Kobzik (1996)
A549	ROFA, α-quartz, TiO_2	In vitro	1 mg/ml	N/A	60 min	Exposure of A549 cells to ROFA, α-quartz, but not TiO_2, caused increased IL-8 production in TNF-α primed cells in a concentration-dependent manner	Stringer and Kobzik (1998)
A549	TiO_2, Fe_2O_3, CAPs, and the fibrogenic particle α-quartz	In vitro	TiO_2 [40 μg/mL], Fe_2O_3 [100 μg/mL], α-quartz [200 μg/mL], or CAPs [40 μg/mL]	N/A	24 h	TiO_2 > Fe_2O_3 > α-quartz > CAP in particle binding; binding of particle was found to be calcium-dependent for TiO_2 and Fe_2O_3, while α-quartz binding was calcium-independent; scavenger receptor, mediate particulate binding; α-quartz, but not TiO_2 or CAP, caused a dose-dependent production of IL-8;	Stringer et al. (1996)
RLE-6TN cells (type II like cell line)	$PM_{2.5}$, Burlington, VT; Fine/ultrafine TiO_2	In vitro	1, 2.5, 5, 10 μg/ml	$PM_{2.5}$: 39 nm Fine TiO_2: 159 nm UF TiO_2: 37 nm	24 and 48 h exposure	Increases in *c-jun* kinase activity, levels of phosphorylated c-Jun immunoreactive protein, and transcriptional activation of activator protein-1-dependent gene expression; elevation in number of cells incorporating 5'-bromodeoxyuridine	Timblin et al. (1998)

TABLE 7-3 (cont'd). EFFECTS OF PARTICULATE MATTER EX VIVO

Species, Cell type, etc.	Particle or Constituent	Exposure Technique	Concentration	Particle Size (μm)	Exposure Duration	Effect of Particles	Reference
BEAS-2B human bronchial epithelial cells	ROFA Birmingham, AL. 188 mg/gr of VO	In vitro	100 μg/ml	N/A	2-6 h	ROFA caused increased intracellular Ca^{++}, IL-6, IL-8, TNF-α through activation of capsicin- and pH-sensitive receptors	Veronesi et al. (1999)

AM - Alveolar Macrophage
CAP - Concentrated Ambient Particles
CB - Carbon Black
CFA - Coal Fly Ash
CMP - Copper Smelter Dust
DEF - Deferoxamine or Desferrioxamine
DMTU - Dimethylthiourea
DNA - Deoxyribonucleic Acid
DPM - Diesel Particulate Matter
ERK - Extracellular Receptor Kinases
F-344 - Fischer 344
Fe_2O_3 - Iron Oxide
Fn - Fibronectin
G-6-PDH - Glucose-6-Phosphate Dehydrogenase
IL-6; Il-8 - Interleukin 6,8
JNK - Jun H_2-Terminal Kinases
LCL - Luminol Enhanced Chemiluminescence
LDH - Lactate Dehydrogenase
LPS - Liopopolysaccharide (Endotoxin)
MAPK - Mitogen-Activated Protein Kinases
MCT - Monocrotaline
MMAD - Mass Median Aerodynamic Diameter
mRNA - Messenger Ribonucleic Acid
NF-κB - Nuclear factor-kappa B
NHBE - Normal Human Broncial Epithelial Cells
PHS - Prostaglandin H Synthetase
PMA - Phorbol Myristate Acetate
PMN - Neutrophil
PTFE - Polytetrafluoroethylene
ROFA - Residual Oil Fly Ash
RTE - Rat Tracheal Epithelial Cells
SD - Sprague Dawley
SICAM-1 - Soluble Intercellular Adhesion Molecule-1
SiO_2 - Silicon Dioxide
SOD - Superoxide Dismutase
SR - Scavenger-Type Receptors
Ti O_2 - Titanuim Dioxide
TNF - Tumor Necrosis Factor
TSP - Total Suspended Paticles
UAP - Urban Air Particles
UF - Ultrafine
WC - Tungsten Carbide
Wis - Wistar

replicated the biological effects observed with particles alone. When normal constituents of airway lining fluid (mucin or ceruloplasmin) were added to BEAS cells, particulate-induced secretion of IL-8 was modified. Mucin reduced IL-8 secretion, while ceruloplasmin significantly increased IL-8 secretion and activation of NF-κB. The authors suggest that copper ions may cause some of the biologic effects of inhaled PM in the Provo region and may provide an explanation for the sensitivity of asthmatics to Provo PM, seen in epidemiologic studies.

Goldsmith et al. (1998) investigated intracellular oxidant production in normal hamster AMs upon in vitro exposure to concentrated ambient particles (CAPs), ROFA, and their water-soluble and particulate fractions. ROFA and CAPs caused increases in dichlorofluorescin (DCFH) oxidation, a fluorescent measure of intracellular reactive oxygen species (ROS) production, comparable to the positive control, phorbol myristate acetate (PMA). The water-soluble component of both CAPs and ROFA significantly increased AM oxidant production over negative control. CAPs samples and components showed substantial day-to-day variability in their oxidant effects. Metal chelation by DEF (1 mM) caused significant inhibition of PM-induced AM oxidant production. ROFA exposure resulted in increased macrophage inflammatory protein-2 (MIP-2) mRNA in AMs and in increased TNF-α production by the monocyte-macrophage cell line, RAW 264.7. TNF-α production was inhibitable by the antioxidant, N-acetylcysteine (NAC). The data suggest that metal components of urban air PM can significantly contribute to the ability of particles to cause oxidant stress and cytokine production in AMs.

Fabiani et al. (1997) investigated the response of peripheral blood monocytes to extracts of ambient particles. Particles in 1 m^3 of air were collected on glass fiber filters and were extracted with acetone for 18 h. At a particulate concentration of 0.17 mg/mL, the production of superoxide (O_2^-) in peripheral blood monocytes was reduced to 22% and 40% of the control values when the cells were stimulated with PMA and Zymosan, respectively. Concomitantly, there was a release of LDH into the supernatant (50% of the total cellular LDH activity), indicating that a large proportion of cells were damaged by the treatment with the PM extract, and some cytosolic components were released from the cells. Giemsa staining of the treated monocytes revealed the presence of many cells with a dispersed cytosol; the nucleus, although not destroyed, had a different shape. This study suggested that the airborne particulate matter has a toxic effect that induces the disintegration of the plasma membrane. Cytosolic factors (proteins

and coenzymes) necessary for O_2^- production leak from the cells and O_2^- generation is therefore reduced. It remains to be determined whether this phenomenon also occurs in vivo.

Becker and Soukup (1998) examined the effect of urban air particles (UAP) on human alveolar macophages and blood monocytes in vitro. UAP decreased expression of receptors important for phagocytosis of opsonized microbes and for interaction with extracellular matrix components. These responses suggest that clearance of microbes from the lung could be impaired by exposure to UAP.

The effects of water soluble as well as organic components of ambient PM were investigated by exposing human PMN to PM extracts (Hitzfeld et al., 1997). PM was collected with high volume samplers in two German cities, Dusseldorf and Duisburg; these sites have high traffic and high industrial emissions, respectively. The collected particles were extracted using water and then dichloromethane, resulting in an aqueous and an organic extract. The production of ROS was determined using luminol-enhanced chemiluminescence (LCL) of resting and zymosan-stimulated PMN. Organic, but not aqueous, extracts of PM alone significantly stimulated the production and release of ROS in resting human PMN. The effects of the PM extracts were inhibited by SOD, catalase and sodium azide (NaN_3). Zymosan-induced LCL was, however, diminished by coincubation with PM extracts, with the aqueous extracts having a stronger inhibitory effect. The mineralogical and chemical characterization of the PM showed that the particles were small (>90% <5μm) and consisted mainly of quartz and other silicates with no difference between the two sites. These authors speculated that PAHs in the organic extract and metals in the aqueous extract may be responsible for the biologic effects.

Mechanisms other than oxidative stress have been proposed to explain cytokine production by epithelial cells. Dong et al. (1996) suggest that activation of cytokine gene expression and secretion in rat AM treated with UAP (collected in St. Louis) is due to the presence of endotoxin on the particles. Cytokine production (TNF-α, IL-1, Il-6, CINC, and MIP-2) was increased in macrophages following treatment with 50 to 200 μg/mL of urban PM. The authors suggest that cytokine expression was not related to ROS because antioxidants, such as catalase, had no effect on TNF-α secretion. However the collection system for the UAP did not exclude large particles and biological materials. Given previous observations that LPS stimulates cytokine secretion in AM (Yoo et al., 1995), the authors suggest that LPS is responsible for the observed cytokine responses. The UAP-induced TNF-α secretion was completely abrogated by treatment with

polymyxin B, an antibiotic that blocks LPS-associated activities (Morrison and Jacobs, 1976). Polymixin B is also an inhibitor of protein kinase C (Cave and Apstein, 1996) and an antagonist of calmodulin (Hegemann et al., 1991) and may alter cellular responses by mechanisms other than inhibition of LPS. Thus, polymixin B may inhibit PM cellular responses by mechanisms other than LPS inhibition. Extrapolation of these in vitro results to a potential role for endotoxin in the adverse effects of ambient PM must be done with caution because the investigators could not exclude the possibility that the presence of endotoxin with the PM was not due to inadvertent contamination during the year long collection process or from the handling of the particles.

Urban PM_{10} collected from north, south, and central regions of Mexico City was used with SD rat AM to examine PM effects on platelet derived growth factor (PDGF) receptors on lung myofibroblasts (Bonner et al., 1998). Mexico City PM_{10} (but not volcanic ash) stimulated secretion of upregulatory factors for the PDGFα receptor, possibly via IL-1β. In the presence of an endotoxin-neutralizing protein, the Mexico City PM_{10} effect on PDGF was partially blocked, suggesting that LPS was partially responsible for the effect of the PM_{10} on macrophages. In addition, both LPS and vanadium (both present in the PM_{10}) acted directly on lung myofibroblasts. However, the V levels in Mexico City PM_{10} were probably not high enough to exert an independent effect. The authors concluded that PM_{10} exposure may lead to airway remodeling by enhancing myofibroblast replication and chemotaxis.

ROFA

Several *in vitro* methodologies have been employed to better examine the role of oxidative stress in particle-induced lung injury. Carter et al. (1997) exposed normal human bronchial epithelial (NHBE) cells for either 2 or 24 h to 0, 5, 50, or 200 μg/mL ROFA. NHBE cells exposed to ROFA produced significant amounts of IL-8, IL-6 and TNF, as well as mRNAs coding for these cytokines. Increases in cytokine production, but not m-RNA expression, were dose-dependent. The cytokine production was inhibited by the addition of either the metal chelator, DEF, or the free radical scavenger, DMTU. In addition, the authors reported that V containing compounds, but not Fe or Ni sulfates, mimicked the effects of ROFA. The authors suggest that certain metals associated with ROFA may be responsible for the production and release of inflammatory mediators by the respiratory tract epithelium and that these mediators may contribute to the toxic effects of PM. Furthermore, the finding that the free radical

scavenger DMTU effectively prevents the induction of IL-6 and IL-8 mRNA expression by ROFA is consistent with an oxidant-dependent mechanism.

Dye et al. (1997) exposed primary cultures of rat tracheal epithelial (RTE) cells to suspensions of ROFA (5, 10, or 20 $\mu g/cm^2$) for 24 h. ROFA exposure resulted in cytotoxicity and detachment of cells from the collagen matrix, along with altered permeability of the RTE cell layer. In addition ROFA exposure caused the cellular glutathione levels to decrease, producing a condition of oxidative stress. Treatment with buthionine sulfoxamine, an irreversible inhibitor of the rate-limiting enzyme involved in glutathione synthesis (γ-glutamyl cysteine synthetase) augmented ROFA-induced cytotoxicity. While treatment with DMTU inhibited ROFA-induced LDH release and permeability changes in a dose-dependent manner, inhibition of nitric oxide synthesis had no effect on ROFA toxicity. The authors suggested that ROFA-induced RTE cell injury may be mediated by hydroxyl-radical-like ROS (scavenged by DMTU) that are generated via non-nitric oxide pathways.

Using a human airway epithelial cell line (BEAS-2B), Quay et al. (1998) observed that ROFA stimulated a time- and dose-dependent increase in IL-6 mRNA, which was preceded by the activation of nuclear proteins binding to the NF-κB sequence motif in the IL-6 promoter region. Transient transfection of BEAS-2B cells with the 5' promoter region of the IL-6 gene linked to a luciferase reporter gene confirmed that NF-κB binding is necessary for the transcription of IL-6 mRNA. The IL-6 response was inhibited by the metal chelator DEF and the free radical scavenger NAC, suggesting that the activation of NF-κB may be mediated through ROS generated by transition metals found in ROFA. These data suggest that activation of NF-κB may therefore be a critical first step in the inflammatory cascade following exposure to ROFA particles.

Prostaglandin metabolism in cultured human airway epithelial cells (BEAS-2B and NHBE) exposed to ROFA was investigated by Samet et al. (1996). Epithelial cells exposed to ROFA for 24 h secreted substantially increased amounts of prostaglandins E2 and F2α. The ROFA-induced increase in prostaglandin synthesis was correlated with a marked increase in activity of the PHS-2 form of prostaglandin H synthase. Increases in PHS2 mRNA were evident by 2 h of continuous ROFA exposure. In contrast, expression of the PHS1 form of the enzyme was not affected by ROFA treatment of airway epithelial cells. These data show that exposure to ROFA

induces PHS2 expression, leading to increased prostaglandin synthesis in cultured human airway epithelial cells.

Samet et al. (1997) also investigated the effect of ROFA on protein tyrosine phosphate metabolism in BEAS-2B cells. Non cytotoxic levels of ROFA induced a significant dose- and time-dependent increase in protein tyrosine phosphate, an important regulator of signal transduction leading to cell growth and proliferation. ROFA-induced increases in protein phosphotyrosines were associated with its soluble fraction and were mimicked by vanadyl [V(IV)]- and vanadate [V(V)]-containing solutions. Tyrosine phosphatase activity is known to be inhibited by V. Tyrosine kinase activity was unaffected. Ferrous, ferric, and nickel (II) ion solutions failed to increase phosphotyrosine levels. It is possible that ROFA exposure induces V ion-mediated inhibition of tyrosine phosphatase activity, leading to accumulation of protein phosphotyrosines in BEAS cells. These findings demonstrate that ROFA exposure disrupts protein tyrosine phosphate homeostasis in BEAS cells.

Stringer and Kobzik (1998) observed that "primed" lung epithelial cells exhibited enhanced cytokine responses to PM. Compared to normal cells, exposure of TNF-α-primed A549 cells to ROFA or α-quartz caused increased IL-8 production in a concentration-dependent manner for particle concentrations ranging from 0-200 μg/ml. Addition of the antioxidant NAC (1.0 mM) decreased ROFA and α-quartz-mediated IL-8 production by approximately 50% in both normal and TNF-α-primed A549 cells. Exposure of A549 cells to ROFA caused an increase in oxidant levels that could be inhibited by NAC. These data suggest that (1) lung epithelial cells primed by inflammatory mediators show increased cytokine production after exposure to PM, and (2) oxidant stress is an important mechanism for this response.

Becker et al. (1996) suggested that the response elicited by oil fly ash (OFA) or UAP may not be due solely to metal components. In this study, AM were tested for a chemiluminescence response (ROS generation) induced by the particles, as well as for IL-6 and TNF-α production. The OFA dose ranged from 10-1000 μg per 2-3 x 10^5 AM. Acute cytotoxicity of OFA and SiO_2 was observed above 100 μg in both human and rat AMs (LDH release at 2 h). Diesel particulate matter (DPM) was found to be nontoxic even at the highest dose. However, after 20 h of coincubation, UAP concentrations >167 μg/ml were also somewhat cytotoxic. Subcytotoxic concentrations of OFA induced a strong immediate chemiluminescence response by AMs. A small but significant chemiluminescence response was also induced by two out of three UAP

tested, but no chemiluminescence was generated in response to DPM. The magnitude of particle-induced chemiluminescence was not predictive of a cytokine response by either human or rat AMs. TNF-α and IL-6 production was strongly induced by UAP, but not DPM or OFA, over a range of noncytotoxic concentrations of particles. The AM cytokine response to UAP was partly inhibitable by polymyxin B, but not by the iron chelator DEF, indicating that endotoxin, but not transitional iron, induced IL-6 production in the UAP preparations.

In summary, exposure of lung cells to non-cytotoxic concentrations of ambient PM or ROFA leads to increased production of cytokines and the effects may be mediated, at least in part, through production of ROS. Day-to-day variations in the components of PM which are critical to eliciting the response are also suggested. The involvement of organic components in ambient PM as well as ROFA was also suggested in some studies.

7.3.5 Susceptibility to the Effects of PM Exposure

Susceptibility of an individual to adverse health effects of PM can vary depending upon a variety of host factors such as age, nutritional status, physiological activity profile, genetic predisposition, or preexistent disease. The potential for pre-existent disease to alter adverse response to toxicant exposure is widely acknowledged but poorly understood. Due to inherent variability and ethical concerns associated with using diseased subjects in clinical research studies, a solid database on human susceptibilities is lacking. For more control over both host and environmental variables, animal models are often used. However, care must be taken in extrapolation from animal models of human disease to humans. Rodent models of human disease, their use in toxicology and the criteria for judging their appropriateness as well as their limitations have been reviewed (Kodavanti et al., 1998b; Kodavanti and Costa, 1999).

7.3.5.1 Effects of PM on Cardiopulmonary Compromised Hosts

Epidemiological studies suggest there may be subsegments of the population that are especially susceptible to effects from inhaled particles (see Chapter 6). The elderly with chronic cardiopulmonary disease, those with pneumonia and possibly other lung infections, and those with asthma (at any age) appear to be at higher risk than healthy people of similar age. Most toxicology studies have used healthy adult animals. Few studies have examined effects of ambient particles in compromised host models. Costa and Dreher (1997) used a rat model of

cardiopulmonary disease to explore the question of susceptibility and the possible mechanisms by which PM effects are potentiated. Rats with advanced monocrotaline (MCT)-induced pulmonary vasculitis/hypertension were given intratracheal instillations of ROFA (0, 0.25, 1.0 and 2.5 mg/rat). The MCT-treated animals had a marked neutrophilic inflammation. In the context of this inflammation, ROFA induced a 4-5 fold increase in BAL PMNs. There was an increased mortality at 96 h that was ROFA-dose dependent. The results of this study indicate that PM enhanced the neutrophilic inflammation and mortality in MCT-treated animals.

The manner in which treatment with MCT can alter the response of rats to inhaled particles was examined by Madl and colleagues (1998). Rats were exposed to fluorescent colored microspheres (1 μm) 2 weeks after treatment with MCT. In vivo and in vitro phagocytosis of the microspheres was altered in the MCT-treated rats in comparison with control animals. Fewer microspheres were phagocytized in vivo by alveolar macrophages and there was a concomitant increase in free microspheres overlaying the epithelium at airway bifurcations. The decrease in in vivo phagocytosis was not accompanied by a similar decrease in vitro. Macrophage chemotaxis, however, was significantly impaired in MCT-treated rats compared with control rats. Thus, MCT-treatment appeared to impair particle clearance from the lungs via inhibition of macrophage chemotaxis.

The sulfur dioxide (SO_2)-induced model of chronic bronchitis has also been used to examine the potential interaction of PM with pre-existing lung disease. Clarke and colleagues pretreated rats for 6 weeks with air or 170 ppm SO_2 for 5 hours/day and 5 days/week (Clarke et al., 1999). Exposure to concentrated air particles for 5 hours/day for 3 days at an average concentration of 515 $\mu g/m^3$ produced changes in pulmonary function as evidenced by significant increases in tidal volume in both air- and SO_2-pretreated rats. Exposure to concentrated ambient PM also produced significant changes in cellular and biochemical markers in lavage fluid. In comparison to control animal values, protein was increased approximately 3-fold in SO_2-pretreated animals exposed to concentrated ambient PM. Lavage fluid neutrophils and lymphocytes were significantly increased in both pretreatment groups of rats exposed to concentrated ambient PM, with greater increases in both cell types in the SO_2-pretreated rats. Thus, exposure to concentrated ambient PM produced adverse changes in the respiratory system in both normal rats and in a rat model of chronic bronchitis. Although the exposure concentrations were much higher than those encountered in urban centers in North America,

these findings are important because few studies have used actual ambient urban PM in inhalation exposures.

In a study to investigate the influence of age on susceptibility to PM, Johnston et al. (1998) exposed 8 week old mice (young) and 18 month old mice (old) to polytetrafluoroethylene fumes (PTFE) (0, 10, 25, and 50 $\mu g/m^3$) for 30 min. Lung lavage endpoints (PMN, protein, LDH, and β-glucuronidase) as well as lung tissue mRNA levels for various cytokines, metallothionein and for Mn superoxide dismutase were measured 6 hours following exposure. Protein, lymphocyte, PMN, and TNF-α mRNA levels were increased in older mice when compared to younger mice. These findings suggest that the inflammatory response to PTFE fumes is altered with age, being greater in the older animals. Although Teflon particles are not a valid surrogate for ambient ultrafine particles, this study did provide evidence to support the hypothesis that particle-induced pulmonary inflammation is different between the young and old organism.

In summary, although these studies are just emerging and are only now being replicated or followed more thoroughly to investigate the mechanisms, they do provide evidence of enhanced susceptibility to inhaled PM in "compromised" hosts.

7.3.5.2 Effect of PM on Allergic Hosts

Relatively little is known about the effects of inhaled particles on humoral (antibody) or cell-mediated immunity. Alterations in the response to a specific antigenic challenge have been observed in animal models at high concentrations of acid sulfate aerosols (above 1,000 $\mu g/m^3$) (Pinto et al., 1979; Kitabatake et al., 1979; Fujimaki et al., 1992). Several studies have reported an enhanced response to non-specific bronchoprovocation agents, such as acetylcholine and histamine, after exposure to inhaled particles. This non-specific airway hyperresponsiveness, a central feature of asthma, occurs in animals and human subjects exposed to sulfuric acid under controlled conditions (Gearhart and Schlesinger, 1986; Utell et al., 1983b). Although, its relevance to specific allergic responses in the airways of atopic individuals is unclear, it demonstrates that the airways of asthmatics may become sensitized to either specific or non-specific triggers that could result in increases in asthma severity and asthma-related hospital admissions (Peters et al., 1997; Jacobs et al., 1997; Lipsett et al., 1997).

Nel et al. (1998) have suggested that the rise in the U.S. prevalence rate for allergic rhinitis (5% in the 1950s to about 20% in the 1980s) may be related to increased DPM, in addition to other combustion related PM. Combustion particles may also serve as carrier particles for allergens (Knox et al., 1997).

A number of in vivo and in vitro studies have demonstrated that DPM can alter the immune response to challenge with specific antigens and suggest that DPM may act as an adjuvant. These studies have shown that treatment with DPM enhances the secretion of antigen-specific IgE in mice (Takano et al., 1997) and in the nasal cavity of human subjects (Diaz-Sanchez et al., 1996, 1997; Ohtoshi et al., 1998). Because IgE levels play a major role in allergic asthma (Wheatley and Platts-Mills, 1996), upregulation of its production could lead to an increased response to inhaled antigen in particle-exposed individuals (See Table 7-4).

Only a small number of studies have examined the mechanisms underlying the enhancement of allergic asthma by ambient urban particles. Ohtoshi et al. (1998) reported that a coarse size-fraction of resuspended ambient PM, collected in Tokyo, induced the production of granulocyte macrophage colony stimulating factor (GMCSF), an upregulator of dendritic cell maturation and lymphocyte function, in human airway epithelial cells in vitro. In addition to increased GMCSF, epithelial cell supernatants contained increased IL-8 levels when incubated with DPM, a principal component of ambient particles collected in Tokyo. Although, the sizes of the two types of particles used in this study were not comparable, the results suggest that ambient PM, or at least the DPM component of ambient PM, can upregulate the immune response to inhaled antigen through GMCSF production. Similarly, Tokano et al. (1998) reported airway inflammation, airway hyperresponsiveness, and increased GM-GSF and IL-5 in diesel exhaust exposed mice.

Gavett et al. (1999) have investigated the effects of ROFA (intratracheal instillation) in ovalbumin (OVA) sensitized and challenged mice. ROFA induced inflammatory and physiological responses in the OVA mice that were related to increases in Th2 cytokines (IL-4, IL-5). ROFA induced greater than additive increases in eosinophil numbers and in airway responsiveness to methacholine.

Goldsmith et al. (1999) have compared the effect of inhalation of concentrated ambient PM for 6 hours/day for 3 days versus the effect of a single exposure to a ROFA leachate aerosol on the airway responsiveness to methacholine in OVA-sensitized mice. Daily exposure to ROFA

TABLE 7-4. IMMUNOLOGICAL EFFECTS OF PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle	Exposure Technique	Mass Concentration (μg) or ($\mu g/m^3$)	Particle Characteristics and Size (μm)	Exposure Duration	Respiratory Effects of Inhaled Particles	Reference
Rats, Fischer 344, males, 10 weeks	ammonium metavanadate	Nose-only inhalation, aqueous aerosol	2000 $\mu g/m^3$ as vanadium	0.32 μm aqueous aerosol	8 hours/day for 4 days	Increased PMN, PAM, LDH, and protein in BAL. Immune competence of PAM also inhibited.	Cohen et al. (1996)
Human subjects, with and without seasonal allergies	DPM	200 μl aerosol delivered directly into each naris.	150 μg of particles per naris	not specified	Single treatment with vehicle or particles	Enhanced expression of IL-4, IL-6, and IL-13, cytokines known to be B-cell proliferation factors; increases in several other cytokines mRNA; increased IgE in nasal lavage fluid.	Diaz-Sanchez et al. (1996)
Human subjects with allergic rhinitis and positive skin test to ragweed	DPM with or without ragweed antigen	200 μl aerosol delivered directly into each naris	150 μg of particles per naris	not specified	Single treatment with ragweed antigen followed by a single treatment with antigen and particles	Combined treatment with ragweed antigen and particles resulted in significantly greater antigen-specific IgE and IgG4. Combined challenge also decreased expression of Th1-type cytokines and increased expression of IL-4, IL-5, IL-10, and IL-13.	Diaz-Sanchez et al. (1997)
Human airway epithelial cells	UAP, DPM	In vitro	2.5 to 2500 μg/ml UAP and 10 to 100 μg/ml DPM	UAP = 7 to 10 μm; DPM = mean diameter of 0.4 μm	Treated in vitro for up to 48 h	Increased release of both GMCSF and IL-8 by epithelial cells treated with DPM, whereas only GMCSF was released by epithelial cells treated with UAP.	Ohtoshi et al. (1998)
Mice, ICR and W/W^-, male, 4 weeks	DPM	Tracheal instillation	100 or 200 μg per instillation	not specified	Instilled once/week for 5 to 16 weeks	Repeated instillation of DPM produced goblet cell hyperplasia, eosinophilia, airway constriction, and airway hyperresponsiveness to acetylcholine. These changes were largely blocked by treatment with PEG-derivitized superoxide dismutase.	Sagai et al. (1996)

TABLE 7-4 (cont'd). IMMUNOLOGICAL EFFECTS OF PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle	Exposure Technique	Mass Concentration (μg) or ($\mu g/m^3$)	Particle Characteristics and Size (μm)	Exposure Duration	Respiratory Effects of Inhaled Particles	Reference
Mice, ICR, male, 6 to 7 weeks	DPM with or without ovalbumin	Intratracheal instillation	100 μg per instillation	mean diameter of 0.4 μm	Instilled once/week for 6 or 9 weeks	Enhanced production of antigen-specific IgG and IgE in combined DPM/ovalbumin animals compared to ovalbumin-alone animals. A similar increase in inflammatory cells and cytokines in lavage fluid of animals treated with DPM/ovalbumin.	Takano et al. (1997)
Transformed IgE producing human B cell line	organic extract of PAH-DPM	*in vitro*	0.1 ng/ml PAH-DPM	dichloromethane extraction of large chain aggregates with individual particles <0.1 μm	Treated *in vitro* for 72 hours	PAH-DPM increased IgE production and altered the levels of epsilon mRNA variants, but did not increase cytokine production.	Tsien et al. (1997)

DPM - Diesel Exhaust Particles
UAP - Urban Air Particles
IL-4, IL-5, 1L-6, IL-8, IL-10, IL-13 - Interleukins
PEG - Polyethylene Glycol
IgE, IgG_4 - Immunoglobulins
Th-1 T1 Helper Cell
GMCSF - Granulocyte Macrophage Colony Stimulating Factor

leachate aerosols significantly enhanced the airway hyperresponsiveness in OVA-sensitized mice. Importantly, exposure to concentrated ambient PM (average concentration of 787 $\mu g/m^3$) had no effect on airway responsiveness in 6 separate experiments. Thus, the effect of the ROFA leachate aerosols on the induction of airway hyperresponsiveness in allergic mice was significantly different than that of a high concentration of concentrated ambient PM. Although airway responsiveness was examined at only one post-exposure time point, these findings suggest that a great deal of caution should be used in interpreting the results of studies using ROFA particles or leachates in the attempt to investigate the biologic plausibility of the adverse health effects of PM.

Hamada et al. (1999) have examined the effect of ROFA leachate aerosol in a neonatal mouse model of allergic asthma. OVA-sensitized, neonatal mice developed airway hyperresponsiveness, eosinophilia, and elevated serum anti-ovalbumin IgE after a challenge with inhaled OVA. Exposure to the ROFA leachate aerosol had no marked effect on the airway responsiveness to inhaled methacholine in non-sensitized mice, but did enhance the airway hyperresponsiveness to methylcholine produced in OVA-sensitized mice. No other interactive effects of ROFA exposure with OVA were observed. Lambert et al. (1999) also examined the effect of ROFA on a rodent model of pulmonary allergy. Rats were instilled intratracheally with 200 or 1,000 μg ROFA 3 days prior to sensitization with house dust mite antigen. HDM sensitization after 1000 μg ROFA produced increased eosinophils, LDH, BAL protein, and IL-10 relative to HDM alone. The immediate bronchoconstrictive and associated antigen-specific IgE response to a subsequent antigen challenge was increased in the ROFA-treated group in comparison with the control group. Together, these studies suggest the components of ROFA can augment the immune response to antigen.

Several other studies have examined in greater detail the contribution to allergic asthma of the particle component and the organic fraction of DPM. Tsien et al. (1997) treated transformed IgE-producing human B lymphocytes in vitro with the organic extract of DPM. The organic phase extraction had no effect on cytokine production but did increase IgE production. Moreover, these experiments determined that DPM appeared to be acting on cells already committed to IgE production, thus suggesting a mechanism by which the organic fraction of combustion particles can directly affect B cells and influence human allergic asthma.

Cultured epithelial cells from atopic asthmatics show a greater response to diesel particulate matter (DPM) exposure when compared with cells from non-atopic non-asthmatics. IL-8, GM-CSF, and soluble ICAM-1 increased in response to DPM at a concentration of 10 μg/ml DPM (Bayram et al., 1998a,b). This study suggests that particles could modulate airway disease through their actions on airway epithelial cells. This study also suggests that bronchial epithelial cells from asthmatics are different from those of nonasthmatics in regard to their mediator release in response to DPM.

Sagai and colleagues (1996) repeatedly instilled mice with DPM for up to 16 weeks and found increased numbers of eosinophils, goblet cell hyperplasia, and non-specific airway hyperresponsiveness, changes which are central features of chronic asthma (National Institutes of Health, 1997). Takano et al. (1997) extended this line of research and examined the effect of repeated instillation of DPM on the specific response to antigen (OVA) in mice. They observed that antigen-specific IgE and IgG levels were significantly greater in mice repeatedly instilled with both DPM and OVA. Because this upregulation in antigen-specific immunoglobulin production was not accompanied by an increase in inflammatory cells or cytokines in lavage fluid, it would suggest that, in vivo, DPM may act directly on immune system cells, as described in the work by Tsien et al. (1997).

Diaz-Sanchez and colleagues (1996) have continued to study the mechanism of DPM-induced upregulation of allergic response in the nasal cavity of human subjects. In one study, a 200 μl aerosol bolus containing 0.15 mg of DPM was delivered into each naris of subjects with or without seasonal allergies. In addition to increases in IgE in nasal lavage fluid (NAL), they found an enhanced production of IL-4, IL-6, and IL-13, cytokines known to be B cell proliferation factors. The levels of several other cytokines were also increased, suggesting a general inflammatory response to a nasal challenge with DPM. In a following study, these investigators delivered ragweed antigen, alone or in combination with DPM, on two occasions, to human subjects with both allergic rhinitis and positive skin tests to ragweed (Diaz-Sanchez et al. 1997). They found that the combined challenge with ragweed antigen and DPM produced significantly greater antigen-specific IgE and IgG4 in NAL. A peak response was seen at 96 h postexposure. The combined treatment also induced expression of IL-4, IL-5, IL-10, and IL-13, with a concomittant decrease in expression of Th1-type cytokines. Although the treatments were not randomized (antigen alone was given first to each subject), the investigators reported that

pilot work showed no interactive effect of repeated antigen challenge on cellular and biochemical markers in NAL. DPM also resulted in the nasal influx of eosinophils, granulocytes, monocytes, and lymphocytes as well as production of various inflammatory mediators. The combined DPM plus ragweed exposure did not increase the rhinitis symptoms beyond those of ragweed alone.

Blomberg et al. (1998) observed a 10-fold increase in NAL fluid ascorbate concentration after a 1 h exposure to diluted diesel exhaust (300 $\mu g/m^3$ particles and 1.6 ppm NO_2). However, there were no effects on BAL ascorbate levels. Rudell et al. (1990) had previously shown increased BAL neutrophils in nonsmoking subjects exposed to 100 $\mu g/m^3$ of DPM in diesel exhaust (gases were present). Thus, diesel exhaust (particles and gases) can produce an enhanced response to antigenic material in the nasal cavity. Extrapolation of these findings, of enhanced allergic response in the nose, to the lung, would suggest that ambient combustion particles containing DPM may have significant effects on allergic asthma. These studies provide biological plausibility for the exacerbation of allergic asthma associated with episodic exposure to PM. Although DPM may make up only a fraction of the mass of urban PM, because of their small size, DPM may represent a significant fraction of the ultrafine particle mode in urban air, especially in cities and countries that rely heavily on diesel-powered vehicles.

7.3.5.3 Resistance to Infectious Disease

The development of an infectious disease requires both the presence of the appropriate pathogen, as well as host susceptibility to the pathogen. There are numerous specific and non-specific anti-microbial host defenses against microbes, and the ability of inhaled particles to modify resistance to bacterial infection could result from a decreased ability to clear or kill microbes. Rodent infectivity models have frequently been used to examine the effect of inhaled particles on host defense and infectivity. Mice or rats are challenged with a bacterial or viral load either before or after exposure to the particles (or gas) of interest; mortality rate, survival time, or bacterial clearance are then examined. A number of studies which have used the infectivity model to assess the effect of inhaled PM were discussed previously (U.S. Environmental Protection Agency, 1982, 1989, 1996a). In general, acute exposure to sulfuric acid aerosols at concentrations up to 5,000 $\mu g/m^3$ were not very effective in enhancing mortality in a bacterially-mediated murine model. In rabbits, however, sulfuric acid aerosols altered antimicrobial defenses after exposure for 2 hours/day for 4 days to 750 $\mu g/m^3$ (Zelikoff et al.,

1994). Acute or short term repeated exposures to high concentrations of relatively inert particles have produced conflicting results. Carbon black (10,000 $\mu g/m^3$) was found to have no effect on susceptibility to bacterial infection (Jakab, 1993), while a very high concentration of TiO_2 decreased the clearance of microbes and the bacterial response of lymphocytes isolated from mediastinal lymph nodes (Gilmour et al., 1989a,b). In addition, exposure to DPM has been shown to enhance the susceptibility of mice to the lethal effects of some, but not all, microbial agents (Hatch et al., 1985; Hahon et al., 1985). Thus, the pulmonary response to microbial agents has been shown to be altered at relatively high particle concentrations in animal models. Moreover, these effects appear to be highly dependent on the microbial challenge and the test animal studied. Pritchard et al. (1996) observed in rats exposed to particles with a high concentration of metals (e.g., ROFA), that the increased mortality rate after streptococcus infection was associated with the amount of metal in the PM.

Despite the reported association between ambient PM and deaths due to pneumonia (Schwartz, 1994), there are few recent studies which have examined the mechanisms which may be responsible for the effect of PM on infectivity. In one study, Cohen and colleagues (1997) examined the effect of inhaled V on immunocompetence. Healthy rats were repeatedly exposed to 2 mg/m^3 V, as ammonium metavanadate, and then instilled with polyinosinic-polycytidilic acid (poly I:C), a double-stranded polyribonucleotide which acts a potent immunomodulator. Induction of increases in lavage fluid protein and neutrophils was greater in animals pre-exposed to V. Similarly, IL-6 and interferon-gamma were increased in V-exposed animals. Alveolar macrophage function, as determined by zymosan-stimulated superoxide anion production and by phagocytosis of latex particles, was depressed to a greater degree after poly I:C instillation in V-exposed rats as compared to filtered air-exposed rats. These findings provide evidence that inhaled V, a trace metal found in combustion particles and shown to be toxic in vivo in studies using instilled or inhaled ROFA (Dreher et al., 1997), has the potential to inhibit the pulmonary response to microbial agents. It must be taken into consideration that these effects were found at very high occupational exposure concentrations of V, and as with many studies, care must be taken in extrapolating the results to the ambient exposure of healthy individuals or those with pre-existing cardiopulmonary disease to trace concentrations (approximately 3 orders of magnitude lower concentration) of metals in ambient PM.

7.4 CARDIOVASCULAR AND OTHER SYSTEMIC RESPONSES TO PM

A small number of epidemiology studies have demonstrated that increases in cardiac-related deaths are associated with exposure to PM (U.S. Environmental Protection Agency, 1996a) and that PM-related cardiac deaths appear to be as great or greater than those attributed to respiratory causes. The toxicological consequences of inhaled particles on the cardiovascular system had not been extensively investigated prior to 1996. Since then (see Table 7-5) Costa and colleagues (Costa and Dreher, 1997) have demonstrated that tracheal instillation of ambient particles can increase or accelerate death related to monocrotaline administration in rats. These deaths did not occur with all types of ambient particles tested. Some dusts, such as volcanic ash from Mount St. Helens, were relatively inert, while other ambient dusts, including those from urban sites, were toxic. These observations suggest that particle composition plays an important role in the adverse health effects associated with episodic exposure to ambient PM, despite the 'general particle' effect attributed to the epidemiological associations of ambient PM exposure and increased mortality in many regions of the U.S. (i.e., regions with varying particle composition). Work which examines the role of inherent susceptibility to the adverse effects of PM in compromised animal models provides a potentially important link to epidemiological observations.

Killingsworth and colleagues (1997) used a fuel oil fly ash to examine the adverse effects of a model urban particle in an animal model (monocrotaline-MCT) of cardiorespiratory disease; MCT causes pulmonary vascular inflammation and hypertension. They observed 42% mortality in MCT-treated rats exposed to approximately 580 $\mu g/m^3$ fly ash for 6 hours/day for 3 consecutive days. These rats showed a massive neutrophillic inflammation from MCT treatment which was further exacerbated by fly ash inhalation. Deaths did not occur in MCT-treated rats exposed to filtered air or in saline-treated rats exposed to fly ash. The increase in deaths in the MCT/fly ash group was accompanied by an increase in neutrophils in lavage fluid and an increased immunostaining of MIP-2 in the heart and lungs of the MCT/fly ash animals. Cardiac immunohistochemical analysis indicated increased MIP-2 in cardiac macrophages. The fly ash-induced deaths did not result from a change in pulmonary arterial pressure; the cause of death was not identified. In a similar experimental model, Watkinson et al. (1998) examined the effect of intratracheally instilled ROFA on ECG measurements in control and MCT-treated rats. As reported by Killingsworth et al. (1997), an increase in spontaneous

TABLE 7-5. CARDIOVASCULAR EFFECTS AND OTHER SYSTEMIC EFFECTS OF PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle	Exposure Technique	Mass Concentration (μg) or (μg/m^3)	Particle Characteristics Size (μm); σ_g	Exposure Duration	Cardiovascular Effects	Reference
Rat, Sprague-Dawley, males, monocrotaline-treated (MCT)	ROFA	Instillation	0, 250, 1000, or 2500 μg in 0.3 ml saline	1.95 μm MMAD $\delta g = 2.19$	Monitored for 96 hours after instillation of ROFA particles	Dose-related increases in the incidence and duration of serious arrhythmic events in normal rats. Incidence and severity of arrythmias were greatly increased in the monocrotaline-treated rats. Deaths were seen at each instillation level in monocrotaline-treated rats only (6/12 died after MCT + ROFA).	Watkinson et al. (1998)
Rats monocrotaline-treated	FOFA	Inhalation	580 ± 110 μg/m^3	MMAD 2.06 μm $\sigma g = 1.57$	6 h/day for 3 days	Death occurred only in MCT rats exposed to ROFA. Neutrophils in lavage fluid was significantly increased in MCT rats exposed to ROFA versus filtered air. MIP-2 mRNA expression in lavage cells was induced in normal animals exposed to fly ash.	Killingsworth et al. (1997)
Rabbit, New Zealand White, female, 1.8 to 2.4 kg	colloidal carbon	Instillation	2 ml of 1% colloidal carbon (20 mg)	<1 μm	Examined for 24 to 192 h after instillation	Colloidal carbon stimulated the release of BRDU-labeled PMNs from the bone marrow. The supernatant of alveolar macrophages treated with colloidal carbon *in vitro* also stimulated the release of PMNs from bone marrow, likely via cytokines.	Terashima et al. (1997)
Rats, M, SD, 60 days old MCT (60/mg/kg), i.p and healthy.	Emission source PM Ambient airshed PM ROFA	Intratracheal instillation	Total mass: 2.5 mg/rat Total transition metal: 46 μg/rat	Emission PM: 1.78-4.17 μm Ambient PM: 3.27-4.09 μm	Analysis at 24 & 96 h following instillation.	ROFA alone induced some mild arrhythumas; MCT-ROFA showed enhanced neutrophilic inflammation; MCT-ROFA animals showed more numerous arrhythmias including S-T segment inversions and A-V block.	Costa and Dreher (1997)

ROFA - Residual Oil Fly Ash
FOFA - Fuel Oil Fly Ash
MMAD - Mass Median Aerodynamic Diameter
MIP-2 - Macrophage Inflammatory Protein-2
BRDU - 5' Bromo 2' Deoxyuridine
MCT - Monocrotaline treated

deaths occurred only in MCT- treated rats treated with ROFA. Deaths were observed at both the 250 and 2,500 μg dose levels. Watkinson et al. (1998) also observed a dose-related increase in the incidence and duration of serious arrhythmic events in control animals exposed to ROFA particles. They examined the effects of ROFA (0, 0.25, 1.0, 2.5 mg ROFA in 0.3 ml saline) in healthy rats and rats treated with MCT, twelve days after MCT treatment, ROFA instilled animals were studied for 4 days. The incidence and duration of serious arrhythmic events were related to the dose of ROFA. Healthy animals treated with ROFA suffered no deaths, but MCT-treated rats had 1, 2, and 3 deaths in the low, medium, and high dose groups. This study suggests that ROFA PM may be implicated in conductive and hypoxemic arrhythmias associated with the cardiac-related deaths.

Kodavanti et al. (1999) exposed MCT-pretreated rats to ROFA by either intratracheal instillation (0.88 or 3.33 mg/kg) or nose-only inhalation (15 mg/m^3, 6 h/d for 3 consecutive days). As reported in Watkinson et al. (1998), intratracheal instillation of ROFA in MCT-pretreated rats resulted in 58% mortality whereas no mortality occurred in MCT-pretreated rats exposed to ROFA by inhalation exposure. No mortality occurred in healthy rats exposed to ROFA or in MCT-pretreated rats exposed to clean air. Despite the fact that mortality was not associated with ROFA inhalation exposure of MCT-pretreated rats, exacerbation of lung lesions and pulmonary inflammatory cytokine gene expression was clearly evident. No deaths have also been observed by Gordon et al. (1998) in MCT-treated rats exposed for a single 3 hour exposure or for 6 hours/day for 3 days to concentrated ambient PM (CAP).

Gordon and colleagues (1998) have reported systemic effects in animals exposed to inhaled CAP. Increases in peripheral blood neutrophils were observed in control and MCT-treated rats at 3 h, but not 24 h, after exposure to 150 to 400 μg/m^3 CAP. This effect, likely a result of vascular demargination, did not appear to be dose-related and did not occur on all exposure days, thus, suggesting that day-to-day changes in particle composition may play an important role in the systemic effects of inhaled particles. However, Terashima et al. (1997) has instilled rabbits with 20 mg colloidal carbon, a relatively inert particle (<1 μm), and observed a stimulation of the release of 5'-bromo-2'deoxyuridine (BrdU)-labeled PMNs from the bone marrow at 2 to 3 days after instillation. Because the instilled supernatant from rabbit AM treated in vitro with colloidal carbon also stimulated the release of PMNs from the bone marrow, they hypothesized that cytokines released from activated macrophages could be responsible for this systemic effect.

In summary, controlled animal studies have provided initial evidence that inhaled or instilled particles can have systemic, especially cardiovascular, effects. In the case of MCT-treated rats, these effects can be lethal. Understanding the pathways by which very small concentrations of inhaled ambient PM can produce systemic, life-threatening changes, however, is far from clear. Among the hypotheses that have been proposed to account for the non-pulmonary effects of PM are activation of neural reflexes, cytokine effects on heart tissue (Killingsworth et al., 1997), alterations in coagulability (Seaton et al., 1995; Sjögren, 1997), and perturbations in homeostatic processes such as heart rate or heart rate variability (Watkinson et al., 1998). A great deal of research using controlled exposures of animal and human subjects to PM will be necessary to test mechanistic hypotheses generated to date, as well as those which are likely to be proposed in the future.

7.5 RESPONSES TO PM AND GASEOUS POLLUTANT MIXTURES

Ambient PM itself is a mixture of varying size and composition. The following discussion examines effects of mixtures of ambient PM, or PM surrogates, with gaseous pollutants. Ambient PM co-exists in indoor and outdoor air with a number of co-pollutant gases, including ozone, sulfur dioxide, oxides of nitrogen, and carbon monoxide. Toxicological interactions between PM and gaseous co-pollutants may be antagonistic, additive, or synergistic (Mauderly, 1993). The presence and nature of any interaction appears to depend upon the size and concentration of pollutants in the mixture, exposure duration, and the endpoint being examined. It is not possible to predict a priori from the presence of certain pollutants whether any interaction will occur and, if there is interaction, whether it will be synergistic, additive, or antagonistic (Table 7-6).

Mechanisms responsible for the various forms of interaction are speculative. In terms of potential health effects, the greatest hazard from pollutant interaction is the possibility of synergy between particles and gases, especially if effects occur at concentrations at which no effects occur when individual constituents are inhaled. Various physical and chemical mechanisms may underly synergism. For example, physical adsorption or absorption of some material on a particle could result in transport to more sensitive sites, or sites where this material would not normally be deposited in toxic amounts. This physical process may explain the interaction found

TABLE 7-6. RESPIRATORY AND CARDIOVASCULAR EFFECTS OF MIXTURES

Species, Gender, Strain Age, or Body Weight	Gases and Particles	Exposure Technique	Mass Concentration (ppm) or ($\mu g/m^3$)	Particle Characteristics Size (μm); σ_g	Exposure Duration	Respiratory Effects of Inhaled Particles on Markers in Lavage Fluid	Reference
Lambs	Ambient NOx, SO2, CO, and PM	Natural 24 hour exposure in urban and rural areas			3 months	Irritation characterized by mucus hypersecretion and morphological changes in the epithelium in the nasopharyngeal mucosa in lambs exposed in urban area	Gulisano et al. (1997)
Pigeons (Columba livia)	Ambient gases and particles	Natural 24 h exposure in urban and rural areas			Continuous ambient exposure	Increased number of AM and decreased number of lamellar bodies in type II epithelial cells in urban pigeons	Lorz and López (1997)
Canine	Ambient gases and particles	Natural 24 h exposure in 4 urban areas of Mexico City and 1 rural area			Continuous ambient exposure	No significant differences in AM or total cell counts in lavage from dogs studied among the 5 regions. A significant increase in lavage fluid neutrophils and lymphocytes in the southwest region, where the highest O_3 levels were recorded, compared to the 2 industrial regions with the highest PM levels.	Vanda et al. (1998)
Rats	O_3 and resuspended urban PM	Inhalation, whole-body	0.8 ppm O_3 and 5,000 or 50,000 $\mu g/m^3$ PM		Single 4 h exposure	PM alone caused no change in cell proliferation in bronchioles or parenchyma. Co-exposure with O_3 greatly potentiated the proliferative changes induced by O_3 alone. These changes were greatest in the epithelium of the terminal bronchioles and alveolar ducts.	Vincent et al. (1997)
Mice, Swiss, female, 5 weeks old	SO_2 and carbon	Inhalation, flow-past nose-only	10,000 $\mu g/m^3$ carbon with or without 5 to 20 ppm SO_2 at 10% or 85% RH	0.3 μm MMAD with GSD of 2.7	Single 4 h exposure	Macrophage phagocytosis was depressed only in animals exposed to the combination of SO_2 and carbon at 85% humidity. This inhibition in macrophage function lasted at least 7 days after exposure.	Jakab et al. (1996)
Rats, Sprague-Dawley, male, 250-300 g	H_2SO_4 and O_3	Inhalation, nose-only	500 $\mu g/m^3$ H_2SO_4 aerosol (2 different particles sizes) with or without 0.6 ppm O_3	Fine (0.3 μm MMD with GSD of 1.7) and ultrafine (0.06 μm with GSD of 1.4)	4 h/day for 2 days	The volume percentage of injured alveolar septae was increased only in the combined ultrafine acid/O_3 animals. BrdU labelling in the periacinar region was increased in a synergistic manner in the combined fine acid/O_3 animals.	Kimmel et al. (1997)

TABLE 7-6 (cont'd). RESPIRATORY AND CARDIOVASCULAR EFFECTS OF MIXTURES

Species, Gender, Strain Age, or Body Weight	Gases and Particles	Exposure Technique	Mass Concentration ($\mu g/m^3$)	Particle Characteristics Size (μm); σ_g	Exposure Duration	Respiratory Effects of Inhaled Particles on Markers in Lavage Fluid	Reference
Rats, Fischer NNia, male, 22 to 24 months old	Carbon, ammonium bisulfate, and O_3	Inhalation	50 $\mu g/m^3$ carbon + 70 $\mu g/m^3$ ammonium bisulfate + 0.2 ppm O_3 or 100 $\mu g/m^3$ carbon +140 $\mu g/m^3$ ammonium bisulfate + 0.2 ppm O_3	0.4 μm MMAD with GSD of 2.0	4 h/day, 3 days/week for 4 weeks	No changes in protein concentration in lavage fluid or in prolyl 4-hydroxylase activity in blood. Slight, but statistically significant decreases in plasma fibronectin in animals exposed to the combined atmospheres compared to animals exposed to O_3 alone.	Bolarin et al. (1997)
Rats	O_3 and Ottawa urban dust	Inhalation	40,000 $\mu g/m^3$ and 0.8 ppm O_3	MMAD = 4.5 μ	Single 4 h exposure followed by 20 h clean air	CO exposure to particles potentiated O_3-induced septal cellurity. Enhanced septal thickening associated with elevated production of macrophage inflammatory protein-2 and endothelin 1 by lung lavage cells	Bouthillier et al. (1998)
Rats	H_2SO_4 and O_3	Inhalation, whole body	20 to 150 $\mu g/m^3$ H_2SO_4 and 0.12 or 0.2 ppm O_3	0.4 to 0.8 μm	Intermittent (12 h/day) or continuous exposure for up to 90 days	No interactive effect of H_2SO_4 and O_3 on biochemical and morphometric endpoints.	Last and Pinkerton (1997)
Healthy and asthmatic children	H_2SO_4 SO_2, and O_3	Inhalation	60 to 140 $\mu g/m^3$ H_2SO_4, 0.1 ppm SO_2, and 0.1 ppm O_3	0.6 μm H_2SO_4	Single 4 h exposure with intermittent exercise	A positive association between acid concentration and symptoms, but not spirometry, in asthmatic children. No changes in healthy children.	Linn et al. (1997)
Sprague-Dawley rats (300 g)	O_3 and H_2SO_4 coated carbon	Inhalation nose-only	0.2 ppm O_3 + 50 $\mu g/m^3$ C + 100 $\mu g/m^3$ H_2SO_4 0.4 ppm O_3 +250 $\mu g/m^3$ C +500 $\mu g/m^3$ H_2SO_4	0.26 μm GSD = 2.2	4 h/day for 1 day or 5 days	No airway inflammation at low dose. Greater inflammatory response at high dose-greater response at 5 days than 1 day. Contrasts with O_3 alone where inflammation was greatest at 0.40 ppm on day 1.	Kleinman et al. (1999)

MMAD - Mass Median Aerodynamic Diameter
GSD - Geometric Standard Deviation
BrdU - See Table 3-C
O_3 - Ozone
SO_2 - Sulfur dioxide
H_2SO_4 - Sulfuric acid

in studies of mixtures of carbon black and formaldehyde or of carbon black and acrolein (Jakab, 1992, 1993).

Chemical interactions between particles and gases can occur on particle surfaces, thus, forming secondary products which may be more toxicologically active than the primary materials and which can then be carried to a sensitive site. The hypothesis of such chemical interactions has been examined in the gas and particle exposure studies by Amdur and colleagues (Amdur and Chen, 1989; Chen et al., 1992) and Jakab and colleagues (Jakab and Hemenway, 1993; Jakab et al., 1996). These investigators have demonstrated that synergism occurs as secondary chemical species are produced, especially under conditions of increased temperature and relative humidity. Thus, these studies suggest that air quality standards for individual air pollutants may not be fully protective of human health for exposure to mixed ambient pollutants.

Another potential mechanism of gas-particle interaction may involve a pollutant-induced change in the local microenvironment of the lung, enhancing the effects of the co-pollutant. For example, Last et al. (1984) indicated that the observed synergism between ozone and acid sulfates in rats was due to a decrease in the local microenvironmental pH of the lung following deposition of acid, enhancing the effects of ozone by producing a change in the reactivity or residence time of reactants, such as radicals, involved in ozone-induced tissue injury.

As noted in U.S. Environmental Protection Agency (1996a), the toxicology database for mixtures containing PM other than acid sulfates is still quite sparse. Vincent et al. (1997) exposed rats to 0.8 ppm ozone in combination with 5 or 50 mg/m^3 of resuspended urban particles for 4 h. While PM alone caused no change in cell proliferation (^{3}H-thymidine labeling), co-exposure to either concentration of resuspended PM with ozone greatly potentiated the proliferative effects of exposure to ozone alone. These interactive changes occurred in epithelial cells of both the terminal bronchioles and the alveolar ducts. The findings of these experiments using resuspended dusts, although at high concentrations, are consistent with studies demonstrating interaction between sulfuric acid (H_2SO_4) aerosols and ozone. Kimmel and colleagues (1997) examined the effect of acute co-exposure to ozone and fine or ultrafine H_2SO_4 aerosols on morphometry in rat lungs. They determined morphometrically that alveolar septal volume was increased in animals co-exposed to ozone and ultrafine, but not fine, H_2SO_4. Interestingly, cell labeling, an index of proliferative cell changes, was increased only in animals co-exposed to fine H_2SO_4 and ozone as compared to animals exposed to ozone alone. Thus,

particle size of acid aerosols can influence the locale of the interactive effects of co-exposure with ozone. Importantly, Last and Pinkerton (1997) have extended their previous work and found that subchronic exposure to acid aerosols (20 to 150 $\mu g/m^3$ H_2SO_4) had no interactive effect on the biochemical and morphometric changes produced by either intermittent or continuous ozone exposure (0.12 to 0.2 ppm). Thus, the interactive effects of ozone and acid aerosol co-exposure in the lung disappeared during the long-term exposure.

Kleinman et al. (1999) examined the effects of ozone plus fine H_2SO_4 coated carbon particles (MMAD = 0.26 μm) for 1 or 5 days. They found the inflammatory response with the ozone-particle mixture was greater after 5 days (4 h/day) than after day 1. This contrasted with ozone exposure alone (0.4 ppm) which caused marked inflammation on acute exposure, but no inflammation after 5 consecutive days of exposure.

Two studies have examined interaction between carbon particles and gaseous co-pollutants. Jakab et al. (1996) challenged mice with a single 4 h exposure to a high concentration of carbon, 10 mg/m^3, in the presence of SO_2 at low and high relative humidities. Macrophage phagocytosis was significantly depressed only in mice exposed to the combined pollutants under high relative humidity conditions. This study demonstrates that fine carbon particles can serve as an effective carrier for acidic sulphates where chemical conversion of adsorbed SO_2 to acid sulfate species occurred. Interestingly, the depression in macrophage function was present as late as 7 days post-exposure. Bolarin et al. (1997) exposed rats to only 50 or 100 $\mu g/m^3$ carbon particles in combination with ammonium bisulfate and ozone. Despite 4 weeks of exposure, they observed no changes in protein concentration in lavage fluid or blood prolyl 4-hydroxylase, an enzyme involved in collagen metabolism. Slight decreases in plasma fibronectin were present in animals exposed to the combined pollutants versus ozone alone. Thus as, previously noted, the potential for adverse effects in the lungs of animals challenged with a combined exposure to particles and gaseous pollutants is dependent on numerous factors including the gaseous co-pollutant, concentration, and time.

Linn and colleagues (1997) examined the effect of a single exposure to 60 to 140 $\mu g/m^3$ H_2SO_4, 0.1 ppm SO_2, and 0.1 ppm ozone in healthy and asthmatic children. The children performed intermittent exercise during the 4 h exposure to increase the inhaled dose of the pollutants. An overall effect on the combined group of healthy and asthmatic children was not observed. A positive association between acid concentration and symptoms was seen, however,

in the subgroup of asthmatic children. The combined pollutant exposure had no effect on spirometry in asthmatic children and no changes in symptoms or spirometry were observed in healthy children. Thus, the effect of combined exposure to PM and gaseous co-pollutants appeared to have less effect on asthmatic children exposed under controlled laboratory conditions in comparison with field studies of children attending summer camp (Thurston et al., 1997). However, prior exposure to H_2SO_4 aerosol may enhance the subsequent response to ozone exposure (Linn et al., 1994; Frampton et al., 1995); the timing and sequence of the exposures may be important.

Three unique animal field studies have examined the adverse respiratory effects of complex mixtures in urban and rural environments. These studies have taken advantage of the differences in pollutant makeup of urban and rural environments and studied animals under natural, continuous exposure conditions. Gulisano et al. (1997) examined the morphologic changes produced by continuous ambient exposure to air pollutants in lambs raised for 3 months in rural (n=2) or urban (n=10) environments. Compared to the lungs of the rural lambs, irritation, as characterized by mucus hypersecretion and morphological changes in the epithelial cells lining the nasopharyngeal region, was present in the lambs exposed to urban air pollution. Lorz and López (1997) performed a similar study using pigeons as the test animal. They observed an increase in the number of AM and a decrease in the number of lamellar bodies in Type II epithelial cells in the lungs of urban pigeons. Extrapolation of these studies is hampered by an incomplete characterization of the exposure atmospheres. A more thorough examination of the ambient level of pollutants was performed in the study by Vanda et al. (1998) who studied the effect of pollutant exposure in dogs raised in four urban regions of Mexico City and one nearby rural area. They found no significant differences in AM number or total cell counts in lavage fluid from the dogs among the 5 regions. A significant increase in lavage fluid neutrophils and lymphocytes was found in dogs from the urban region with the highest ozone levels in comparison to the regions with the highest PM levels. Thus, the effect of ozone on cellular parameters in lavage fluid appeared to be greater than that for PM. In summary, each of these 3 animal field studies provides evidence that urban air pollutants can produce greater lung changes than would occur from exposure to rural pollution. However, extrapolation of these results is severely hampered by the uncontrolled exposure conditions, small sample size,

behavior patterns, and nutritional factors. Thus, in these field studies, it is difficult to assign a role to PM in the observed adverse pulmonary effects.

7.6 MECHANISMS OF PM TOXICITY AND PATHOPHYSIOLOGY

7.6.1 Introduction

The characteristics of particles which may be responsible for lung injury after exposure to ambient air pollution are not known. However injury has been postulated to be mediated by ultrafine particles, biological agents (e.g., endotoxin), acid aerosols, organic fraction of PM and oxidant generation catalyzed by transition metals associated with particles. Furthermore the mechanisms which underlie injury are also unclear. This section discusses potential mechanisms in relation to PM characteristics based upon available data.

7.6.2 Soluble Metals and Reactive Oxygen Intermediates

PM contains transition metals such as iron (most abundant), copper, nickel, vanadium, and cobalt. These metals are capable of catalyzing the one-electron reductions of molecular oxygen necessary to generate reactive oxygen species (ROS). These reactions can be demonstrated by the iron-catalyzed Haber-Weiss reactions below:

$$\text{Reductant}^{n} + \text{Fe(III)} \leftrightarrow \text{Reductant}^{n+1} + \text{Fe(II)} \quad (1)$$

$$\text{Fe(II)} + O_2 \rightleftharpoons \text{Fe(III)} + O_2^{\bullet -} \quad (2)$$

$$HO_2^{\bullet} + O_2^{\bullet -} + H^{+} \rightarrow O_2 + H_2O_2 \quad (3)$$

$$\text{Fe(II)} + H_2O_2 \rightleftharpoons \text{Fe(III)} + OH^{-} + HO^{\bullet} \text{ (Fenton Reaction)} \quad (4)$$

Iron will continue to participate in the redox cycle in the above reactions as long as there is sufficient O_2 or H_2O_2 and reductants.

Soluble metals from inhaled PM dissolved into the milieu of the airway lumen can directly react with biological molecules (acting as a reductant in the above reactions) to produce ROS. For example, ascorbic acid in the human lung epithelial lining fluid can react with Fe(III) from inhaled PM to cause single strand breaks in supercoiled plasmid DNA, ϕX174 RFI (Smith and Aust, 1997). The DNA damage caused by a PM_{10} suspension can be inhibited by mannitol, an hydroxyl radical scavenger, further confirming the involvement of free radicals in these reactions (Gilmour et al., 1996; Donaldson et al., 1997; Li et al., 1997). Since the clear supernatant of the centrifuged PM_{10} suspension contained all of the suspension activity, the free radical activity is derived either from a fraction that is not centrifugable (on a bench centrifuge) or the radical generating system is released into solution (Gilmour et al., 1996; Donaldson et al., 1997; Li et al., 1997).

In addition to measuring the interactions of ROS and biomolecules directly, the role of ROS in PM-induced lung injury can also be assessed by measuring the electron spin resonance (ESR) spectrum of radical adducts or fluorescent intensity of dichlorofluorescin (DCFH), an intracellular dye that fluoresces upon oxidation by ROS. Alternatively, ROS can be inhibited using free radical scavengers such as dimethylthiourea (DMTU); or antioxidants such as glutathione or N-acetylcysteine (NAC); or antioxidant enzymes, such as superoxide dismutase (SOD). The diminished response to PM after treatment with these antioxidants indicates the involvement of ROS.

As described earlier, Kadiiska et al. (1997) used the ESR spectra of POBN adducts to measure ROS in rats instilled with ROFA and demonstrated the association between ROS production in lung lipid extracts and soluble metals in ROFA. Using DMTU to inhibit ROS production, Dye et al. (1997) had shown that systemic administration of DMTU impeded development of the cellular inflammatory response to ROFA, but did not ameliorate biochemical alterations in BAL fluid. Goldsmith et al. (1998), as described earlier, showed that ROFA and CAPs caused increases in ROS production in AMs. The water-soluble component of both CAPs and ROFA significantly increased AM oxidant production over negative control values. In addition, increased PM-induced cytokine production was inhibited by NAC. Li et al. (1996, 1997) instilled rats with PM_{10} particles (collected on filters from an Edinburgh, Scotland monitoring station). Six hours after intratracheal instillation of PM_{10}, they observed a decrease in glutathione (GSH) levels in the BAL fluid. Although this study does not describe the

composition of the PM_{10}, the authors suggest that changes in GSH, an important lung antioxidant, support the contention that the free radical activity of PM_{10} is responsible for its biological activity *in vivo*.

In addition to ROS generated directly by PM, resident or newly recruited AMs or PMNs are also capable of producing these reactive species upon stimulation. The ROS produced during the oxidative burst can be measured using a chemiluminescence (CL) assay. With this assay, AM CL signals in vitro had been shown to be greatest with ROFA containing primarily soluble V and were less with ROFA containing Ni plus V (Kodavanti et al., 1998a). As described earlier, exposures to Dusseldorf and Duisburg PM increased the resting ROS production in PMNs which could be inhibited by SOD, catalase and sodium azide (Hitzfeld et al., 1997). Stringer and Kobzik (1998) showed that addition of NAC (1.0 mM) decreased ROFA-mediated IL-8 production by approximately 50% in normal and TNF-α-primed A549 cells. In addition, exposures of A549 cells to ROFA caused a substantial (and NAC inhibitable) increase in oxidant levels as measured by DCFH oxidation. In human AM, Becker et al. (1996) found a CL response for ROFA but not urban air particles (Ottawa, Dusseldorf) or volcanic ash.

Metals are the most probable species capable of catalyzing ROS generation upon exposure to PM. Soluble metals can be mobilized into the epithelial cells or AMs to produce ROS intracellularly. Using ROFA and colloidal iron oxide, Ghio et al. (1997b, 1998a,b,c) have shown that exposures to these particles disrupted iron homeostasis and induced the production of ROS in vivo and in vitro. Treatment of animals or cells with metal-chelating agents such as DEF with an associated decrease in response has been used to infer the involvement of metal in PM-induced lung injury. Metal chelation by DEF (1 mM) caused significant inhibition of particulate-induced AM oxidant production, as measured using DCFH (Goldsmith et al., 1998). DEF treatment also reduced NF-κB activation and cytokine secretion in BEAS-2B cells exposed to Provo, Utah PM (Kennedy et al., 1998). However, treatment of ROFA suspension with DEF was not effective in blocking leachable metal induced acute lung injury (Dreher et al., 1997). Dreher et al. (1997) indicated that DEF could chelate $Fe^{(III)}$ and $V^{(II)}$, but not $Ni^{(II)}$, suggesting that nickel played a role in the observed lung injury.

Other than Fe, several vanadium compounds have been shown to increase mRNA levels for selected cytokines in BAL cells and also to induce pulmonary inflammation (Pierce et al., 1996). $NaVO_3$ and $VOSO_4$, highly soluble forms of vanadium, tended to induce pulmonary

inflammation and inflammatory cytokine mRNA expression more rapidly and more intensely than the less soluble form, V_2O_5, in rats. Neutrophil influx was greatest following exposure to $VOSO_4$ and lowest following exposure to V_2O_5.

7.6.3 Intracellular Signaling Mechanisms

In has been shown that the intracellular redox state of the cell modulates the activity of several transcription factors, including NF-κB, a critical step in the induction of a variety of proinflammatory cytokine and adhesion-molecule genes. NF-κB is a heterodimeric protein complex that in most cells resides in an inactive state in the cell cytoplasm by binding to inhibitory kappa B alpha (IκBα). Upon appropriate stimulation by cytokines or ROS, IκBα is phosphorylated and subsequently degraded by proteolysis. The dissociation of IκBα from NF-κB allows the latter to translocate into the nucleus and bind to appropriate sites in the DNA to initiate transcription of various genes. Two studies in vitro have shown the involvement of NF-κB in particulate-induced cytokine and intercellular adhesion molecule-1 (ICAM-1) production in human airway epithelial cells (BEAS-2B) (Quay et al., 1998; Kennedy et al., 1998). Cytokine secretion was preceded by activation of NF-κB and was reduced by treatment with antioxidants or metal chelators. These results suggest that metal-induced oxidative stress may play a significant role in the initiation phase of the inflammatory cascade following particulate exposure.

A second well-characterized human transcription factor, AP-1, also responds to the intracellular ROS concentration. AP-1 exists in two forms, either in a homodimer of c-jun protein or a heterodimer consisting of c-jun and c-fos. Small amounts of AP-1 already exist in the cytoplasm in an inactive form, mainly as phosphorylated c-jun homodimer. Many different oxidative stress-inducing stimuli, such as UV light and IL-1, can activate AP-1. Exposure of rat lung epithelial cells to ambient PM in vitro resulted in increases in c-jun kinase activity, levels of phosphroylated c-jun immunoreactive protein, and transcriptional activation of AP-1-dependent gene expression (Timblin et al., 1998). This study demonstrated that interaction of ambient particles with lung epithelial cells initiates a cell signaling cascade related to aberrant cell proliferation.

Early response gene transactivation has been linked to the development of apoptosis, a unique type of programmed cell injury and a potential mechanism to account for PM induced

changes in cellular response. Apoptosis of human AMs exposed to ROFA (25 μg/ml) or urban PM was observed by Holian et al. (1998). In addition, both ROFA and urban PM upregulated the expression of the $RFD1^+$ AM phenotype, while only ROFA decreased the $RFD1^+7^+$ phenotype. It has been suggested that an increase in the AM phenotype ratio of $RFD1^+/RFD1^+7^+$ may be related to disease progression in patients with inflammatory diseases. These data showed that ROFA and urban PM can induce apoptosis of human AMs and increase the ratio of AM phenotypes toward a higher immune active state and may contribute to or exacerbate lung inflammation.

Another intracellular signaling pathway that can lead to diverse cellular responses such as cell growth, differentiation, proliferation, apoptosis, and stress responses to environmental stimuli, is the phosphorylation-dependent mitogen-activated protein kinase (MAPK). Noncytotoxic levels of ROFA have been shown to induce significant dose- and time-dependent increases in protein tyrosine phosphate levels in BEAS cells (Samet et al., 1997). In a subsequent study, the effects of As, Cr, Cu, Fe, Ni, V, and Zn on the MAPK, extracellular receptor kinase (ERK), c-jun N-terminal kinase (JNK), and P38 in BEAS cells were investigated (Samet et al., 1998). Noncytotoxic concentrations of As, V, and Zn induced a rapid phosphorylation of MAPK in BEAS cells. Activity assays confirmed marked activation of ERK, JNK, and P38 in BEAS cells exposed to As, V, and Zn. Cr and Cu exposure resulted in a relatively small activation of MAPK, whereas Fe and Ni did not activate MAPK. Similarly, the transcription factors c-Jun and ATF-2, substrates of JNK and P38, respectively, were markedly phosphorylated in BEAS cells treated with As, Cr, Cu, V, and Zn. The same acute exposure to As, V, or Zn that activated MAPK was sufficient to induce a subsequent increase in IL-8 protein expression in BEAS cells. These data suggest that MAPK may mediate metal-induced expression of inflammatory proteins in human bronchial epithelial cells.

To investigate the interaction between respiratory cells and PM, Kobzik (1995) showed that scavenger receptors are responsible for AM binding of charged PM and that different mechanisms mediate binding of carbonaceous dusts such as DPM. In addition, surfactant components can increase AM phagocytosis of environmental particulates in vitro, but only slightly relative to the already avid AM uptake of unopsonized particles (Stringer and Kobzik, 1996). Respiratory tract epithelial cells are also capable of binding with PM to secrete cytokine IL-8. Using a respiratory epithelial cell line (A549), Stringer et al. (1996) found that binding of

particles to epithelial cells was calcium-dependent for TiO_2 and Fe_2O_3, while α-quartz binding was not calcium-dependent. In addition, as observed in AM, PM binding by A549 cells was also mediated by scavenger receptor(s), albeit those distinct from the heparin-insensitive acetylated-LDL receptor. Furthermore, α-quartz, but not TiO_2 or CAPs, caused a dose-dependent production of IL-8 (range 1-6 ng/mL), demonstrating a particle-specific spectrum of epithelial cell cytokine (IL-8) response.

7.6.4 The Role of Particle Size and Surface Area

Most particles used in laboratory animal toxicology and occupational studies are greater than 0.1 μm in size. However, the enormous numbers and huge surface area of the ultrafine particles demonstrate the importance of considering the size of the particle in assessing response. Ultrafine particles with a diameter of 20 nm when inhaled at the same mass concentration have a number concentration that is approximately 6 orders of magnitude higher than for a 2.5 μm diameter particle; particle surface area is also greatly increased (Table 7-7).

TABLE 7-7. NUMBERS AND SURFACE AREAS OF MONODISPERSE PARTICLES OF UNIT DENSITY OF DIFFERENT SIZES AT A MASS CONCENTRATION OF 10 $\mu g/m^3$

Particle Diameter (μm)	Particle Number (per cm^3 Air)	Particle Surface Area (μm^2 per cm^3 Air)
0.02	2,400,000	3,016
0.1	19,100	600
0.5	153	120
1.0	19	60
2.5	1.2	24

Source: Oberdörster et al. (1995).

Many studies summarized in U.S. Environmental Protection Agency (1996a), as well as in this document, suggest that the surface of particles, or substances that are released from the

surface (e.g., transition metals), interact with the biological system and that surface-associated free radicals or free radical-generating systems may be responsible for toxicity. Thus, if ultrafine particles were to cause toxicity by a transition metal-mediated mechanism, for example, then the relatively large surface area for a given mass of ultrafine particles would mean high concentrations of transition metals being available to cause oxidative stress to cells.

Several groups have examined the toxic differences between fine and ultrafine particles, with the general finding that the ultrafine particles show a significantly greater response at similar mass doses (Oberdörster et al., 1992; Yoo et al., 1995; Li et al., 1996, 1997). However, only a few studies have investigated the ability of ultrafine particles to generate a greater oxidative stress when compared to fine particles of the same material. Studies by Gilmour et al. (1996) have shown that at equal mass, ultrafine TiO_2 caused more plasmid DNA strand breaks than fine TiO_2. This effect could be inhibited with mannitol. Osier and Oberdörster (1997) compared the response of rats (F344) exposed by intratracheal inhalation to "fine" (approximately 250 nm) and "ultrafine" (approximately 21 nm) TiO_2 particles with rats exposed to similar doses by intratracheal instillation. Animals receiving particles through inhalation showed a smaller pulmonary response, measured by BAL parameters, in both severity and persistence, when compared with those animals receiving particles through instillation. These results demonstrate a difference in pulmonary response to an inhaled vs an instilled dose, which may be due to differences in dose rate, particle distribution, or altered clearance between the two methods. Consistent with these in vivo studies, Finkelstein et al. (1997) has shown that exposing primary cultures of rat Type II cells to 10 μg/ml ultrafine TiO_2 (20 nm) causes increased TNF and IL-1 release throughout the entire 48 h incubation period. In contrast, fine TiO_2 (200 nm) had no effect.

Oberdörster et al. (1999) recently completed a series of studies in rats and mice using ultrafine particles of various chemical compositions (PTFE, TiO_2, C, Fe, Fe_2O_3, Pt, V, V_2O_5). In old rats sensitized with endotoxin, and exposed to ozone plus ultrafine carbon particles, they found a nine-fold greater release of reactive oxygen species in the old than in similarly treated young rats. Exposure to ultrafine PM alone in sensitized old rats also caused an inflammatory response. These investigators also demonstrated translocation of UF Pt to the liver. Recovery of ultrafine Pt after exposure was less than for fine particles, suggesting less uptake of ultrafine PM by AM.

Only one study examined the influence of specific surface area on biological activity (Lison et al., 1997). The biological responses to various MnO_2 dusts with different specific surface area (0.16, 0.5, 17 and 62 m^2/g) were compared in vitro and in vivo. In both systems, the results show that the amplitude of the response is dependent on the total surface area which is in contact with the biological system, indicating that surface chemistry phenomena are involved in the biological reactivity. Freshly ground particles with a specific surface area of 5 m^2/g were also examined in vitro. These particles exhibited an enhanced cytotoxic activity, which was almost equivalent to that of particles with a specific surface area of 62 m^2/g, indicating that undefined reactive sites produced at the particle surface by mechanical cleavage may also contribute to the toxicity of insoluble particles.

7.6.5 Summary

The mechanisms which underlie the biological responses to ambient PM are not clear. Various studies using particulate matter having diverse physicochemical characteristics have shown that these characteristics have a great impact upon the specific response which is observed. Thus, there may, in fact, be multiple biological mechanisms that may be responsible for observed morbidity/mortality due to exposure to ambient PM, and these mechanisms may be highly dependent upon the type of particle in the exposure atmosphere. However, it should be noted that many controlled exposure studies used concentrations of particulate matter which were much higher than those occurring in ambient air. Thus, some of the mechanisms elicited may not occur with exposure to lower levels. Clearly, controlled exposure studies have not as yet been able to unequivocally determine the particle characteristics and the toxicological mechanisms by which ambient PM may affect biological systems.

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8. INTEGRATIVE SYNTHESIS OF KEY POINTS: PM EXPOSURE, DOSIMETRY, AND HEALTH RISKS

8.1 INTRODUCTION

This chapter integrates key information on exposure-dose-response risk assessment components drawn from the preceding detailed chapters (Chapters 3 to 7), in order to provide a coherent framework for assessment of human health risks posed by ambient particulate matter (PM) in the United States. Given that substantial additional important new information is expected to become available during the next 6 to 9 mo for incorporation into a second external review draft of this document, only very provisional conclusions can now be drawn from the information discussed in earlier chapters and a preliminary attempt at an integrative synthesis framework set forth below. The key elements of the integrative synthesis framework include discussion of: (a) atmospheric science and exposure research evidence substantiating distinctions between fine and coarse particles as separate subclasses of ambient PM air pollutants; (b) factors affecting PM dosimetry, especially in the human respiratory tract; (c) the expanding epidemiologic evidence regarding effects of ambient PM on human health; and (d) new toxicological evaluations of pathophysiologic effects of PM and potential mechanisms of action.

8.2 AIRBORNE PARTICLES: DISTINCTIONS BETWEEN FINE AND COARSE PARTICLES AS SEPARATE POLLUTANT SUBCLASSES

As discussed in detail in Chapter 3 of this document, airborne PM is not a single pollutant but several classes of pollutants, each consisting of a number of chemical species. One classification is based on the natural division of the atmospheric aerosol into fine-mode and coarse-mode particles. Fine-mode particles, in addition to being smaller than coarse-mode particles, differ in many aspects such as formation mechanisms, chemical composition, sources, physical behavior, human exposure relationships, and control approaches required for risk reduction. Such differences alone are sufficient to justify consideration of fine-mode and coarse-mode particles as separate pollutants. Table 8-1 compares several key points that

TABLE 8-1. COMPARISON OF PHYSICAL AND CHEMICAL PROPERTIES OF AMBIENT PARTICLES: FINE MODE (Nuclei Mode Plus Accumulation Mode) AND COARSE MODE

	Fine		Coarse
	Nuclei	Accumulation	
Formed from:	Combustion, high temperature processes and atmospheric reactions		Break-up of large solids/droplets
Formed by:	Nucleation Condensation Coagulation	Condensation Coagulation Evaporation of fog and cloud droplets in which gases have dissolved and reacted	Mechanical disruption (crushing, grinding, abrasion of surfaces) Evaporation of sprays Suspension of dusts Reactions of gases in/on particles
Composed of:	Sulfates Elemental carbon Metal compounds Organic compounds with very low saturation vapor pressure at ambient temperature	Sulfate, SO_4^{-2} Nitrate, NO_3^- Ammonium, NH_4^+ Hydrogen ion, H^+ Elemental carbon, Large variety of organic compounds Metals: compounds of Pb, Cd, V, Ni, Cu, Zn, Mn, Fe, etc. Particle-bound water	Suspended soil or street dust Fly ash from uncontrolled combustion of coal, oil, wood Nitrates/chlorides from HNO_3/HCl Oxides of crustal elements, (Si, Al, Ti, Fe) $CaCO_3$, NaCl, sea salt Pollen, mold, fungal spores Plant/animal fragments Tire, break pad, road wear debris
Solubility:	Probably less soluble than accumulation mode	Largely soluble, hygroscopic and deliquescent	Largely insoluble and non-hygroscopic
Atmospheric half-life:	Minutes to hours	Days to weeks	Minutes to hours
Removal Processes:	Grows into accumulation mode	Forms cloud droplets and rains out Dry deposition	Dry deposition by fallout Scavenging by falling rain drops
Travel distance:	<1-10s of km	100s to 1000s of km	<1 to 10s of km (100s-1000s in dust storms)

Source: Adapted from Wilson and Suh (1997).

differentiate fine-mode from coarse-mode particles. Various physical and chemical differences between fine-mode particles and coarse-mode particles, their sources, factors affecting human exposure, and their respiratory tract deposition are also summarized below as a prelude to more in-depth discussion of key health effects associated with ambient PM exposures and other information useful in assessing PM-related public health risks in the United States.

8.2.1 Size Distinctions

Four approaches are used to classify particles by size: (1) modes, based on formation mechanisms and the modal structure observed in the atmosphere; (2) size cut point, based on the 50% cut point of the specific sampling device; (3) occupational classification based on dosimetry, the ability of particles to enter certain regions of the respiratory tract, and (4) regulatory size cuts. The modal structure is shown in Figure 8-1. In the ambient atmosphere the fine particle mode ($\leq$1.0 μm diameter) is composed of the nuclei mode and the accumulation mode. The nuclei mode is clearly observable only near sources of condensible gases. Particles in the nuclei mode rapidly grow into the accumulation mode but the accumulation mode does not grow further into the coarse particle mode. The lognormal distribution (in units of particle diameter) is frequently used to approximate the distribution of particle number, surface area, volume, or mass. The nuclei mode ($\leq$0.1 μm) includes ultrafine particles (toxicology terminology) and nanoparticles (aerosol physics terminology). Particle diameters are usually given as aerodynamic equivalent diameter, d_{ae}, defined as the diameter of a particle with a settling velocity equal to that of a sphere with unit density (1 g/cm^3). This is the most appropriate diameter for discussion of lung deposition and particle collection. The accumulation mode typically has a mass median aerodynamic diameter (MMAD) of 0.3 to 0.7μm and a geometric standard deviation, σ_g (a measure of the size dispersion), of 1.5 to 1.8. The coarse particle mode may also contain multiple modes but they are not readily distinguished. Therefore, the coarse particle mode tends to have a broader size distribution, with σ_g = 2.2 to 2.4. Measured MMADs typically range from 6 to 20 μm diameter in the ambient atmosphere, but these values may be low because of the difficulty of collecting particles in the upper tail of the coarse-mode distribution.

Agreement has been reached between the International Standards Organization (ISO) and American Council of Government Industrial Hygienists (ACGIH) who have promulgated

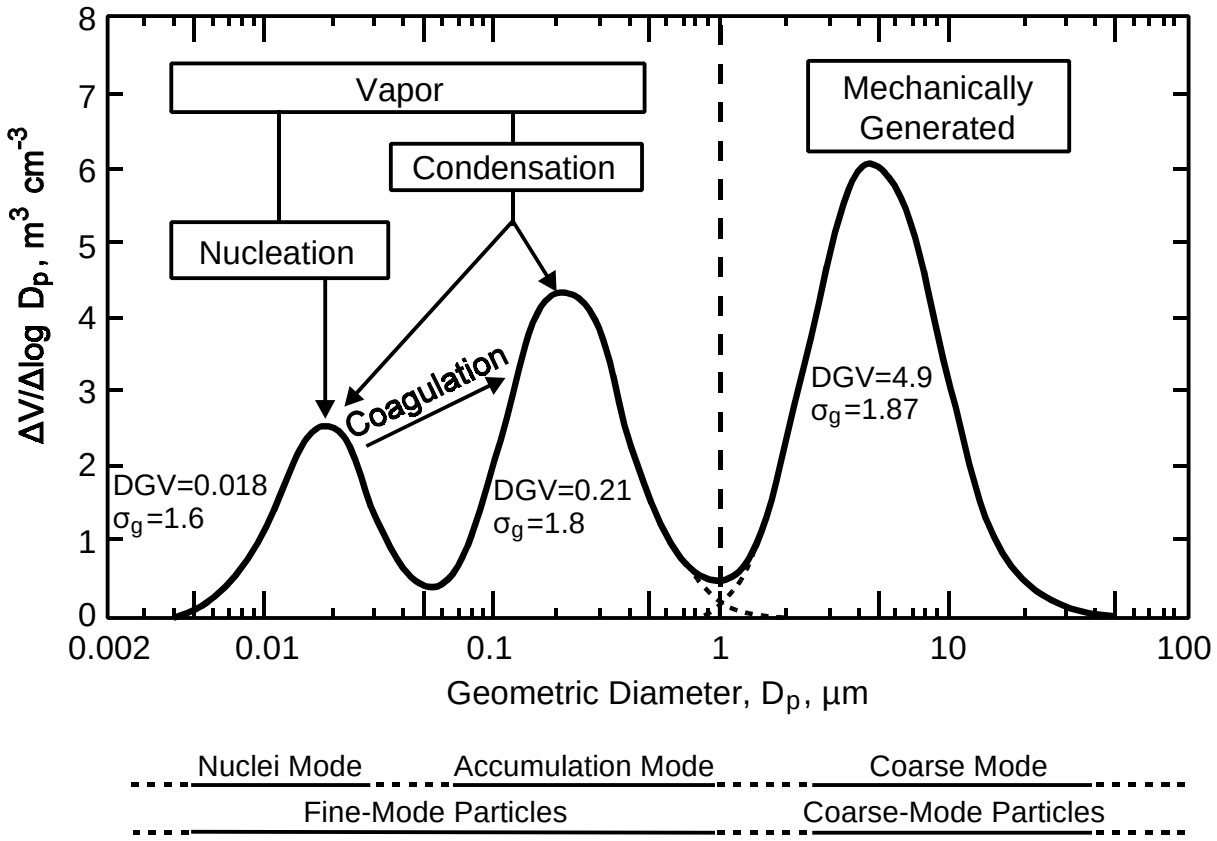

Figure 8-1. Volume size distribution, measured in traffic, showing fine-mode and coarse-mode particles and the nuclei and accumulation modes within the fine-particle mode. DGV (geometric mean diameter by volume, equivalent to volume median diameter) and σ_g (geometric standard deviation) are shown for each mode. Also shown are transformation and growth mechanisms (e.g., nucleation, condensation, and coagulation).

Source: Wilson et al. (1977).

definitions of particle size fractions that are based on the ability of particles to penetrate to various depths within the respiratory tract (Vincent, 1995). *Inhalable* refers to particles which can enter beyond the external airway openings and, as discussed in Chapter 10, has a practical upper limit of 40 to 60 μm. *Thoracic* refers to particles which can penetrate beyond the larynx; about 50% of particles of 10 μm aerodynamic diameter will penetrate beyond the larynx. *Respirable* refers to particles which can reach the air exchange portion of the lung.

The appropriate division between the fine and coarse fractions is not sharply defined, but falls in the range between 1.0 and 3.0 μm d_{ae}, where fine-mode and coarse-mode particles overlap but where particle mass is at a minimum. Thus, in general, particles less than 1.0 μm d_{ae} are fine-mode particles and particles greater than 2.5μm d_{ae} are coarse-mode particles. However, as the relative humidity approaches 100%, fine particles may grow beyond 1.0 μm and even beyond 2.5 μm d_{ae}; and, in very dry environments, it may also be possible to find particles less than 1.0 μm d_{ae} in the small size tail of the coarse particle mode. It is important to note that $PM_{2.5}$ may sometimes contain an appreciable quantity of coarse-mode particles in the 1 to 2.5 μm d_{ae} size range.

$PM_{2.5}$ particles are frequently referred to as fine particles, while the difference between $PM_{2.5}$ and PM_{10} ($PM_{(10-2.5)}$), is sometimes referred to as coarse particles or as the coarse fraction of PM_{10}. In the present discussion, fine-mode particles and coarse-mode particles are used to emphasize that important distinctions include not just size but also other additional fundamental differences in sources, formation mechanisms, and chemical composition.

The indicators for the current PM standards are PM_{10} and $PM_{2.5}$. Since neither the respiratory tract nor particle samplers can separate particles with a sharp cut, PM_{10} is defined as having a 50% cutpoint at 10 μm d_{ae}. PM_{10} samplers collect all fine-mode particles. They also collect a decreasing fraction of coarse particles as the diameter increases above 10 μm d_{ae} and an increasing fraction of particles as the diameter decreases below 10 μm d_{ae}. The mass of the coarse fraction ranges from 20% of PM_{10} in some eastern urban areas to 80% of PM_{10} in some dry western areas. The penetration curve for PM_{10} is very close to that of thoracic particles (Figure 3-6). PM_{10} is a design standard where the specified design provides a 50% cut point at 10 μm d_{ae}. $PM_{2.5}$ is a combination of design and performance specifications which provide a 50% cut at 2.5 μm d_{ae}. This cut insures that virtually all fine particles will be collected, even under high relative humidity conditions, but it also includes a fraction of the small-size tail of the coarse particle distribution.

8.2.2 Formation Mechanisms

Fine particles may be formed during combustion processes. Fine particles are also formed from condensible gases by nucleation (gas molecules coming together to form a new particle), and grow by condensation (gas molecules condensing onto a pre-existing particle). Condensible

gases (low saturation vapor pressure at ambient temperature) may be formed by volatilization of material during combustion or other high temperature processes or by atmospheric reactions that generate condensible gases. Gases may dissolve in a liquid droplet (either a solution particle or a cloud or fog droplet), react with another dissolved gas, and form a low vapor pressure product. When fog and cloud droplets evaporate, particulate matter remains, usually in the fine particle mode. Gases may also react directly with solid particles or in water films on solid particles.

Coarse particles are formed by mechanical processes which produce small particles from large ones. Energy considerations normally limit coarse mode particles to sizes greater than about 1.0 μm d_{ae}.

Particles are designated as primary if they are emitted directly into the air as particles or as vapors which condense to form particles without chemical reaction. Examples of primary particles are (a) elemental carbon chain agglomerates formed during combustion and (b) chemical species such as lead, cadmium, selenium, or sulfuric acid which are volatile at combustion temperature but form PM rapidly as the combustion gases cool.

Particles are designated as secondary if they form following a chemical reaction in the atmosphere which converts a gaseous precursor to a product which either has a low enough saturation vapor pressure to form a particle or reacts further to form a low saturation vapor pressure product. Examples are the conversion of sulfur dioxide (SO_2) to sulfuric acid (H_2SO_4) which nucleates or condenses on existing particles, or the conversion of nitrogen dioxide (NO_2) to nitric acid (HNO_3) which may react further with ammonia (NH_3) to form particulate ammonium nitrate (NH_4NO_3).

Coarse particles are normally primary since they are formed by mechanical rather than by chemical processes. An exception is the reaction of acid gases with carbonate ($CO_3^=$) containing particles in which the $CO_3^=$ may be replaced by sulfate (SO_4^{-2}), nitrate (NO_3^-), or chloride (Cl^-). Other exceptions are the reaction of HNO_3 with NaCl to form $NaNO_3$ and HCl gas and the reaction of SO_2 with wet NaCl to form Na_2SO_4 and HCl gas. Similar reactions may occur between other basic and acidic species.

8.2.3 Chemical Composition

8.2.3.1 Fine-Mode Particulate Matter

In the ambient atmosphere, fine-mode particulate matter is mainly composed of varying proportions of sulfate, nitrate, hydrogen, and ammonium ions; elemental and organic carbon; trace elements such as metals; and particle-bound water.

Sulfates/Acid. Sulfur dioxide (SO_2), emitted mainly from combustion of fossil fuel, is oxidized in the atmosphere to form sulfuric acid (H_2SO_4) particles. The H_2SO_4 may be partially or completely neutralized by reaction with ammonia (NH_3). Since the particles usually contain water, the actual species present are H^+, HSO_4^-, SO_4^{-2}, and NH_4^+, in varying proportions depending on the amount of NH_3 available to react with the H_2SO_4. Particle strong acidity is due to free H^+ or H^+ available from HSO_4^- or H_2SO_4.

Nitrates. Nitrogen oxides (NO_x= NO + NO_2) are formed during combustion and other high temperature processes involving air. The NO is converted to NO_2 by ozone (O_3) or other atmospheric oxidants. During the daytime, NO_2 reacts with the hydroxyl radical (OH) to form nitric acid (HNO_3). During nighttime, it forms nitric acid through a sequence of reactions involving ozone and the nitrate radical (NO_3). Ammonia reacts preferentially with sulfuric acid to form sulfate particles, but, if sufficient NH_3 is available, particulate ammonium nitrate (NH_4NO_3) will also form.

Elemental Carbon. Chain agglomerates of very small elemental carbon (EC) particles are formed during combustion, such as in open hearth fireplaces, wood stoves and diesel engines.

Organic Carbon. Several heterogenous categories of organic carbon (OC) compounds are also often found in ambient air, as follows:

- **Primary-anthropogenic.** Incomplete combustion also leads to hundreds of organic compounds with low enough vapor pressure to be present in the atmosphere as particles, including mutagenic species such as some polyaromatic hydrocarbons (PAHs).
- **Secondary-anthropogenic.** Some organic compounds, including aromatics (larger than benzene), cyclic olefins and diolefins, and other C_7 or higher hydrocarbons, react with O_3 or OH to form polar, oxygenated compounds with ambient temperature, saturation vapor pressures low enough to form particles.
- **Primary biogenic.** Viruses, some bacteria, and plant and/or animal cell fragments may be found in the fine mode.

- **Secondary biogenic.** Monoterpenes, C_{10} cyclic olefins released by plants, and other organic compounds from plants, also react in the atmosphere to yield organic particulate matter.

Trace Elements. A variety of transition metals and non-metals are volatilized during the combustion of fossil fuels, smelting of ores, and incineration of wastes and are emitted as fine particles (or vapors which rapidly form fine particles).

Water. Sulfates, nitrates, and some organic compounds are hygroscopic, i.e., they absorb water and form solution droplets. A variety of atmospheric pollutant gases can dissolve in the water component of the particle. This provides a possible mechanism for carrying into the lung soluble species such as SO_2, H_2O_2, HCHO, etc., which, when in the gas phase, would normally be removed in the nose, throat, or upper airways. The amount of particle-bound water increases as the relative humidity increases; relative humidity in the respiratory tract approaches 100%.

8.2.3.2 Coarse-Mode Particulate Matter

Coarse-mode PM sources are primarily crustal, biological, or industrial in nature.

Crustal. Crustal material, from soil or rock, primarily consists of compounds that contain Si, Al, Fe, Mg, and K (small amounts of Fe and K are also found among fine-mode particles but come from different sources). In urban areas, much crustal material arises from soil which is tracked onto roads during wet periods and is suspended in the air by vehicular traffic. In rural areas, tilling, wind blowing over disturbed soil, or vehicles traveling on unpaved roads can generate coarse particles. Where farms have been treated with persistent pesticides or herbicides, these materials may also be present in suspended soil particles.

Biological. Biological materials such as bacteria, pollen, spores, and other plant and animal fragments are mostly found in the coarse size range (i.e., 2.0 to 10 μm d_{ae} for most, >20 μm d_{ae} for some).

Industrial. A variety of industrial operations generate coarse particles. Examples are construction and demolition, open pit mining, grain handling, coal handling, etc. Also, coal and oil combustion generate fly ash which is similar in chemical composition to soil and crustal material but can be differentiated by microscopic examination. In the U.S. almost all fly ash from large scale coal and oil combustion is removed by effective particle control technologies.

8.2.4 Atmospheric Behavior

Coarse-mode particles are large enough so that the force of gravity exceeds the buoyancy forces of the air. Therefore, large particles tend to rapidly fall out of the air. Coarse-mode particles are also too large to follow air streams, so they tend to be easily removed by impaction on surfaces. The atmospheric half-life of coarse particles depends on their size, but is usually only minutes to hours. However, vigorous mixing and convection, such as occurs during dust storms, can lead to longer lifetimes for the smaller size range of coarse-mode particles.

In contrast, fine-mode particles are small enough that gravitational forces are largely overcome by the random forces from collisions with gas molecules. Thus fine particles tend to follow air streams and are typically not removed by impaction (unless the air stream is accelerated in a particle sampler). Accumulation-mode particles are sufficiently larger than gas molecules that their diffusion velocity is low. Removal by dry deposition is inefficient since they do not readily diffuse through the boundary layer of still air next to surfaces. Therefore, accumulation-mode particles have very long half-lives in the atmosphere, travel long distances, and tend to be more uniformly distributed over large geographic areas than coarse-mode particles. The atmospheric half-life of accumulation-mode particles with respect to dry deposition is on the order of weeks. Removal of accumulation-mode particles occurs when the particles absorb water, grow into cloud droplets, grow further to rain drops, and fall out as rain. This process reduces the atmospheric half-life of accumulation-mode particles to a few days.

Nuclei-mode particles, formed by nucleation of low saturation-vapor-pressure substances, tend to exist as disaggregated individual particles for very short periods of time (<minutes) in the ambient atmosphere due to rapid aggregation into accumulation- mode particles. Thus, nuclei-mode particles, possibly present in continuously supplied high concentrations near high temperature sources, tend to grow rapidly into larger accumulation-mode particles that may be dispersed more widely over long distances.

8.2.5 Sources

The major sources of $PM_{2.5}$ and $PM_{(10-2.5)}$ components are summarized in Table 8-2. The nature of fine and coarse PM sources are very different. Fine particulate matter is produced mainly by the condensation of gases in the high temperature environment of combustion chambers; the condensation of atmospheric precursor gases, some of which may undergo further

TABLE 8-2. CONSTITUENTS AND MAJOR SOURCES OF ATMOSPHERIC PARTICLES

Aerosol species	Sources					
	Primary (PM < 2.5 μm)		Primary (PM > 2.5 μm)		Secondary PM Precursors (PM < 2.5 μm)	
	Natural	Anthropogenic	Natural	Anthropogenic	Natural	Anthropogenic
SO_4^{-2} Sulfate	Sea Spray	Fossil fuel combustion	Sea Spray	—	Oxidation of reduced sulfur gases emitted by the oceans and wetlands; and SO_2 and H_2S emitted by volcanism and forest fires	**Oxidation of SO_2 emitted from fossil fuel combustion**[1]
NO_3^-	—	Motor vehicle exhaust[2]	—	—	Oxidation of NO_x produced by soils, forest fires, and lightning	**Oxidation of NO_x emitted from fossil fuel combustion; and in motor exhaust**
Minerals	Erosion, re-entrainment	Fugitive dust; paved, unpaved roads; agriculture and forestry	Erosion, re-entrainment	**Fugitive dust; paved, unpaved road dust, agriculture and forestry**	—	—
NH_4^+ Ammonium	—	Motor vehicle exhaust[2]	—	—	Emissions of NH_3 from wild animals, undisturbed soil	**Emissions of NH_3 from animal husbandry, sewage, fertilized land**
Organic carbon (OC)	Wild fires	**Open burning, wood burning, motor vehicle exhaust,** cooking	—	Tire and asphalt wear, paved road dust	Oxidation of hydrocarbons emitted by vegetation, (terpenes, waxes); wild fires	Oxidation of hydrocarbons emitted by motor vehicles, open burning, wood burning
Elemental carbon (EC)	Wild fires	**Motor vehicle exhaust, wood burning,** cooking	—	—	—	—
Metals	Volcanic activity	**Fossil fuel combustion, smelting,** brake wear	Erosion, re-entrainment, organic debris	—	—	—
Bioaerosols	Viruses, bacteria	—	Plant, insect fragments, pollen, fungal spores, bacterial agglomerates		—	—

[1]Major source of each component shown in **boldface type**.
[2]Relatively minor primary source of substance, included only for the sake of completeness.

reactions in particles; and the condensation of low vapor pressure photochemical reaction products. Coarse particles, on the other hand, are produced mainly by the mechanical processes (e.g., wind erosion, tire friction).

For a variety of reasons, concentrations of aerosol constituents measured at specific monitoring sites do not reflect the composition that would be obtained from a straightforward application of the emissions shown in Chapter 4. Although mineral dust, from wind erosion, agricultural activities and fugitive dust, represents the largest single category of $PM_{2.5}$ emissions by mass (accounting for 62% of the total), it rarely accounts for more than half of the mass of ambient samples.

In contrast, the results of a number of monitoring studies show that in the eastern and central United States, mineral dust contributes less than 10% of $PM_{2.5}$ and about 15% of $PM_{2.5}$ in the West. During dust storms in arid regions of the West, the fractional contribution of mineral dust to $PM_{2.5}$ can be much higher. Sulfate and associated water of hydration constitute a larger fraction of $PM_{2.5}$ in the East than in the West.

There has been a marked improvement in recent years in the ability of receptor models to apportion PM to its sources. This improvement has come about because of the use of organic species (i.e., organic compounds in the OC fraction) as tracers to distinguish among different forms of combustion (e.g., gasoline vs diesel fueled vehicles, biomass burning, and meat cooking) and even to identify vegetative detritus. The removal of Pb from gasoline had limited the ability of receptor models to apportion PM to mobile sources in the past. However, the use of organic compounds as tracers has been employed in a few studies, mainly in the western United States.

8.2.6 Community and Personal Ambient PM Concentrations Exposure Relationships

As discussed in Chapter 5, atmospheric behavior differences between fine-mode and coarse-mode particles lead to important differences in relationships between personal exposure to these ambient PM constituents and their ambient concentrations measured at a central fixed-site monitor. Fine particles tend to have long atmospheric half-lives, can travel long distances, and therefore can result from distant or widely distributed sources. Evidence from some cities (e.g., Philadelphia), suggest that the concentrations of fine particles may be uniform over large urban

areas. Thus, a $PM_{2.5}$ measurement at one site may give a reasonable estimate of the fine particle concentration across a city or even wider regional areas, assuming the site is not unduly influenced by a local source of fine particles. Ambient coarse particles, however, have more localized and variable sources and, because such particles are rapidly removed, their concentration decreases with distance from the source and the distribution of $PM_{(10-2.5)}$ may not be uniform across a city or region. Thus, people in one part of a city may experience high concentrations of coarse fraction particles on one day while people in a different part of the city may experience high concentrations on another day, even though the city-wide average concentration may be the same on both days. This unevenness of coarse mode particle distribution across a city may need to be taken into account when assessing health impacts in community epidemiological studies.

A further consideration arises with regard to relationships between ambient (outdoor) PM concentrations and personal or indoor exposures to PM of the same AD size. Because people spend most of their time indoors, the particle concentrations indoors tend to dominate personal exposures. However, indoor exposure is due both to particles generated indoors and to ambient particles generated outdoors but which have infiltrated indoors. Major indoor sources of fine particles are smoking and cooking. The major indoor sources of coarse particles are indoor activities that resuspend previously settled PM and that stir up and suspend other materials, including a variety of biological materials such as mold spores and insect debris. Household cleaning, especially dusting and vacuuming, can dramatically increase indoor coarse particle concentrations. When doors and windows are open, both fine-mode and coarse-mode particles will penetrate from outdoors to indoors with little loss in passage. When doors and windows are closed, particle penetration depends on AD size and air exchange rate, with penetration of ambient particles to indoor microenvironments decreasing with increasing AD size. Once indoors, particle sizes influence their half-lives in that microenvironment. Coarse-mode particles are rapidly removed by deposition, whereas ultrafine and accumulation-mode particles have longer half-lives. The production of indoor-generated particles is controlled by daily indoor activities, which Mage et al. (1999) have shown to be independent of ambient PM concentrations. The exposure to indoor-generated particles will often not be significantly correlated with the concentration of ambient (outdoor-generated) particles. Therefore,

time-series epidemiology based on ambient PM measurements is not capable of identifying health effects related to indoor-generated particles.

The various penetration and removal processes for PM can be modeled, and the equilibrium ratio of the concentration of ambient particles which have penetrated indoors and remained suspended to the concentration of ambient particles outdoors (called the infiltration ratio) can be calculated as a function of the air exchange rate, the penetration factor, and the deposition removal rates which are a function of particle AD size. Infiltration ratio calculations, based on data from the Particle Total Exposure Assessment Methodology Study (PTEAM), were depicted in Figure 13-2 of U.S. Environmental Protection Agency (1996). As is evident in Figure 5-13 (Chapter 5, this document) the infiltration ratio of sulfate, which is almost completely of outdoor origin and expected to be in the fine-mode, is greater than that of $PM_{2.5}$. Figure 5-4 (Chapter 5, this document) shows that $PM_{2.5}$, in turn, has a greater infiltration ratio than $PM_{(10-2.5)}$.

The more uniform distribution of ambient fine-mode particles across a city and the higher infiltration ratio for fine particles means that an ambient measure of fine particles at a central site may provide a useful estimate of the average exposure of people in the community to fine-mode particles of ambient origin. For example, experimental data on personal exposure to sulfates, which are predominantly of outdoor origin and in the fine-mode particle size range, show consistently high correlation of total human exposure to sulfate with outdoor central-site measurements of ambient sulfates ($0.78 < R^2 < 0.92$) (Figure 5-13). However, because of the non-uniform regional concentrations and lower infiltration ratios, an ambient measure of coarse particles, such as $PM_{(10-2.5)}$ at a central site, may not provide nearly as good an indication of exposure of people in the community to coarse particles of ambient origin. Much of the time-series epidemiology currently available is based on ambient TSP or PM_{10} measurements, which represent the sum of both fine and coarse (in the case of TSP) or the sum of fine particles and the coarse-mode fraction of TSP less than 10 μm AD (in the case of PM_{10}). In Philadelphia, and in some other cities to a lesser extent (where PM_{10} is not dominated by coarse wind-blown dust), it has been shown that TSP and PM_{10} concentrations correlate better with $PM_{2.5}$ concentrations than with the coarse fraction of PM_{10} ($PM_{(10-2.5)}$). It is thus possible that the observed statistical relationships between various ambient particle indicators and health outcomes are largely due to an underlying relationship between fine-mode particles and health outcomes, or an undiscovered pollutant highly correlated with ambient $PM_{2.5}$ concentrations.

This hypothesis is supported by recent epidemiological analyses (e.g., Schwartz et al., 1996) for cities where both $PM_{2.5}$ and $PM_{(10-2.5)}$ data are available.

8.3 FACTORS AFFECTING PM DOSIMETRY

A full characterization of the exposure-dose-response continuum is needed to reduce uncertainty in extrapolations from laboratory animals or healthy humans to susceptible humans. In the case of PM, this characterization requires understanding of particle deposition and clearance, toxicant-target interactions, and tissue responses.

8.3.1 Factors Determining Deposition and Clearance

Particles are deposited in the respiratory tract by mechanisms of impaction, sedimentation, interception, diffusion, and electrostatic precipitation. Differences in ventilation rates, in the upper respiratory tract structure, and in the size and branching pattern of the respiratory tract may alter particle deposition. Air flow in the extrathoracic (ET) region is characterized by high velocity and abrupt directional changes and, thus, deposition in this region, especially for PM > 1 μm, is mainly by inertial impaction. However, for ultrafine particles, deposition in the ET region is mainly by diffusion although electrostatic precipitation may also play a role. In the alveolar (A) region, deposition by diffusion is important.

Disposition and retention of deposited particles depends on clearance and translocation mechanisms that vary across respiratory tract regions. Sneezing and nose wiping or blowing and mucociliary transport to the gastrointestinal tract via the pharynx are important clearance processes for particles deposited in the ET region, whereas coughing, mucociliary transport, endocytosis by macrophages or epithelial cells and dissolution and absorption into the blood or lymph are important in the tracheobronchial (TB) region. Endocytosis by macrophages or epithelial cells and dissolution and absorption into blood or lymph are important mechanisms in the A region. The fate of a deposited particle depends on the deposition site, physicochemical properties of the particle (e.g., solubility), and time.

Variation in respiratory tract architecture, especially in the smaller conducting airways and gas exchange regions, can be critical to the dosimetry of inhaled particles. Deposition of ambient particles in the lung depends in part upon their aerodynamic and physicochemical properties.

Structural changes in the respiratory tract with chronic obstructive pulmonary disease (COPD) affect airflow and the aerodynamic behavior of inhaled particles. In severe COPD, the healthy portion of the lung receives more of the tidal volume resulting in some ventilatory units receiving a larger particle burden than others. Kim and Kang (1997) demonstrated greater deposition of 1 μm particles in people with varying degrees of airway obstruction than in healthy subjects. The increase in deposition was greatest for COPD patients and asthmatics but was also increased for smokers. Svartengren et al. (1994) showed enhanced deposition in asthmatics. Bennett et al. (1997) reported a greater deposition rate (particles/time) in COPD patients and an increased ventilation which resulted in a total deposition approximately 2.5 fold greater than in healthy adults. Model simulations also predict that dose expressed in particle numbers per anatomical unit would be increased in people with compromised lungs (Miller et al., 1995). Not only may patients with preexisting COPD be susceptible because of an enhanced or altered deposited dose pattern, but their disease may also predispose these patients to altered responses to the toxic effects of ambient PM.

Physicochemical characteristics of particles (e.g., particle diameter, distribution, hygroscopicity) interact with the anatomic (e.g., branching pattern) and physiologic (e.g., ventilation rate, clearance processes) factors to influence deposition and retention of inhaled aerosols. Two key parameters which characterize size distribution are the MMAD and the σ_g of the particles. The relative contribution of these anatomic, physiologic, and physicochemical properties as well as ambient concentration and exposure duration must be integrated to assess overall deposition.

The influence of the particle size distribution on the fraction of particles deposited in the respiratory tract is illustrated in Figure 8-2. This figure depicts the predicted deposition fractions for an adult male, using a typical ventilation pattern, in the alveolar (A), tracheobronchial (TB), and thoracic (A + TB) regions. The difference between total respiratory tract and total thoracic deposition fractions represents the extrathoracic (ET) or upper airway deposition fraction. The deposition fraction in the respiratory tract, relative to unit mass concentration in air, is shown for particles of different MMAD, in the range of 0.1 to 100 μm, for a geometric standard deviation of 1.8. A recent model simulation considered regional deposition in the respiratory tract regions (nasopharyngeal, tracheobronchial, and pulmonary) for the fine and coarse fraction of PM_{10} for both mass and number deposition (Table 8-3). This simulation is for a healthy person breathing

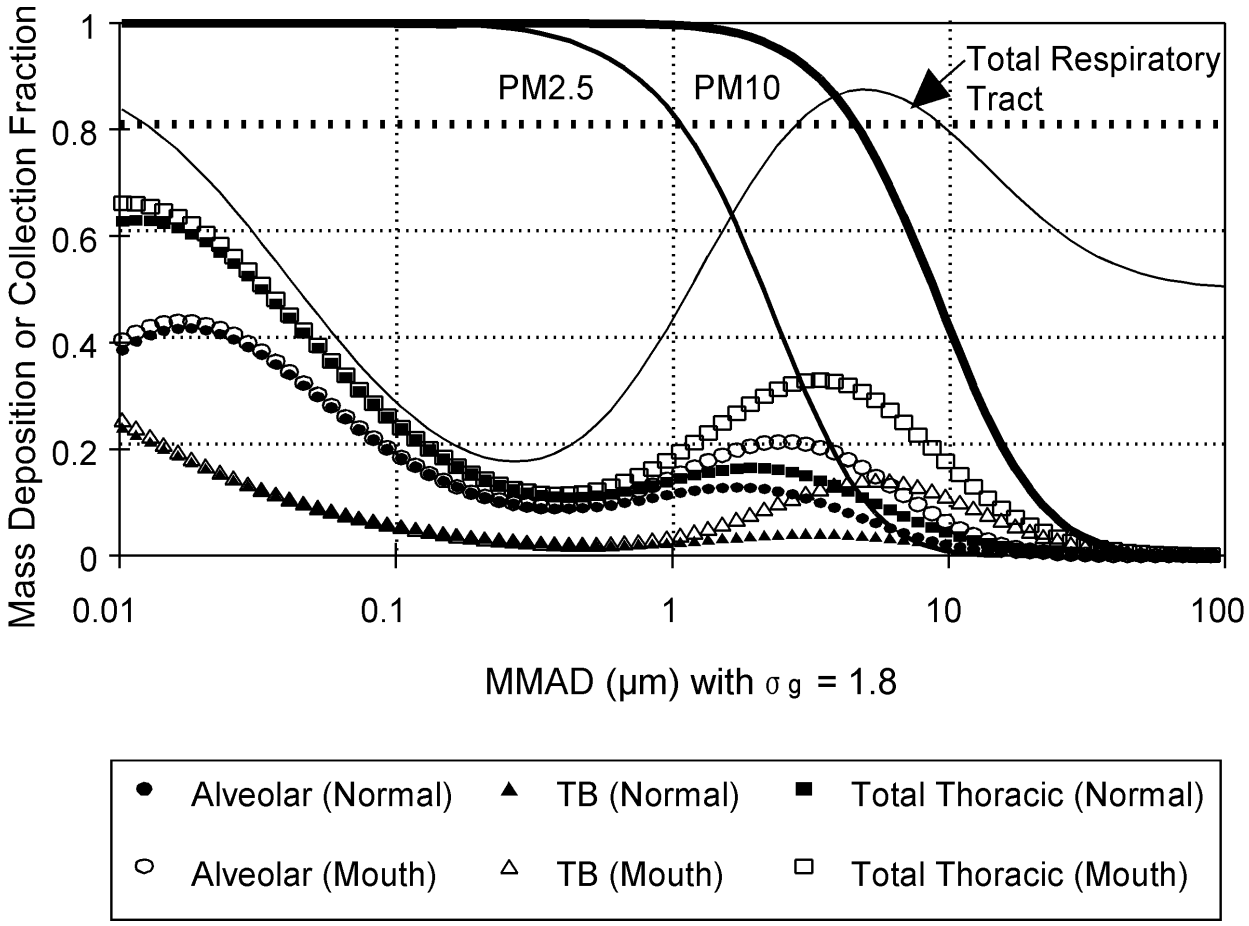

Figure 8-2. Human respiratory tract PM deposition fraction and PM_{10} or $PM_{2.5}$ sampler collection versus mass median aerodynamic diameter (MMAD) with geometric standard deviation, σ_g = 1.8. Alveolar, tracheobronchial, or total thoracic deposition fractions predicted for normal augmenter versus mouth breather adult male using a general population (ICRP66) minute volume activity pattern and the 1994 ICRP66 model.

150 $\mu g/m^3$ PM_{10} (57% $PM_{2.5}$) for 24-h at varying activity and ventilation patterns. The results indicate the clear dominance of both mass and number of fine mode particles in the pulmonary region and the dominance of coarse mode mass in the extrathoracic region.

Simulations, performed for U.S. Environmental Protection Agency (1996), showed that alveolar deposition fraction is fairly uniform for aerosols between 0.5 and 4.0 μm MMAD. Alveolar region deposition increases for particles less than 0.5 μm. Particles in the 0.3 to 0.5 μm

TABLE 8-3. MODEL SIMULATION CONSIDERING REGIONAL DEPOSITION FOR FINE AND COARSE PM_{10} FOR MASS AND NUMBER

Region	For PM_{10} = 150 $\mu g/m^3$ (57% = $PM_{2.5}$) 24 h exposure		
Mass Dose	Fine/ Coarse	Fractional Mass Deposited, μg/day	% of Inhaled Fraction Mass Deposited
NPL	Fine	25-51	1.5%
	Coarse	413-687	30%
TBL	Fine	29-38	1.5%
	Coarse	50-52	4%
PUL	Fine	108-194	6%
	Coarse	44-55	2%
Number Dose	Fine/ Coarse	Fractional Number of Particles Deposited/day	% of Inhaled Fraction Number Deposited
NPL	Fine	5-15 x 10^8	0.06%
	Coarse	6-10 x 10^6	13%
TBL	Fine	2.2-3.1 x 10^{10}	2%
	Coarse	10.7-11.1 x 10^5	2%
PUL	Fine	9.3-16.7 x 10^{10}	9%
	Coarse	13.6-17 x 10^5	3%

NPL = Nasopharyngeal
TBL = Tracheobronchial
PUL = Alveolar - Pulmonary region
Fine = $PM_{2.5}$
Coarse = $PM_{(10-2.5)}$

Source: Venkataraman and Kao (1999)

range undergo the lowest deposition rate in the respiratory tract. In the aerodynamic range of particles ($\geq$ 1.0 μm MMAD), deposition fraction increases as particle size increases and sedimentation and impaction become important deposition mechanisms, especially for larger particles (> 5 μm MMAD) in the TB region. This pattern is altered slightly for mouth breathing versus normal breathing, in that mouth breathers have a greater TB deposition of particles larger than 2.5 μm (i.e., the coarse fraction of PM_{10}) than they would if breathing PM only via the nose.

8.3.2 Factors Determining Toxicant-Target Interactions and Response

Differences in susceptibility can be due to factors influencing deposited and retained particle mass or number, toxicant-target interaction, or tissue response. Deposited particle dose may be characterized in terms of particle mass, particle number, or particle surface area. Furthermore each of these parameters can be expressed per gram of tissue, per cm^2 of respiratory tract surface area, or as dose/unit time. The most suitable metric to characterize a response will likely depend upon the mechanism of action of the particle or particle constituent. The biologically-effective dose may be described by particle mass or number deposition alone if the particles exert their primary action on the surface contacted (Dahl et al., 1991). For longer-term effects, the deposited dose may not be a useful metric, since particles clear at varying rates from the different respiratory tract regions. When considering the epidemiologic data, dose metrics could be separated into two categories, pattern and quantity of acute deposition and the pattern and quantity of retained dose. The deposited dose may be more important for daily mortality, hospital admissions, work loss days, etc. On the other hand the retained dose may be more important for chronic responses.

Many analyses have relied upon the particle mass concentration ($\mu g/m^3$) breathed by exposed individuals. If relative risk (RR) estimates were calculated based on various internal dose metrics (e.g., deposited dose [mass] normalized per unit tracheobronchial or alveolar surface area or normalized per critical cell type such as the alveolar macrophage), relationships could change. The fine fraction contains by far the largest number of particles, and those particles have a larger aggregate surface area than coarse-mode particles. Retardation of alveolar macrophage phagocytosis due to particle overload appears to be better correlated with particle surface area than particle mass (Morrow, 1988; Oberdörster et al., 1995a,b). Also, ultrafine particles have been shown to be less effectively phagocytosed by macrophages than larger particles (Oberdörster et al., 1992a,b).

Figure 8-3 presents an example which illustrates the complexities of considering PM "dose" using different metrics (e.g., such as mass, surface area, and number of particles). For the accumulation mode, which constitutes about 40% of the total mass in the illustrated sample, the geometric mean for the volume distribution, DGV, equivalent to the volume median diameter, is 0.31 μm. When the median diameter is expressed in terms of surface area, or count, the respective median diameters of the accumulation mode are 0.19 μm and 0.07 μm. By far the

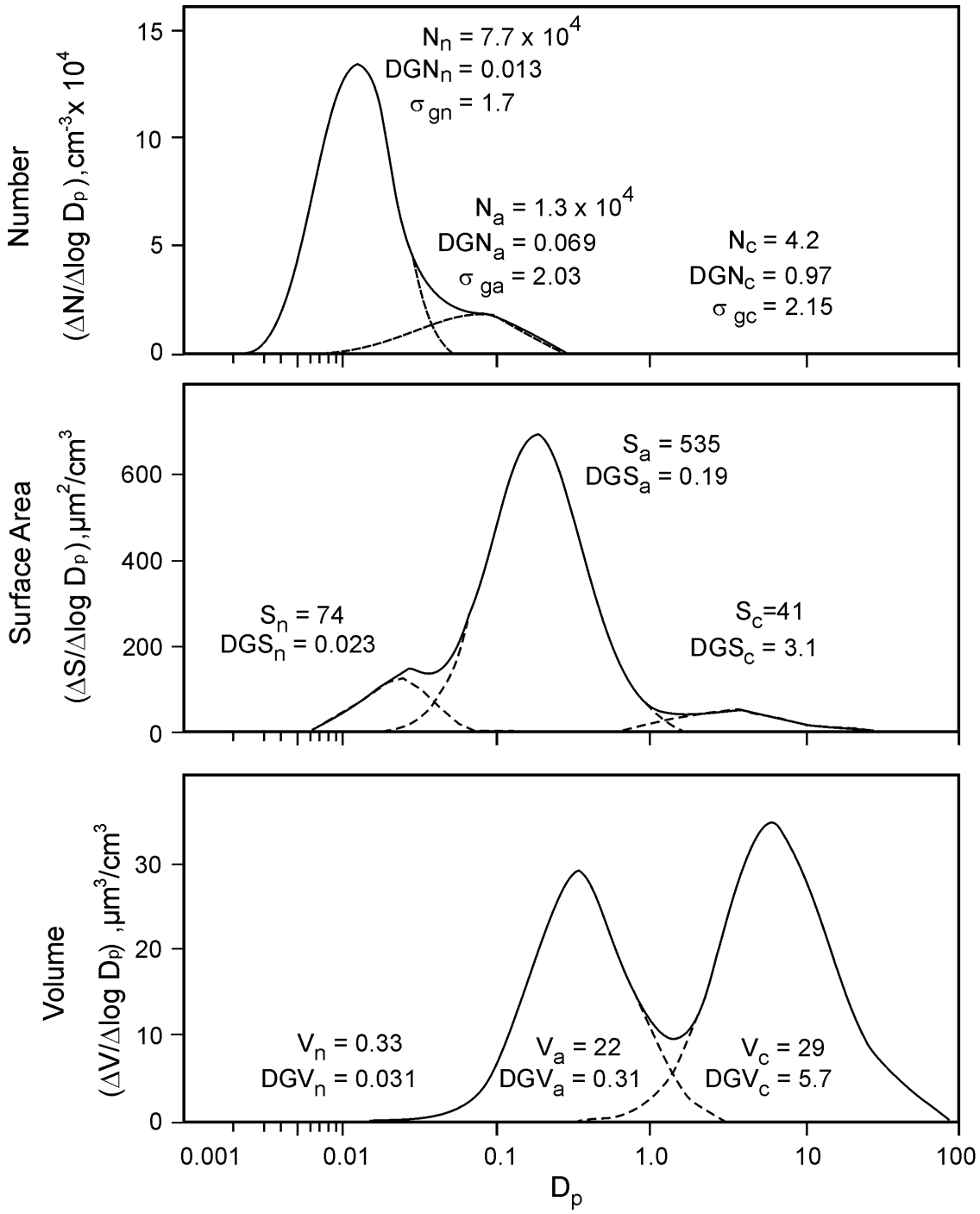

Figure 8-3. Distribution of coarse (c), accumulation (a), and nuclei or ultrafine (n) mode particles by three characteristics: volume (V), surface area (S), and number (N) for the grand average continental size distribution. DGV = geometric mean diameter by volume; DGS = geometric mean diameter by surface area; DGN = geometric mean diameter by number; D_p = geometric diameter.

Source: Whitby (1978).

largest number of particles are contained in the nuclei mode, which is inconsequential in terms of mass. The composition of the particles in each mode is different, as are their hygroscopicity, solubility, translocation pathways, and toxicity.

How could particle size be important in biological activity? The mass of the particle may be important if the mechanism of action of the particle is related to its persistence. Larger particles will typically take longer to dissolve or to be degraded enzymatically. If presentation of active groups to cell surfaces by less soluble particles is important in the mechanisms of action, then the total surface area of the particles should be important. The largest aggregate surface area is in the accumulation mode. Biological effects on epithelial cells or macrophages may depend on the number of cell surface receptors that are contacted or the number of particles ingested by a phagocytic cell.

8.3.3 Construction of Exposure-Dose-Response Continuum for PM

Toxicological data in laboratory animals typically can aid the interpretation of human clinical and epidemiological data because these studies provide concentration- and duration-response information on a more complex array of effects and exposures than can typically be evaluated in humans. However the use of laboratory animal toxicological data has typically been limited because of difficulties in quantitative extrapolation to humans. The various species used in inhalation toxicological studies do not receive identical doses in comparable respiratory tract regions (ET, TB, A) when exposed to the same aerosol (same composition, mass, concentration, and size characteristics). Furthermore, a number of recent toxicological studies of *in vivo* PM effects use intratracheal instillation, which is problematic in terms of extrapolation to inhalation in humans. Such interspecies and methodological differences are important because the adverse toxic effects are likely related more to the quantitative pattern of deposition within the respiratory tract than to the exposure alone; this pattern determines not only the initial respiratory tract tissue dose, but also the specific pathways by which the inhaled particles are cleared and redistributed.

Another difficulty in elucidating the exposure-dose-response continuum using laboratory animal data is that different endpoints are typically assayed in the laboratory animals and the relationship of these endpoints to the human health outcomes have not been established. Epidemiological studies evaluate endpoints such as illness, hospital admissions, and emergency room/doctor visits; homologous biochemical or pathological endpoints in laboratory animal

models are unknown. However, a growing number of newer PM laboratory animal studies have been performed on compromised animal models and, increasingly, human clinical studies are examining the responses of older adults and those with cardiac or pulmonary disease.

In summary, until the mechanism(s) of action for effects induced by ambient PM or its important constituents can be more definitively characterized, the linkage between exposure and response provided by dosimetry cannot be considered quantitative. Thus, any insights to be derived from dosimetry will be limited until the dose metrics that correlate well with PM mechanism(s) of action are determined.

8.4 EXPANDING EPIDEMIOLOGIC INFORMATION ON HEALTH EFFECTS OF PARTICULATE MATTER

8.4.1 Introduction

The purpose of this section is to update the most recent previous assessment (U.S. Environmental Protection Agency 1996) of the information on human health epidemiology studies of effects of exposure to ambient PM. This includes assessment of new scientific evidence in the following areas by: (1) reporting the strengths and limitations of the available epidemiologic findings, particularly those that tend to support or to refute the findings previously reported; (2) assessing the biomedical significance and the coherence of the new studies, including aspects of human exposure to ambient PM and biological consequences of such exposure; (3) evaluating the plausibility of inferences about the relationship(s) between human health and ambient PM exposure based on aerometric studies, exposure assessments, studies of deposited PM dose, and studies on mechanisms of toxicity; (4) assessing the extent to which adverse health effects may be attributable to PM and to other environmental factors, with particular attention to PM size fractions, sources, or specific chemical components; (5) quantifying the relationships between ambient PM concentrations and adverse health effects in susceptible sub-populations at different time scales, where epidemiologic and toxicologic evidence supports such quantification. Table 8-4 summarizes some of this information for fine and coarse mode particles.

In recent years, many epidemiologic studies have shown associations of short-term ambient air pollution exposure with mortality, exacerbation of pre-existing illness, and physiologic

TABLE 8-4. FINE AND COARSE MODE: EXPOSURE, DEPOSITION, EPIDEMIOLOGY, AND BIOLOGICAL EFFECTS

	FINE MODE PARTICLES (FMP)	COARSE MODE PARTICLES (CMP)
EXPOSURE	Ambient monitor representative of personal exposure to FMP mass	Ambient monitor not as representative of personal exposure to CMP mass
LUNG DEPOSITION[1]		
Mass:	AL deposition exceeds combined NP and TB deposition by two fold. Approximately 9% of inhaled mass is deposited	AL deposition is about half of TB deposition. NP deposition about 5x (AL + TB). Approximately 35% of inhaled particles are deposited
Number:	Responsible for > 99% alveolar, > 99% TB	Responsible for < 1% alveolar, < 1% TB
Particles/macrophage:	> 99%	< 1%
EPIDEMIOLOGY		
Acute: Increase in daily mortality		
	2% per increase of 10 $\mu g/m^3$. Statistically significant	0.5% or less per increase of 10 $\mu g/m^3$. Often not statistically significant
Chronic: Decrease in life span		
	Relationship statistically significant	Relationship not statistically significant
INITIATORS OF BIOLOGICAL EFFECTS (Hypotheses, Speculation)	Strong acidity, transition metals, ultrafines, dissolved gases	Silica, biological substances: spores, insect and plant fragments

NP - Nasopharyngeal
TB - Tracheobronchial
AL - Alveolar

[1]Venkataraman and Kao (1999)

changes. These studies have increased concern as to whether ambient air pollution exposure can promote, and perhaps even produce, harmful health outcomes, even when pollutant concentrations are at or below current U.S. air quality standards.

The epidemiologic database regarding short-term ambient air pollution exposure is growing rapidly, and its interpretation is evolving with insights from the new data. As recently as the mid-1990's, many epidemiologic studies had reported associations of mortality and exacerbation of pre-existing disease with ambient levels of PM, some of which had not only demonstrated significant PM associations in single (PM) or multipollutant models but also had investigated or reported such associations with gaseous pollutants (including CO and O_3). Since then, a growing number of epidemiologic studies have given more thorough consideration to both PM and gaseous pollutants, and many have frequently observed positive, statistically significant associations of harmful effects with both. Thus, although associations of PM with harmful effects continue to be observed consistently across most of the new studies, the newer findings appear to complicate further the task of trying to sort out relative contributions to the observed epidemiologic associations of (a) PM acting alone; (b) PM acting in combination with gaseous co-pollutants; (c) the gaseous pollutants *per se*; or (d) the overall ambient pollutant mix. With considerable new experimental evidence also in hand, and after more analysis of this issue, it is possible to hypothesize ways in which ambient exposure to multiple air pollutants (including not only PM acting alone but also in combination with others) could plausibly be involved in the complex chain of biological events leading to harmful health effects in the human population.

In epidemiologic studies of ambient air pollution, small positive estimates of air pollutant health effects have been observed quite consistently. These estimates have frequently been statistically significant at $\alpha \leq 0.05$. If ambient air pollution actually promotes or produces harmful health effects, relatively small effect estimates from current PM concentrations in the U.S. and many other countries would generally be expected on biological and epidemiologic grounds. Also, the magnitudes and significance levels of observed air pollution-related effects estimates have varied somewhat from place to place. This would also be expected if the observed epidemiologic associations denote actual effects, because, not only would the complex mixture of PM vary from place to place but also the affected populations may also differ in characteristics that could affect susceptibility to air pollution health effects. These characteristics include demographic and socioeconomic factors, underlying health status, indoor-outdoor activities, diet, medical care systems and access to them, and exposure to risk factors other than ambient air pollution, such as extreme weather conditions.

Thus, although it has been argued that the observed effects estimates for ambient air pollution are not sufficiently constant across epidemiologic studies and that epidemiologic studies are trustworthy only if they show relatively large effects estimates (e.g., large relative risks), these arguments have only limited weight in relation to ambient air pollution studies. Also, in any large population exposed to ambient air pollution, even a small relative risk for a widely prevalent health disorder could calculate to a substantial public health burden attributable to air pollution exposure.

The ambient atmosphere contains numerous air pollutants, and it is important to continue to recognize that health effects associated statistically with any single pollutant may actually be mediated by multiple components of the complex ambient mix. Specific attribution of effects to any single pollutant may therefore be overly simplistic. PM is one of many air pollutants derived from combustion sources, including mobile sources. These pollutants include PM, CO, sulfur oxides, nitrogen oxides, and ozone, all of which have been considered in various epidemiologic studies to date. Numerous volatile or semivolatile organic compounds are also emitted by combustion sources or formed in the atmosphere, which have not yet been systematically considered in relation to the non-cancer health outcomes usually associated with exposure to criteria air pollutants. In many of the newly available epidemiologic studies, harmful health outcomes are often associated with multiple combustion-related or mobile source-related air pollutants, and some investigators have raised the possibility that PM may be a surrogate or marker for a larger subset of the overall ambient air pollution mix. However, others have reserved judgment on this issue, and many, including the National Research Council (National Research Council, 1998, 1999), have emphasized the need for further research on PM in order to better address this issue.

As discussed above, small health effects estimates have generally been observed for ambient air pollutants, and small effects would indeed be expected on biological and epidemiologic grounds. In contrast to effects estimates derived for the 1952 London smog episode with RR > 4 for extremely high ($\geq$2 mg/m^3) ambient PM concentrations, effects estimates in most current epidemiology studies at distinctly lower PM concentrations (often $\leq$200 to 500 μg/m^3) are small and the statistical estimates (a) are more often subject to relatively small (but proportionately large) differences in estimated effects of PM and other pollutants, (b) may be sensitive to a variety of methodological choices; and (c) may sometimes not be

statistically significant, reflecting low statistical power of the study design to detect a small but real effect.

It seems likely that pollutant effects estimates in multi-pollutant models would be more biologically and epidemiologically sound than those in single-pollutant models, although it is conceivable that single pollutant models might also be credible if independent biological plausibility evidence supported designation of PM or some other single pollutant as likely being the key toxicant in the ambient pollutant mix being evaluated. However, neither of these possibilities have been convincingly demonstrated, and scientific consensus as to optimal modeling strategies for time series air pollution studies has not yet been achieved. Therefore, the choice of effects estimates to employ in risk assessments for short-term ambient air pollution effects remains open to question.

In available studies, statistical uncertainty has generally been assessed rather superficially, without formal consideration of the model tuning performed by the investigators. For example, lag times and averaging times for air pollutant metrics have usually been selected to maximize statistical effects estimates for pollutants. This technique may have led not only to unrealistically large reported effects estimates, but also to inappropriately narrow confidence intervals. In future studies, uncertainty arising from model tuning should be more carefully assessed. In this effort, resampling or simulation procedures, which would recreate the entire model estimation process, should be considered.

Exacerbation of heart disease has been epidemiologically associated not only with ambient PM, but also with other combustion-related ambient pollutants such as NO_2 and CO. Thus, the quantitation of the proportion of risk for such exacerbation specifically attributable to ambient PM exposure is unclear. Recent studies, e.g. concentrated ambient particle studies (CAPS), have demonstrated cardiovascular effects in response to ambient particle exposures and studies utilizing other techniques have also produced various results suggesting some plausible mechanisms for cardiovascular effects. However, much remains to be resolved with regard to delineation of dose-response relationships for the induction of such effects and the extrapolation of such to estimate effective human equivalent exposures to ambient PM (or specific constituent) concentrations.

If observed associations of ambient PM with heart disease exacerbation prove to be causal and specific to PM, they would be of genuine public health concern. In the U.S. in 1997, there

were about 4,188,000 hospital discharges with heart disease as the first-listed diagnosis (Lawrence and Hall, 1999). Among these, about 2,090,000 (50%) were for ischemic heart disease, 756,000 (18%) for myocardial infarction or heart attack (a subcategory of ischemic heart disease), 957,000 (23%) for congestive heart failure, and 635,000 (15%) for cardiac dysrhythmias. Also, there were 726,974 deaths due to heart disease (Hoyert et al., 1999). Even a small percentage reduction in admissions or deaths due to heart disease would predict a large number of avoided cases.

Many investigators have also observed associations of short-term fluctuations in ambient PM with daily frequency of respiratory illness. In most cases, exacerbation of pre-existing respiratory illness has been assessed, though some cases of acute respiratory infection may be considered as occurrence of new illness, especially in young people. Symptoms of acute respiratory distress in children have been linked to elevated PM concentrations in studies in the U.S. and other countries, with asthmatics apparently more susceptible than non-asthmatics. However, some studies have also found associations between child respiratory symptoms or reduced lung function and other pollutants (such as O_3) in addition to PM, or no significant relationship with air pollution. The credibility of ambient PM plausibly being linked to exacerbation of pre-existing respiratory disease (e.g., asthma) is enhanced by newly reported dosimetry study results noted earlier, which show greater lung deposition of 1 μm particles in people with varying degrees of airway obstruction than in healthy subjects. The increased deposition was greatest for COPD patients and asthmatics, but smokers also showed increased deposition as well.

In the United States in 1997, there were 3,475,000 hospital discharges for respiratory diseases; 38% for pneumonia, 14% for asthma, 13% for chronic bronchitis, 8% for acute bronchitis, and the remainder not specified (Lawrence and Hall, 1999). Of the 195,943 deaths due to respiratory diseases, 44% were due to acute infections, 10% for emphysema and bronchitis, 2.8% for asthma, and 42% for unspecified COPD (Hoyert et al., 1999).

A small number of recent studies have identified young infants as an additional subgroup potentially at risk from PM exposures. Effects may include intrauterine growth reduction or low birth weight, known to be infant health risk factors, as well as excess infant mortality. Some studies have found that PM is not as good a predictor of these endpoints as other pollutants, such as CO for example.

The epidemiologic evidence has expanded greatly in quantity, increasing the number and quality of both reported positive findings and some null or negative findings. The most important additions to the database assessed in the 1996 PM AQCD (as evaluated in Chapter 6 of this document) are:

– More studies of health endpoints using ambient PM_{10} and closely related mass concentration indices (e.g., PM_{13} and PM_{7}), which lessen the need to rely on non-gravimetric indices (e.g., BS or CoH);

– New studies on a variety of endpoints for which information on the ambient coarse PM fraction ($PM_{(10-2.5)}$), the ambient fine particle fraction ($PM_{2.5}$), and even ambient ultrafine particle mass concentrations ($PM_{0.1}$ and smaller) were observed or estimated from site-specific calibrations, with somewhat mixed results. Also, a few new studies in which the relationship of some health endpoints to ambient particle number concentrations were evaluated;

– Many new studies which evaluated the sensitivity of estimated PM effects to the inclusion of gaseous co-pollutants in the model;

– Preliminary attempts to evaluate the effects of air pollutant combinations or mixtures including PM components, based on empirical combinations (e.g., factor analysis) or source profiles;

– New studies of infants and children as a potentially susceptible population;

– New studies of cardiovascular endpoints with particular emphasis on assessment of cardiovascular risk factors as well as symptoms;

– Studies on asthma and other respiratory conditions exacerbated by PM exposure.

The new studies are discussed below from the point of view of the aspects (1-5) listed in the first paragraph of this section.

8.4.2 Strengths and Limitations of Newly Available Daily Time-Series Studies

The new studies show a somewhat greater diversity of findings than in U.S. Environmental Protection Agency (1996), shifting attention to the possibility of a multiplicity of PM health effects (and perhaps some non-effects) being associated with PM of different size ranges or chemical composition in a variety of different environmental contexts. While a number of daily time-series studies continue to show significant excess mortality or hospital admissions associated with PM_{10} or $PM_{2.5}$ exposure, some other credible new studies show smaller

non-significant (but positive) associations with ambient PM, whereas a few others report some negative associations.

These differences are often found in multiple-city studies in which the investigators used the same analytical strategies, and models adjusted for the same or similar co-pollutants and meteorological conditions, raising the possibility of different findings being attributable to statistical variability. Examples of newly reported multiple-city studies include the APHEA mortality studies in several European cities (Katsouyanni et al., 1997; Zmirou et al., 1998), mortality in the three Wasatch Front SMSAs in Utah (Pope et al., 1999), mortality in Seoul and Ulsan, Korea (Lee et al., 1999), and hospital admissions in eight U.S. counties (Schwartz, 1999). Findings of some apparent different effects between the adjacent "Twin Cities" of Minneapolis and St. Paul, and between the nearby cities of Seattle and Tacoma (Schwartz et al., 1999) suggest that some components of variability may not be adequately explained by the statistical models, or that differences in adverse health effects attributable to PM may exist at a sub-regional scale. Differences between findings for Western European cities (with relatively high and statistically significant mortality), and for Central-Eastern European cities (with little indication of excess mortality) are most likely attributable to differences in the PM index used and/or differences in implementation of the analytical strategy, although statistical variability cannot be entirely ruled out. The large 20-city and 100-city NMMAPS studies of mortality in U.S. cities now in progress are expected to provide further useful information about (a) the relative importance of PM in the presence of varying ambient co-pollutants and (b) between-region and within-region differences.

8.4.3 Combining Results from Hospital Admissions Studies

Questions about the proper way to combine information from diverse studies need to be considered. It is clear that combined analyses of independent studies at different locations are the most appropriate for meta-analyses, especially when carried out by the same team of researchers, using common methods for data collection and analysis. Independent studies from different investigators, reporting the same endpoints for the same exposure metrics, are next most useful. Many studies for hospital admissions data are discussed in Section 6.2.3. Table 6-19 shows 21 studies of hospital admissions at various locations related to PM_{10}. Some studies were adjusted for two or more co-pollutants, with results shown for PM_{10} RR with O_3 as a co-pollutant, whereas other studies were not adjusted for O_3. Some studies in the same city

report two or more different endpoints, some studies report results for two or more cities using the same or similar methods, and sometimes the same city is analyzed by different investigators, e.g., all-ages respiratory disease in Toronto in Thurston et al. (1994) and Burnett et al. (1997a,b). Consequently, the combined analyses in Table 6-21 involve a smaller number of cities within the same respiratory hospital admissions category and age sub-group: all-age respiratory admissions and asthma admissions, elderly admissions for all respiratory admissions, pneumonia, and COPD, with smaller numbers yet for the multi-pollutant models.

Both the single-pollutant models and two-pollutant combined analyses show positive RR associated with PM_{10}, statistically significant in four of the five endpoints. In two-pollutant models with PM_{10} and O_3, PM_{10} RR ranged from 1.02 (not significant) for all-ages asthma admissions to 1.12 for all respiratory admissions and 1.14 for elderly COPD. Tables 6-20 and 6-22 show similar findings for SO_4^{-2} as the PM metric, with fewer endpoints. The SO_4^{-2} results are positive and significant for all-ages respiratory admissions in single-pollutant and two-pollutant models.

New PM_{10} studies emphasizing cardiovascular outcomes are also described, but are not integrated with the findings for respiratory hospital admissions. A quantitative synthesis across eight U.S. counties reported by Schwartz (1999) shows a statistically significant relative risk of 2.48 per 25 $\mu g/m^3$ (6.15 $\mu g/m^3$ per 50 $\mu g/m^3$ PM_{10}) for hospital admissions for heart disease, in a model that also includes CO as a co-pollutant; the CO effect was also positive and significant. Schwartz's U.S. meta-analyses for cardiovascular disease admissions do not include results from Canada (Burnett et al., 1997a,b; 1999) or Morris and Naumova's (1998) Chicago findings. The results are quantitatively consistent with elevated risk of hospital admission for heart disease, especially in elderly populations exposed to PM_{10}.

Meta-analyses for mortality studies have been reported for the APHEA studies in Europe (Katsouyanni et al. 1997; Zmirou et al., 1998). No recent meta-analyses for mortality have been reported for U.S. cities. The Zmirou et al. (1998) study tends to support findings of significant excess cardiovascular and respiratory mortality associated with PM (as BS) exposure in western European cities, but not in Central-Eastern European cities. These results, and earlier single-city results of daily-time series studies, also find some evidence for effects on total mortality and cause-specific mortality in many (but not all) U.S. cities, and are consistent with the findings of the combined hospital admissions studies.

8.4.4 Strengths and Limitations of Prospective Cohort Studies

The estimation of effects associated with long-term exposure to PM was discussed in some detail in the previous PM AQCD (U.S. Environmental Protection Agency, 1996). The Harvard Six Cities Study (Dockery et al., 1993), the American Cancer Society data base (ACS) Study (Pope et al., 1995), and the Adventist Health Study of Smog in California (AHSMOG (Abbey et al., 1991, 1995) all used the prospective cohort study design. In this design, a cohort of individuals is recruited at the beginning of the study and followed for a long period. Individual subject data are collected at the beginning of the study, and may or may not be updated during followups. Whenever the health outcome of interest occurs, its time of occurrence is recorded. Data analysis compares time to occurrence of the outcome in subjects with different levels of air pollution exposure. These studies are not always designed to be representative of a certain population; they may depend on recruiting volunteers, some of whom may live in the same household or may choose to participate because their friends and relatives participate. Greater randomization may be possible within focused sub-populations, as in AHSMOG.

The shortcomings of this study design in available air pollution studies were discussed in U.S. Environmental Protection Agency (1996). The most important are: (1) community-level concentrations measured at SAM; (2) exposure metrics in the Six Cities and ACS Studies were limited to long-term averages; (3) adjustments for co-pollutants were often not made; (4) important personal covariates may have been omitted; and (5) important personal covariates may have changed during the course of the study. The Six Cities and ACS Studies found rather similar effects of $PM_{2.5}$ or SO_4^{-2} between the most and least polluted cities in the study, for both sexes, including substantially larger effects of PM on total and cardiopulmonary mortality than in the daily mortality studies, and suggested an elevated lung cancer risk. New analyses of the Harvard Six Cities and ACS Studies, sponsored by the Health Effects Institute, are expected to evaluate the sensitivity of the findings to alternate model specifications, inclusion of other personal risk factors, and inclusion of co-pollutants when feasible.

New results from the AHSMOG study (Beeson et al., 1998; Abbey et al., 1999) are somewhat different, as discussed in section 6.3.3. No excesses were found for long-term PM exposure (nor almost any other pollutant) for females for almost all mortality endpoints. There was a very strong relationship between PM_{10} and mortality in males for two causes of death: (1) death from any nonmalignant contributing respiratory cause in the death certificate (as

opposed to the first-listed cause in the other prospective cohort studies); and (2) lung cancer. Males also had a significantly increased incidence of diagnosed lung cancer, but females did not.

The results are summarized in the following Tables, 8-5 to 8-7. These data show the relative risks of total mortality, cardiopulmonary mortality, and lung cancer, by sex and smoking status, for the three prospective cohort studies. The AHSMOG subjects are included with never-smokers, although some past smokers may be misclassified. Smoking status is also subject to mis-classification in the other studies. The statistically most significant results are in the ACS Study, due to the much larger sample sizes than in the other two studies.

TABLE 8-5. RELATIVE RISK (RR) OF TOTAL MORTALITY IN THREE PROSPECTIVE COHORT STUDIES, BY SEX AND SMOKING STATUS

SEX	SMOKING STATUS	STUDY	PM INDEX	PM INC.[1]	RR	RR LCL	RR UCL
F	NON-SMOKER	Six Cities	PM_{10}	50	1.280	0.704	2.345
		ACS	$PM_{2.5}$	25	1.215	1.020	1.440
			SO_4	15	1.147	1.045	1.261
		AHSMOG	PM_{10}	50	0.879	0.713	1.085
	PAST	Six Cities	PM_{10}	50	1.999	0.704	5.632
	PAST + CURRENT	ACS	$PM_{2.5}$	25	1.102	0.898	1.338
			SO_4	15	1.104	0.977	1.240
	CURRENT	Six Cities	PM_{10}	50	1.442	0.719	3.166
M	NON-SMOKER	Six Cities	PM_{10}	50	1.568	0.674	3.678
		ACS	$PM_{2.5}$	25	1.245	1.000	1.554
			SO_4	15	1.104	0.977	1.247
		AHSMOG	PM_{10}	50	1.242	0.955	1.616
	PAST	Six Cities	PM_{10}	50	1.611	0.930	2.825
	PAST + CURRENT	ACS	$PM_{2.5}$	25	1.164	1.051	1.297
			SO_4	15	1.104	1.037	1.176
	CURRENT	Six Cities	PM_{10}	50	1.858	1.090	3.166

Sources: Dockery et al. (1993); Pope et al. (1995); Abbey et al. (1999).
[1]PM increment in $\mu g/m^3$

TABLE 8-6. RELATIVE RISK (RR) OF CARDIOPULMONARY MORTALITY IN THREE PROSPECTIVE COHORT STUDIES, BY SEX AND SMOKING STATUS

SEX	SMOKING STATUS	STUDY	PM INDEX	PM INC.	RR	RR LCL	RR UCL
F	NON-SMOKERS	ACS	$PM_{2.5}$	25	1.585	1.235	2.039
			SO_4	15	1.316	1.147	1.518
		AHSMOG	PM_{10}	50	0.841	0.639	1.107
		AHSMOG - CRC	PM_{10}	50	1.219	0.739	2.011
	PAST + CURRENT	ACS	$PM_{2.5}$	25	1.276	0.918	1.760
			SO_4	15	1.219	1.008	1.465
M	NON-SMOKERS	ACS	$PM_{2.5}$	25	1.245	0.929	1.668
			SO_4	15	1.205	1.023	1.412
		AHSMOG	PM_{10}	50	1.219	0.862	1.616
		AHSMOG - CRC	PM_{10}	50	1.537	0.879	2.688
	PAST + CURRENT	ACS	$PM_{2.5}$	25	1.235	1.061	1.440
			SO_4	15	1.126	1.037	1.233
F+M	ALL	Six Cities	PM_{10}	50	1.744	1.202	2.501

Sources: Dockery et al. (1993); Pope et al. (1995); Abbey et al. (1999).

The only significant Six Cities finding in Table 8-5 is for male current smokers; the AHSMOG subjects have similar RR for total mortality as the ACS and Six Cities Studies. A similar finding in shown in Table 8-6 for cardiopulmonary mortality (no Harvard Six Cities data available by sex), with ACS results significant for non-smokers and smokers in both sexes, and AHSMOG males similar to ACS non-smoking males (though not significant). Lung cancer mortality is not significant for females in any study in Table 8-7, but male lung cancer is highly significant for AHSMOG non-smokers and for ACS smokers in the 151-city study (SO_4).

All of these long-term studies report many statistically significant findings associated with long-term mean PM concentrations. The AHSMOG study also reports more significant and larger relationships with a different PM metric, the mean number of days in the a year in which PM_{10} levels exceed 100 $\mu g/m^3$ (or some other level). Due to the small number of prospective cohort studies, the differences in findings by sex and smoking status, and the "patchy" pattern of

TABLE 8-7. RELATIVE RISK (RR) OF LUNG CANCER MORTALITY IN THREE PROSPECTIVE COHORT STUDIES, BY SEX AND SMOKING STATUS

SEX	SMOKING STATUS	STUDY	PM INDEX	PM INC.	RR	RR LCL	RR UCL
F	NON-SMOKERS	ACS	$PM_{2.5}$	25	0.644	0.203	2.091
			SO_4	15	1.432	0.731	2.800
		AHSMOG	PM_{10}	50	1.808	0.343	9.519
	PAST + CURRENT	ACS	$PM_{2.5}$	25	0.949	0.563	1.595
			SO_4	15	1.074	0.781	1.479
M	NON-SMOKERS	ACS	$PM_{2.5}$	25	0.483	0.086	2.714
			SO_4	15	1.261	0.501	3.190
		AHSMOG	PM_{10}	50	12.385	2.552	60.107
	PAST + CURRENT	ACS	$PM_{2.5}$	25	1.123	0.827	1.533
			SO_4	15	1.316	1.104	1.577
F+M	ALL	Six Cities	PM_{10}	50	1.744	0.689	4.390
		ACS	$PM_{2.5}$	25	1.031	0.796	1.338
			SO_4	15	1.261	1.082	1.465

Sources: Dockery et al. (1993); Pope et al. (1995); Abbey et al. (1999).

comparisons shown in Tables 8-5 to 8-7, a quantitative meta-analysis does not seem to be feasible at this time. Reanalyses of the Harvard Six Cities and ACS Studies by HEI may report the results in a form that facilitates comparison with the AHSMOG findings.

8.4.5 Evaluating the Coherence of the New Studies

Aspects of coherence (Bates, 1992) were discussed in detail by U.S. Environment Protection Agency (1996). Determination of coherence involves assessment of the entire body of epidemiology studies, as well as supporting medical and toxicological data, for consistency across a variety of health outcomes by repeated observation in different populations of individuals, under different circumstances of duration and level of ambient PM concentration, and in different places. The adverse health effects associated with PM are: (1) lung function decrements; (2) respiratory symptoms, or exacerbation of symptoms requiring bronchodilator

therapy; (3) hospital admissions for respiratory and cardiovascular causes; (4) emergency medical visits; and (5) death largely from cardiopulmonary causes in the elderly. None of the currently available time series studies are based on a temporal sequence of these outcomes in single individuals. Panel studies of respiratory symptoms have assessed the repeated occurrence of symptoms in individuals, but not at the progression of, for example, repeated respiratory symptoms into hospital admissions, or repeated hospital admissions into cardiopulmonary mortality. Indeed, the extent to which this progression occurs in the population is uncertain. While some studies are currently underway that will examine large public health data bases, no preliminary results have been published. It is therefore necessary to look at indirect indicators of the quantitative consistency at a group level.

For example, from asthmatic panel studies, it is apparent that mild asthmatics selected for study are seldom hospitalized; their asthma symptoms can largely be controlled by medication. They may be sufficiently mild that changes in pulmonary function or occurrence of symptoms can be detected and self-treated. Although less likely to be selected to participate in panel studies, moderate to severe asthmatics are more likely to go to a hospital or emergency department for asthmatic episodes. There is no clear evidence that ambient PM concentrations are associated with a progression from mild to severe asthmatic symptoms as studied; mild and severe asthmatics appear to be distinct sub-groups.

It is by no means self-evident that the numbers of events on some appropriate baseline of time and reference group will follow a sequence of: lung function decrements > respiratory symptoms > ER visits > hospital admissions > death. There are many causes other than PM for each of these endpoints. For example, lung function decreases with age and chronic respiratory illness and is affected by cigarette smoking and exposure to occupational air pollution.
A number of studies have found an association of mortality with reduced lung function (Strachan, 1992; Higgins and Keller, 1970). Strachan (1992) notes that little is known about the constitutional or environmental determinants of lung function decline. Longitudinal studies such as the Harvard Six Cities Study might possibly be used to evaluate a hypothetical causal pathway. Ambient PM concentration $\longrightarrow$ PM exposure $\longrightarrow$ FEV_1 decrease $\longrightarrow$ death in individuals. The decline of FEV_1 may be either a precursor of ambient-PM-induced health effects, or an independent factor in susceptibility to air pollution effects leading to hospital respiratory admissions or mortality. The relationship of declines of lung function with death is

that a decline in FVC or FEV_1, is prognostic mainly in the later stages of CHF or COPD. This does not necessarily imply that modest declines in healthy people will be prognostic of life shortening.

The relationship of hospital admissions and mortality in independent studies has been studied. Hospital admissions may be affected by health status as well as by environmental factors. For an individual, the relationship of prior hospital admissions to mortality is uncertain. In general non-environmental studies (Seneff et al., 1995), hospitalization in the preceding few months or year is a good predictor of subsequent hospital admissions or death. The major risk factor for subsequent death was the development and severity of non-respiratory organ system dysfunction. Medical intervention is typically provided to the most seriously ill individuals, but if these interventions reduce the likelihood of death associated with elevated ambient PM concentration and exposure, then it is possible that many of the deaths attributed to ambient PM may occur in a less frequently hospitalized population. Consistency would be suggested if there were more cause-specific hospital admissions than deaths from respiratory or cardiovascular causes as described in U.S. Environmental Protection Agency (1996).

The results of peak flow analyses in acute asthma studies consistently show small decrements for both PM_{10} and $PM_{2.5}$. This was observed for both morning (AM) and afternoon (PM) peak flow. Most studies showed increases in cough, phlegm, difficulty breathing, and bronchodilator use, although these increases were generally not statistically significant. The results for nonasthmatic groups of the acute peak flow analyses consistently show small decrements for increases in PM_{10}, similar to those found for asthmatics. The results of the chronic morbidity studies are not consistent. Some studies show effects for some endpoints, but other studies fail to find the same effects. It is generally more difficult to find a gradient in long term exposures than for short term exposure studies. For this reason, it is not surprising that the long-term studies show less consistency than the acute studies.

The results of recent studies of the association of PM mass with hospital admission are generally consistent with and supportive of the studies presented in U.S. Environmental Protection Agency (1996). Moreover, mathematical syntheses of multiple hospital admissions studies for the various age and disease categories were conducted as part of this current assessment. Statistically significant and reasonably consistent RR effect sizes (i.e., within their

respective confidence intervals) were generally found across admissions categories for both PM_{10} and SO_4^{-2}.

A review of the studies summarized in U.S. Environmental Protection Agency (1996) indicated that previously-available epidemiologic studies of chronic PM exposures collectively indicated increases in mortality to be associated with long-term exposure to airborne particles of ambient origin. The PM effect size estimates for total mortality from these studies also suggested that a substantial portion of these deaths reflected cumulative PM impacts above and beyond those exerted by acute exposure events.

The new AHSMOG study (Abbey et al., 1999) provides all-cause mortality RR estimates for adult males that are quantitatively and qualitatively consistent with prior semi-individual studies, especially the Six Cities Study. Extensive new by-gender, by-cause, and multiple pollutant sensitivity analyses, as well as a more comprehensive analyses of numerous potentially uncontrolled factors in this study (such as of the effects of variations in the time spent outdoors) provide important new evidence that is largely supportive of the association of mortality with PM of ambient origin previously reported by the Six Cities and ACS Studies.

Published cross-sectional studies collectively indicate that older adults and infants are the age groups most affected by ambient PM, while both the cross-sectional and semi-individual studies indicate that deaths involving respiratory disease (either malignant or not) are most associated with exposure to PM air pollution. These results are biologically plausible and consistent with a causal relationship between mortality and exposure to PM of ambient origins.

With regard to the role of various PM constituents in the PM-mortality association, cross-sectional studies have generally found that the fine particle component, as indicated either by $PM_{2.5}$ or sulfates, was the PM constituent most consistently associated with mortality. In addition, the Six-cities prospective semi-individual study also indicates that the fine mass components of PM are more strongly associated with the mortality effects of PM than the coarse PM components.

Recent investigations of the public health implications of these PM mortality effect estimates were also reviewed. Life table calculations by Brunekreef (1997) found that relatively small differences in long-term exposure to airborne particulate matter of ambient origin can have substantial effects on life expectancy. For example, a calculation from the 1969-71 life table for

U.S. white males indicated that a chronic exposure increase of 10 $\mu g/m^3$ PM was associated with a reduction of 1.31 years for the entire population's life expectancy at age 25.

Deaths due to respiratory causes may not be consistently observed over different time scales for ambient PM exposures. For example, PM exposures on a short time scale are reported as being associated with excess cardiopulmonary deaths and respiratory hospital admissions. However, it is not clear that such deaths or hospital admissions in association with high ambient PM concentrations represent a long-term difference in the mortality rate, or a displacement of events that would have occurred a few days later without the high PM levels. The prospective cohort mortality studies do not yet allow assessment as to whether the occurrence and frequency of deaths from short-term exposures are consistent with a higher rate of occurrence of deaths, associated with longer-term exposures, on a scale of months or years.

There is as yet little basis (conceptual, experimental, or mathematical) that would allow a quantitative linkage of endpoints between mortality attributable to short ambient PM exposures ("acute") and mortality attributable to longer ambient PM exposures ("chronic" or "sub-chronic"). Exposure indices are more easily compared at different time scales when endpoints are identified (Evans et al., 1984). One hypothesis for discussion is that an individual with high susceptibility to ambient PM at a given moment (e.g., elderly, with an acute respiratory infection as well as COPD or other serious pre-existing conditions) may succumb to a moderately elevated ambient PM exposure or to some coincident cause, although that individual may have survived the same PM exposure if it had occurred during a time of lesser susceptibility to ambient PM.

U.S. Environmental Protection Agency (1996) reported that the relative risk for excess daily mortality associated with a large PM increment (50 $\mu g/m^3$ or 25 $\mu g/m^3$) was only about 1.05, whereas the excess risk associated with 20 $\mu g/m^3$ $PM_{2.5}$ between Portage and Steubenville was 1.26 in the Six Cities Study, and a comparable $PM_{2.5}$ increment found a mortality RR of 1.17 in (Pope et al., 1995) for 50 U.S. cities. This is consistent with the hypothesis that there is a risk from long-term exposure to PM that is substantially larger than just the accumulation of mortality due to PM episodes involving short-term PM exposures.

8.4.6 Evaluating the Plausibility of Inferences about the Relationships Between Human Health and Ambient PM Concentrations

Chapter 5 reviewed the PM exposure literature and the latest advances in our understanding of the relationships between human exposure to PM of ambient origin and ambient PM concentrations (Mage et al., 1999). Until recently, there was some confusion in the air pollution community between the correlation of personal exposure to total PM (PM of ambient origin plus PM of non-ambient origin) and ambient PM concentrations, and correlations of personal exposure to PM of ambient origin and ambient PM concentrations (e.g., Gamble, 1998). PM generated from sources that influence ambient PM concentrations (such as traffic, industry and photochemical reactions) is distinctly different in chemical and toxicological character from PM generated from indoor sources, such as smoking and human-generated detritus (Siegmann et al., 1999). Consequently, these categories of PM need to be treated separately, as they represent distinctly different classes of pollutants.

Chapter 5 shows that the cross-sectional correlation of a group of people's personal total PM exposures and ambient PM concentrations of same AD size is often of order zero because of the highly variable large amounts of non-ambient PM generated by personal activities and indoor sources independently of the ambient PM concentration. However, the longitudinal correlation between a given person's total-exposure to PM and concentration of ambient PM of the same AD size is often of order 0.7 to 0.9. Because people tend to visit the same residential and occupational environments from day to day, where sources of PM and air exchange rates usually have a small variability, the higher individual longitudinal correlations with total PM exposure reflect the correlation of personal exposure to PM of ambient origin with ambient PM concentrations.

Therefore the correlation of human health effects with ambient PM concentrations is a reasonable basis for inferring (a) that there is either an actual relationship between ambient PM concentrations and health effects or (b) that the statistical relationship is confounded by some other gaseous pollutants or ambient PM constituents highly correlated with the total mass of ambient PM.

8.4.7 Assessing the Extent To Which Adverse Health Effects Are Attributable to PM Size Fractions or Components, or Other Environmental Factors

8.4.7.1 Introduction

Recent epidemiology studies have greatly extended the data base from which inferences may be drawn about the health effects of PM size fractions, chemical components, or source categories. The size categories of most current interest ($PM_{1.0}$, $PM_{2.5}$, $PM_{(10-2.5)}$) are now included in new epidemiologic studies of ultrafine particles (Peters et al., 1997; Norris et al., 1999) and in new studies of morbidity and mortality specifically addressing $PM_{2.5}$ and $PM_{(10-2.5)}$, discussed in Section 6.4.6. Effects associated with $PM_{2.5}$ have been found in some new studies, but not all.

The effects of aerosol acidity and sulfate concentration were extensively reviewed in U.S. Environmental Protection Agency (1996) and are assessed again here in Chapter 6 of this document. In general, H^+ and SO_4^{-2} are less consistently reported to be significantly associated with adverse health effects than are $PM_{2.5}$ and PM_{10}, but positive findings occur sufficiently frequently that a contributing role of these species in causing or promoting health effects (possibly in the presence of other pollutants or factors) cannot be eliminated. While toxicological studies of the effects of acids, transition metals, and other specific chemical components of PM (alone or in combination) on animals suggest that adverse effects in humans may also occur, there is as yet little epidemiologic evidence to confirm the predicted effects.

A number of toxicological studies have been carried out with complex materials that simulate specific sources or components of airborne particles, including residual oil fly ash (ROFA) and diesel exhaust emissions (DE), as well as studies with concentrated particles sampled directly from urban air. These studies show numerous physiological and biochemical responses in laboratory animals, particularly in animals with natural or artificially induced pre-existing disease. Only very limited data on concentrated ambient particles and some constituents are available for humans.

Finally, much recent interest has focused on aspects of urban air pollution that can be constructed or derived from multiple-element or multiple-component data. One approach is to construct “source profiles” analogous to those used in various source apportionment studies, and then to estimate the contribution of each source (identified by elemental tracers, for example) to the airborne aerosol mass. Laden et al. (1999) has used this approach to conclude that particle components of “crustal” origin (presumably rich in Al and Si) appear to have no effect on excess

mortality attributable to $PM_{2.5}$ in the Harvard Six Cities Study. A second approach is to construct factors that are combinations of air pollutants and meteorological variables, and to use these factors as predictors of adverse health effects. In a study in Toronto, Ozkaynak et al. (1996) found that some factors predictive of excess mortality involved combinations of air pollutants (including TSP and gaseous co-pollutants), whereas others were almost "pure" factors involving only a single component such as ozone. In particular, weather effects on mortality were largely separable from air pollution effects in Toronto. This tends to confirm the findings of other investigators that effects of weather on health may be large, but are also largely separable from those of air pollution.

It is likely that U.S. cities have important similarities and differences in their source profiles for PM. The "crustal" particles are likely relatively higher in the western states than in the east, and in areas where agriculture or construction produce significant soil turnover. Particles from mobile source internal combustion engines are widespread, although related PM levels may vary substantially from city to city and season to season. In some cities, a measurable contribution to airborne particles may also arise from use of wood or oil for home heating, which may be nearly absent in other cities. In the absence of specific information, it would reasonable to assume that the human health hazards associated with these components may vary from time to time and place to place, so that a single PM mass concentration may imply different levels of potential hazard to human health. Risks associated with a specific PM component within a specific exposure scenario, for example, "heating oil combustion particles during winter air stagnation with temperatures less than 0°C" may be comparable. However, it is unlikely that the sum of the PM components in different exposure scenarios would all consistently add up to an equivalent health risk at equivalent PM mass concentrations within a specific size range. This argument is sufficiently important to warrant evaluation, in some detail, of the evidence for differential toxicity for so-called "crustal" particles.

8.4.7.2 Epidemiology Evidence Suggesting that Crustal Particles Are Less Clearly Harmful to Human Health

Three informative assessments published since 1996 deal explicitly with health effects of PM_{10} in the western U.S. states. PM_{10} is sometimes dominated by particles of crustal or geological origin that are believed to have been transported by wind from rural areas into the

metropolitan areas of Spokane, WA, (Schwartz, 1999) and the Utah MSAs of Ogden, Salt Lake City, and Provo/Orem (Pope et al., 1999). PM_{10} in the Coachella Valley of California is also dominated by coarse particles. The very high PM_{10} concentrations on certain days were presumably not dominated by the typical urban sources of $PM_{2.5}$ and coarse particles. Concentrations of urban source particle mixtures tend to be highest on days with low wind speed, not high wind speed. None of these epidemiology studies used $PM_{(10-2.5)}$ as an index.

The identification of these particles as "crustal" is an indirect inference. Studies reviewed in the 1996 PM AQCD (Gordian et al., 1996; Hefflin et al., 1994) also did not rely on specific identification of coarse crustal particles. The assumption is that most $PM_{2.5}$ particles are produced by combustion sources, and that high concentrations of $PM_{2.5}$ particles occur when locally-produced particles are 'trapped' in an urban airshed by stagnant air (see Chapter 4). During periods of high wind, elevated concentrations of PM_{10} will often be associated with non-local particle sources, such as dusts from agriculture or mineral extraction processes, construction, forest fires, and transport of sand or natural dusts. This can be indirectly assessed by determining whether elevated PM_{10} concentrations occur at the same time as below-average concentrations of $PM_{1.0}$ or of gaseous pollutants that are typically produced by urban combustion sources.

Spokane Study (Schwartz et al., 1999)

There was only limited information about $PM_{2.5}$ particle (FP) concentrations in the Spokane study (Schwartz et al., 1999). Measured $PM_{1.0}$ concentrations were typically less than 10 $\mu g/m^3$ even when PM_{10} concentrations were > 150 $\mu g/m^3$ during dust storm episodes. Fluctuations in $PM_{2.5}$ tended to be proportional to PM_{10} from 12:00 to 24:00 during the high-wind episode. There were also large and proportional fluctuations in $PM_{(10-2.5)}$ and $PM_{(2.5-1.0)}$ during the episode while $PM_{1.0}$ concentrations were reduced and stable. It is likely then that much of the $PM_{2.5}$ was also of crustal origin, especially in the "large fine particle" or "inter-modal" ($PM_{(2.5-1.0)}$) fraction in Spokane.

Conversely, dust episodes may lead primarily to increases in the $PM_{(10-2.5)}$ fraction, with little change in $PM_{2.5}$ or $PM_{1.0}$ based on size-fractionated PM measurements near Fort Ord, California. The large increase in PM_{10} occurs almost completely in the $PM_{(10-2.5)}$ fraction, leaving $PM_{2.5}$ and $PM_{1.0}$ fractions little changed. As shown in Figure 8-4, the lower "hump" represents

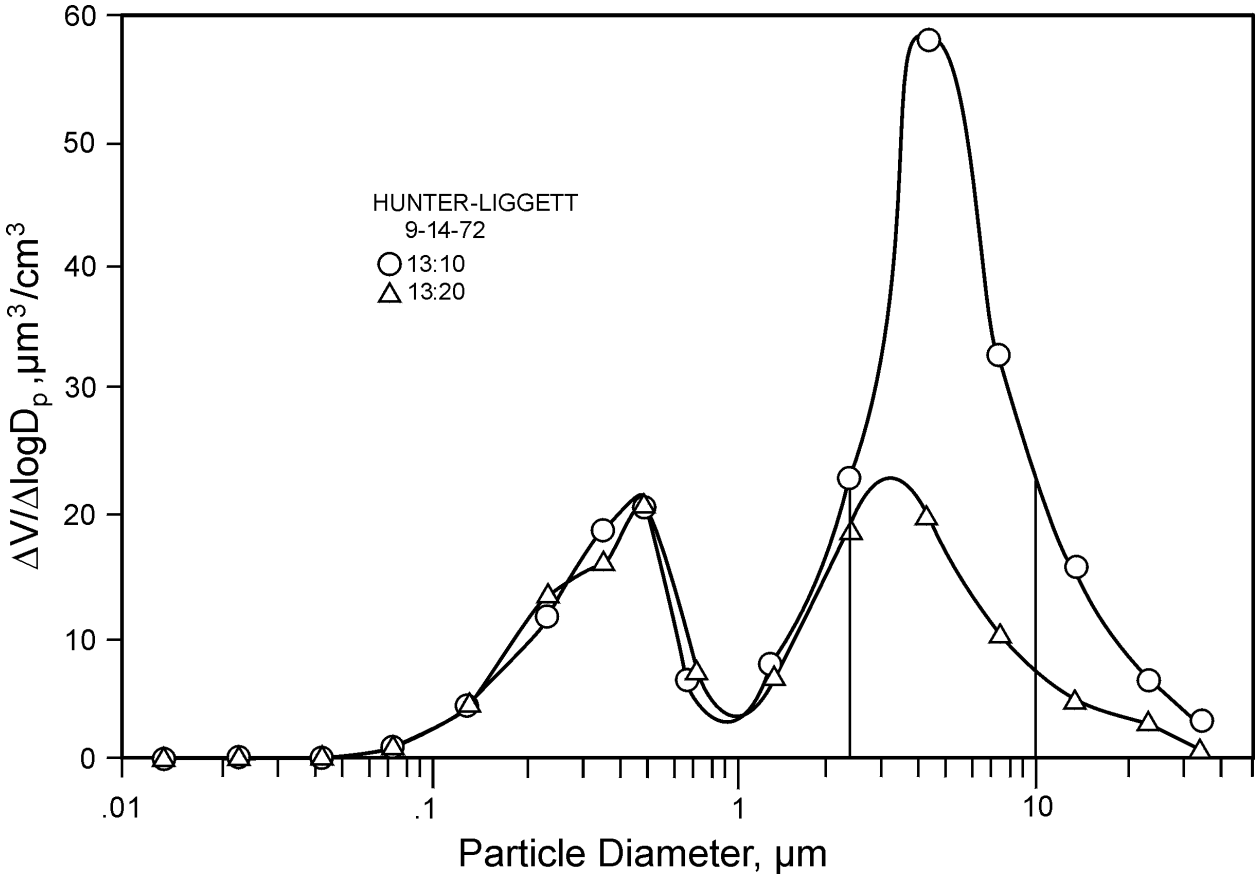

Figure 8-4. Fort Ord CA dust episode: fine and coarse particles.

fine "accumulation mode" particles, typically less than 1 μm. The upper hump represents "coarse-mode" particles. The area between 1.0 and 2.5 μm includes a mixture of "accumulation mode" and "coarse mode" particles. In these figures, $PM_{(2.5-1.0)}$ is dominated by small coarse-mode particles.

In typical urban environments, most of the mass in $PM_{2.5}$ is in the lower accumulation mode hump, but this may be reversed during high wind episodes. The 24-hour particle size distribution for high-wind episodes may be better represented by that shown in Figure 8-5. In Figure 8-5, the coarse mode particles are the predominant component of $PM_{2.5}$ and $PM_{(2.5-1.0)}$, but a very minor component of $PM_{1.0}$. Under these conditions,it is possible that a high concentration of $PM_{2.5}$ of largely crustal origin would not be predictive of toxicity on the assumption that the $PM_{1.0}$ fraction is more toxic. If the $PM_{1.0}$ concentration (primarily from

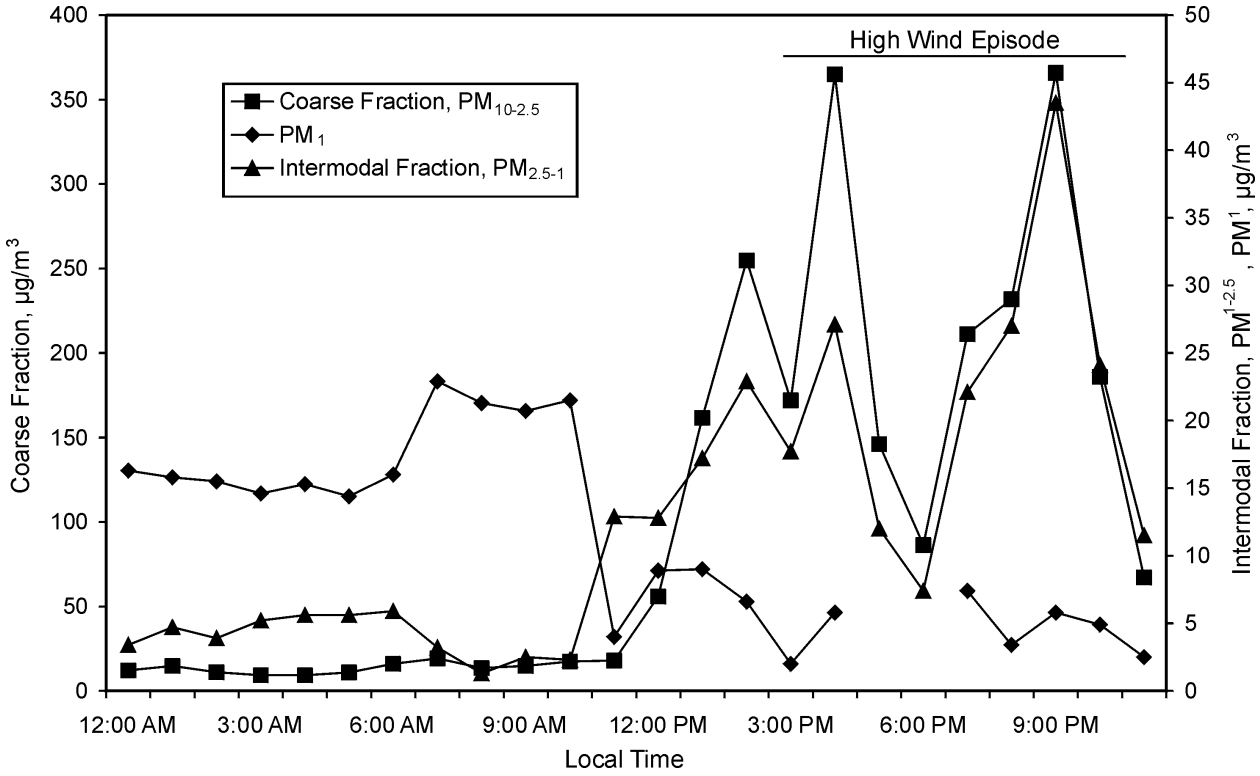

Figure 8-5. Spokane dust storm episodes.

urban particles) is also very low under these circumstances, then there may be little excess mortality associated with $PM_{2.5}$. The findings of Schwartz (1999) support this hypothesis in that they observed no excess mortality during summer dust storms.

Thus, there are at least some conditions under which high concentrations of crustal $PM_{2.5}$ may not be associated with excess mortality in Spokane, and the original nature of the $PM_{2.5}$ particles (both physical and chemical properties) likely determines its toxicity. The findings of Laden et al. (1999) for the very low toxicity of the 'crustal component' of $PM_{2.5}$ in the Six Cities particles tends to support this interpretation.

The above interpretation may not apply to locations where there are substantial contributions of non-crustal $PM_{2.5}$ from non-local sources during high wind episodes. However, it is unlikely that high wind episodes in the Wasatch Front region or in Spokane are associated with greatly elevated $PM_{2.5}$ or $PM_{1.0}$ concentrations transported from other urban areas.

Utah Study (Pope et al., 1999)

Similarly, the Utah studies by Pope et al. (1999) strongly suggest that mortality may be much greater in three Wasatch Front communities during periods when PM_{10} pollution is not attributable to wind-blown dust, as characterized by elevated levels of the clearing index during periods of elevated PM_{10}. The 'clearing index' is an indicator for air movement calculated by the National Weather Service for the Wasatch Front region. It characterizes vertical and horizontal motion of the atmosphere, using wind speed and direction, mixing height, moisture, and temperature, on a scale of 0 (no movement, stagnant air) to 1000. Under stagnant atmospheric conditions, Salt Lake City PM_{10} was dominated by small particles, 55 to 70% in the fraction <1 μm, and 70 to 90% in the fraction <2.5 μm during the winter of 1995-1996. Occurrences of high PM_{10} in Salt Lake City were common during days of high clearing index in Salt Lake City, probably due to wind-blown transport of dust from mine tailings piles, gravel pits, cement plants, salt flats, agricultural fields etc (see Figure 8-6). Such episodes were rare in Ogden and Provo.

It should be noted that elevated PM_{10} concentrations were significantly associated with excess mortality in all three Wasatch Front cities during periods in which crustal particles were unlikely to have dominated the PM concentrations. This suggests that the usual combination of PM from mobile and stationary sources and from secondary aerosols in these SMSAs constituted the major contributions to adverse health effects, but that even higher concentrations of PM_{10} from crustal particles added little additional hazard.

Coachella Valley, California, Study (Ostro et al., 1999)

Recent published studies by Ostro et al. (1999, in press) in the Coachella Valley of California (Palm Springs and Indio) suggest that adverse health effects may be associated with the coarse fraction of PM_{10}. These studies have not been evaluated with respect to the crustal versus non-crustal components of PM_{10} in the coarse and $PM_{2.5}$ fractions. The mortality analyses covered the years 1989-1992, when no $PM_{2.5}$ particle monitoring was carried out. $PM_{2.5}$ particle monitoring during April 1996 - Feb. 1997 showed that PM_{10} in the Coachella Valley was dominated by the coarse fraction ($PM_{(10-2.5)}$) comprising 59% of PM_{10} mass at the Palm Springs site and 64% of PM_{10} mass at the Indio site. The crustal fraction can exceed 90% of PM_{10} during wind events.

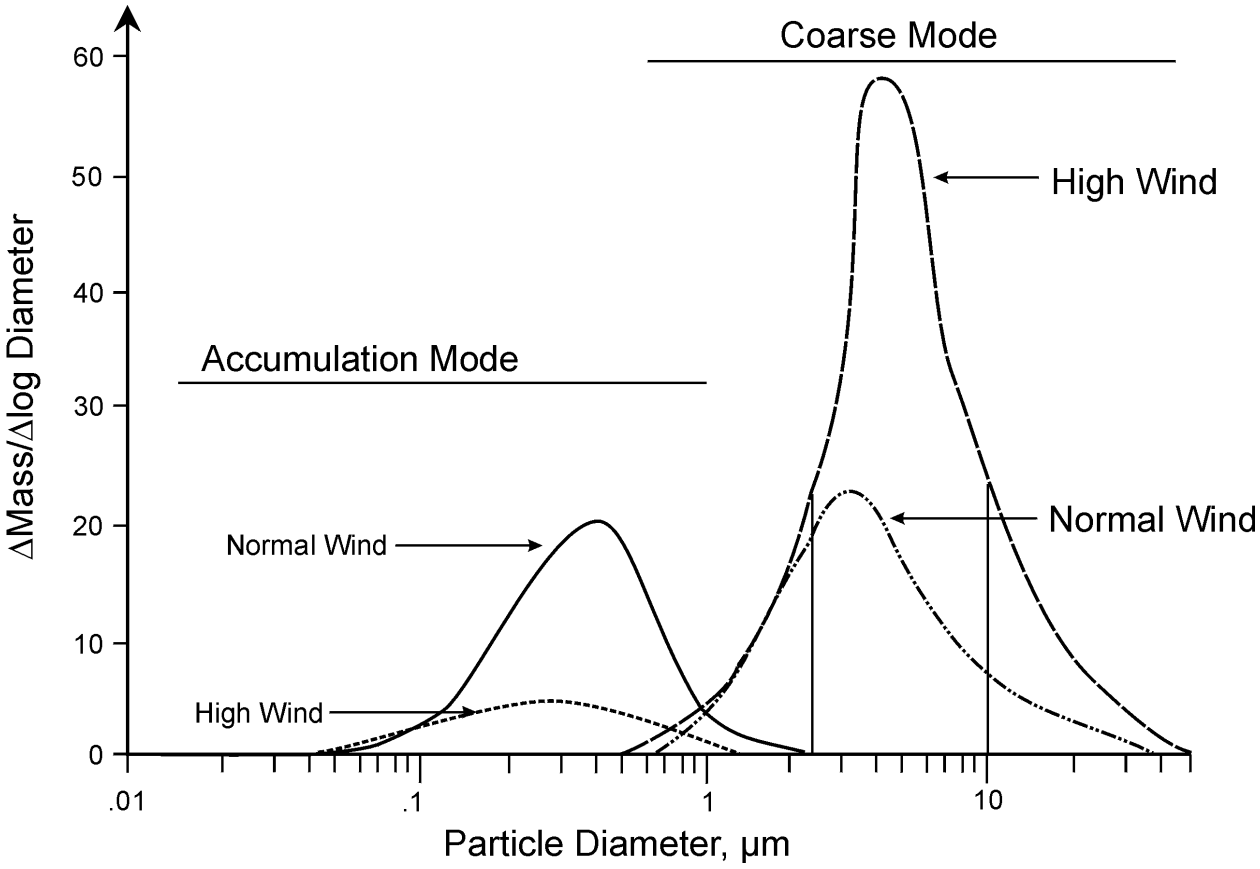

Figure 8-6. During normal wind conditions, accumulation mode particles dominate $PM_{2.5}$. During high-wind conditions, coarse mode particles may dominate $PM_{2.5}$ in some western sites, where coarse particle are predominantly of crustal origin.

Statistically significant associations of total mortality, cardiovascular and respiratory mortality, and mortality in age 50+ populations were found for PM_{10} at lag 2 days, and with 3-day and 5-day moving averages, and were similar in magnitude (RR 1.04 to 1.05 per 50 $\mu g/m^3$ PM_{10} for total mortality) to other U.S. urban areas. The PM_{10} effects were hardly changed when gaseous co-pollutants were included in the models, whereas inclusion of PM_{10} rendered effects of O_3, NO_2, and CO non-significant.

PM_{10} source apportionment studies in the Coachella Valley during 1989 showed that crustal particles comprised 50 to 60 percent of the annual average PM_{10} mass, and much more during 'exceptional' (likely wind) events. During 'exceptional event' days, the percentage of "marine"

particles was also elevated (South Coast Air Quality Management District [SCAQMD], 1990), likely reflecting contributions from the Salton Sea (especially at Indio). Windblown $PM_{(10-2.5)}$ and $PM_{2.5}$ from the Los Angeles region and the Pacific Ocean are probably not highly correlated, due to distance > 160 km and intervening mountains. Thus, crustal particles in the Coachella Valley may have components specific to this airshed. Coarse particles of biogenic origin contribute 13 to 15% of annual average PM_{10} in the Coachella Valley.

Days with highly elevated PM_{10} concentrations probably included days with high wind speed. When days with extremely elevated PM_{10} concentrations (> 91 $\mu g/m^3$) were removed from the data set, the relative risk increased from 1.044 to 1.053 and was more significant. It is therefore likely that the excess mortality was not attributable to elevated concentrations of crustal material on days with elevated wind speed. This finding by Ostro et al. (1999) is thus consistent with Schwartz et al. (1999) and Pope et al. (1999).

A complicating factor is that behavior affecting PM exposure may change substantially on windy days. It is likely that many people spend more time indoors on days with blowing dust and high winds, where coarse particle penetration is less than for fine PM, and their concentrations may be further reduced by the use of air conditioning (especially in the Coachella Valley). The resulting reduction in personal PM exposure during such episodes could contribute to the finding of little ambient PM_{10} effect during such episodes. The extent to which the reduction in personal PM exposure might offset the higher ambient PM_{10} concentrations is unknown.

Six Cities Study (Laden et al., 1999)

The recent abstract by Laden et al. (1999) also describes a method for identification of a crustal component in $PM_{2.5}$ using elemental composition for source apportionment. The "crustal" component shows little relation to excess mortality.

Summary

Several hypotheses may be advanced as interpretations of these findings: (1) Crustal materials in some western PM_{10} appear to have little influence on morbidity/mortality during high wind episodes; (2) On days with high wind speed in which PM_{10} is dominated by crustal materials, the atmospheric conditions also reduce the concentrations of anthropogenic $PM_{2.5}$ and other gaseous co-pollutants presumably associated with PM_{10} toxicity; (3) during non-wind

events with high concentrations of coarse particles, effects may be associated with coarse-mode PM. Exposure to crustal materials in $PM_{2.5}$ is not likely to be greatly reduced on windy days, since a fraction of these particles readily penetrate indoors. The most plausible interpretation of these findings is that either the composition of crustal $PM_{2.5}$ particles or their environmental co-factors contribute to the reduced mortality.

8.4.7.3 Toxicology Evidence Suggesting That Crustal Particles Are Less Harmful to Human Health

Animal toxicology studies of "crustal" particles are mostly limited to inhalation or instillation of volcanic ash particle or amorphous silica. Very high concentrations (>10,000 $\mu g/m^3$) can produce transient inflammation. There are no comparable controlled human exposures. Lifetime (human) occupational exposure to respirable quartz is, however, associated with silicosis and occurs at average concentrations of 50 to 100 $\mu g/m^3$ with a prevalence of up to 20%. Nevertheless, exposure to ambient crustal particles is unlikely to have adverse effects in healthy humans. It is likely that the composition of crustal particles in the ambient environment is not the key factor in their relatively low apparent toxicity, but rather the fact that the particles are large and therefore well filtered out in the upper respiratory tract (URT) and easily cleared after their deposition, mainly in the conducting airways. Nevertheless, it should be noted that 75% of $PM_{2.5}$ particles retained in lung parenchyma in one autopsy study were crustal in nature (Churg et al., 1997). Key components of crustal materials are silicates; both ultrafine crystalline and amorphous silicates are reported to be more toxic than diesel UF particles (Murphy et al., 1998) in laboratory animal inhalation studies.

8.4.8 Quantifying Relationships Between Ambient PM Concentrations and Health Effects in Susceptible Subpopulations at Different Time Scales

Children

Children are often at greater risk of adverse health effects from environmental toxicants than are adults, usually attributable to their greater exposure for body size, greater deposition or uptake, reduced clearance and elimination, or greater susceptibility. On the other hand, sometimes they may be at lower current risk, for example, from toxicants requiring a very long duration of exposure to exert their effects. Some recent new studies appear to suggest that

prenatal or postnatal exposure to ambient PM may be associated with adverse effects at several time scales. Other effects are associated with very short term PM or O_3 exposures, 1 h or 8 h (Delfino et al. 1998), as well as with 24 h exposures. Also, deposition studies tend to show increased extrathoracic deposition of respirable particles in children. Deposition rate may or may not be increased in children, but the higher relative ventilation of children coupled with a smaller lung surface area suggests that greater deposition per unit surface area may occur in children (Bennett et al., 1997b; Bennett and Zeman 1998).

Significant short term effects of PM on lung function and respiratory symptoms in asthmatics, discussed in Sections 6.2.1.1 and 6.4.2, are frequently found in children aged 5 to 17 years. Peak expiratory flow reductions (PEFR) are not generally significantly associated with PM_{10}. Evening PEFR reductions were significant in one study and marginally significant in two of six pediatric studies (lags of 2 to 5 days), with an average reduction of about 1 L/min per 50 $\mu g/m^3$ PM_{10}. Similarly, coughing, phlegm production, and difficulty breathing were elevated with odds ratios on the order of 1.1-1.2 per 50 $\mu g/m^3$ PM_{10}.

Smaller effects have been found in non-asthmatic children (Section 6.2.1.2) with PEFR reduction of about 0.4 L/min per 50 $\mu g/m^3$ PM_{10}. There was less indication of increased incidence of coughing, lower respiratory illness (LRI), or URI in children, except for increased coughing in the Utah Valley. Bronchodilator use and respiratory symptoms associated with sulfates, ozone, or PM_{10} were also found in some studies, but not in others (Tables 6-17, 6-18). The inclusion of co-pollutants in the models slightly reduced the magnitude of the estimated effects, which remained statistically significant.

These studies suggest that children aged 5 to 17 years are susceptible to a variety of respiratory symptoms and pulmonary function decrements associated with PM (Table 6.4.4.2). Various PM indexes such as PM_{10}, BS, or H^+ were significantly associated with increased contact with the medical care system emergency department visits, hospital admissions, or doctor's visits in about half of the studies, particularly for asthma.

Intrauterine or child mortality were reported to be significantly associated with short term exposure to PM in four recent studies. $PM_{2.5}$, PM_{10}, or TSP were significantly related to mortality in three of the five outcomes reported (Table 6.4.4.2.3). Additionally, five of seven studies show long-term ambient PM indices were associated with neonatal and infant health effects (Table 6.4.4.2.5), including total infant mortality, SIDS, infant mortality from respiratory

causes, low birth weight, or premature birth. At this time, however, no biological mechanisms to explain how PM may cause these effects are evident.

The Elderly

Few of the recent time-series studies of mortality have explicitly examined age subsets, particularly ages > 64-65 vs. ages < 64-65 years. Earlier studies evaluated in the 1996 PM AQCD found higher mortality RR for older subjects.

One new study in Mexico City (Borja-Aburto et al., 1997) found RR for TSP of 1.059 for age > 65 compared to 1.058 for all ages. Using $PM_{2.5}$ as the PM indicator, Borja-Abuto et al. (1999) found RR of 1.058 for age > 65, compared to RR of 1.043 for all ages, in a three-pollutant model with O_3 and NO_2 (Table 6.4.6.11), without presenting comparisons for other age groups. Loomis et al. (1999), in another study, found a RR of infant mortality from $PM_{2.5}$ of 1.16 (marginally significant) in a similar three-pollutant model (Table 6.4.6.12). This suggests that both the very young and the elderly may be elevated risk from ambient $PM_{2.5}$ in Mexico City, compared to those at intermediate ages. As for some new Western European studies, Bremner et al. (1999) report effect sizes for mortality in London UK for age groups 0-64 yr, 65-74 yr, > 74 yr, > 64 yr, and all ages. The respiratory and cardiovascular effects appeared to be much larger for age groups 0-64 yr to 65-74 yr than 75+, using BS as an indicator, whereas only respiratory deaths showed a higher elderly rate using PM_{10}. As Bremner et al. (1999) note, "... the number of deaths was three to four times greater in the older elderly group [> 74 years]; this means that the attributable deaths were considerably greater in the older group. ... Young elderly people, however, seem to be more susceptible to the effects of air pollution as judged by the relative risks than their older counterparts who could perhaps be seen as healthy survivors." Also, Prescott et al. (1998) showed BS to be related to significant excess mortality in people of aged > 64 years and smaller positive excess mortality in people of age < 65 years, based on a 14.5 year time series study in Edinburgh UK. In the elderly group, excess mortality was significant for respiratory causes and positive but not significant for cardiovascular causes.

Two Australian studies also found age effects. Morgan et al. (1998) found excess heart disease hospital admissions in Sydney of 2.82% (significant) for ages > 64 years, but only 1.02% (NS) in younger people associated with PM. Simpson et al. (1997) found slight increases in

elderly versus non-elderly mortality RR in Brisbane: 1.010 (signif.) versus 1.001 (NS) for total mortality. Both studies used nephelometer measurements as the PM index.

Two studies of Asian populations (Ostro et al., 1998; Cropper et al., 1997) tended to see a decline in the RR with increasing age, with the largest risk in young children. The relevance of these studies, from a very different socioeconomic situation, to U.S. populations is dubious. These findings may reflect a healthy survivor effect.

Combined analyses for respiratory hospital admissions, presented in Section 6.2, suggest little basis for inferring different age-specific hospital respiratory admissions rates.

Overall the new studies in Mexico, western Europe, and Australia tend to support the findings of somewhat larger associations of mortality and cardiopulmonary hospital admissions with ambient PM in the elderly than in the non-elderly, excepting infants. The findings are not wholly consistent, and suggest that differences between countries in socio-demographic factors such as age structure, distribution of wealth, access to medical care and public health interventions, as well as climate, may be responsible for differences in the susceptibility of the elderly to ambient PM concentrations.

New findings on cardiovascular effects related to ambient PM are particularly important in assessing PM effects on the elderly. The studies described in Section 6.2.4 and discussed in Section 6.4.2.3 (e.g., Peters et al., 1997; Pope et al., 1999; Dockery et al., 1999) include studies in elderly subjects exposed to ambient air, who may or may not have pre-existing respiratory or cardiovascular conditions. These studies suggest adverse biological changes that could have serious consequences in less healthy or more susceptible subjects and add to the plausibility of cardiovascular hospital admissions or deaths associated with current ambient PM levels.

8.5 TOXICOLOGIC EVALUATION OF PATHOPHYSIOLOGIC EFFECTS OF PM CONSTITUENTS AND MECHANISMS OF ACTION

8.5.1 Possible Mechanisms of PM-Induced Injury

Several potential pathophysiologic mechanisms can be proposed by which ambient particles could conceivably contribute to morbidity and mortality. As discussed in Chapter 7, PM has been identified as causing a variety of health effects including respiratory symptoms, mechanical changes in lung function, alteration of mucociliary clearance, pulmonary

inflammatory responses and morphological alterations in the lung. In addition, PM has been associated with respiratory illness, hospital admissions, and increased daily mortality.

In this section, attention is directed at pulmonary and cardiovascular mechanisms which could hypothetically contribute to increased morbidity and mortality. The phenomenon of particle related mortality may include: (1) "premature" death (or mortality displacement), that is the hastening of death for individuals already near death (i.e., hastening of certain death by hours or days); (2) increased susceptibility to infectious disease; and (3) exacerbation of chronic underlying cardiac or pulmonary disease (Utell and Frampton, 1995). The distribution of deposition of particles inhaled into the respiratory tract depends on their size, shape, chemical composition, and the airway geometry and pulmonary ventilation characteristics of the organism. The mechanisms responsible for the broad range of particle-related health affects will vary depending on the site of deposition. Once deposited, the particles may be cleared from the lung, translocated into the interstitium, sequestered in the lymph nodes, metabolized or otherwise transformed.

Deposition of particulate matter in the human respiratory tract could initiate events leading to increased airflow obstruction, impaired clearance, impaired host defenses, or increased epithelial permeability. Airflow obstruction could result from laryngeal constriction or bronchoconstriction secondary to stimulation of receptors in extrathoracic or intrathoracic airways. In individuals with airways disease and localized airway narrowing or obstruction, PM accumulates more rapidly.

Acid aerosols are known to cause slowing of mucociliary clearance. Since this mechanism is important in clearing particles from the lung, including biologically active particles such as spores, fungi, and bacteria, impairment of mucociliary clearance could lead to increased PM burdens, inflammation, and infection. Alveolar clearance may also be impaired through alterations in macrophage function including decreased phagocytosis, depression of mobility, and decreased adherence to surfaces. Retention of PM may be associated with the initiation and/or progression of COPD. Macrophages play an important role in removing and digesting particles and may be involved in facilitating translocation of PM to either other parts of the lung or into the vascular system.

Soluble transition metals such as iron, copper, nickel, vanadium and cobalt, are capable of catalyzing the production of reactive oxygen species, such as hydroxyl radical. These reactive

oxygen species can cause cellular injury and DNA damage which can be inhibited by antioxidants or free radical scavengers. The responses to residual oil fly ash are due in large part to the presence of soluble transition metals; these responses (e.g., inflammation) are much reduced when free radical scavengers are added to the milieu. Concentrated air particles and PM from various sources also show evidence of generating reactive oxygen species. Furthermore, metal chelating agents are capable of reducing responses to PM and ROFA. Both vanadium and nickel appear to be important toxic constituents of ROFA; their role in ambient PM is likely to be much less. The ability of "ambient PM" to induce production of ROS is variable based on the geographic, seasonal, and chemical characteristics of the PM.

Both ROFA and ambient PM can induce or enhance inflammation in the lung; such an effect may depend on particle size and deposition site as well as on chemical or biological composition of the particles. Inflammatory responses can lead to increased permeability and possibly diffusion abnormality. Metal compounds (e.g., $NaVO_3$; Fe_2O_3; $NiSO_4$), either individually or as part of a complex mixture, can initiate an inflammatory cascade using intracellular signaling mechanisms. In addition, ROS can initiate a signaling cascade in epithelial cells that is related to cell proliferation.

Pulmonary changes that contribute to cardiovascular responses include mechanisms which can lead to hypoxemia, including bronchoconstriction, apnea, impaired diffusion, and inflammation. Hypoxic episodes can lead to cardiac arrhythmias and other cardiac electrophysiologic responses. Additionally, many respiratory receptors have direct cardiovascular effects. Stimulation of C-fibers leads to bradycardia and hypertension, while stimulation of laryngeal receptors can result in hypertension, cardiac arrhythmia, bradycardia, apnea, and even cardiac arrest. Nasal receptor or pulmonary J-receptor stimulation can lead to vagally mediated bradycardia and hypertension (Widdicombe et al., 1988). Little is known about age-related changes in airway receptor reflexes and their cardiac effects. Exposure to high concentrations of particles (mainly by instillation) can hasten death in animals with compromised cardiopulmonary systems. These responses are associated with increased inflammation and increased incidence of serious arrhythmias. It is not clear that either inflammation or hypoxia is related to increased mortality; few systemic effects have been examined. Among the systemic effects being investigated are changes in blood coagulation parameters, peripheral blood neutrophil levels, and levels of inflammatory mediators in heart tissue.

Particles that deposit in the lung can also damage respiratory tract cells. The response of the respiratory tract to such particles includes the release of numerous cytokines from alveolar macrophages and epithelial lining cells that promote healing and repair. Repeated cycles of acute lung injury and repair can lead to fibrotic changes in the lung. Such responses are well known in animal models and they typically occur after several weeks of exposure to particle concentrations much higher than those in ambient air.

8.5.2 Ultrafine Particles

In U.S. Environmental Protection Agency (1996), concern was expressed over the potential role of ultrafine particles (UF; defined as particles <100 nm) in human health effects of PM. Ultrafine particles have a high deposition efficiency in the extrathoracic airways (naso- and oropharyngeal). The abundant vascularity of the nasal region and the ability of UF to rapidly enter the interstitium suggests that uptake of UF into the vascular system could occur relatively quickly. Although UF also have a high deposition efficiency in the alveolar region, they constitute a relatively small fraction of the deposited PM mass. However, because of their small size, UF tend to evade endocytosis by macrophages.

Human exposures to ultrafine particles result in varying responses depending upon the composition and concentration of the particles. Zinc oxide UF particles induce metal fume fever and airway inflammation whereas magnesium oxide UF particles do not (Kuschner et al., 1997). Polymer fumes (UF polymer particles) can also lead to fever, diffusion impairment, and respiratory symptoms in humans; similar responses are seen in animals. Ultrafine metal particles cause lung injury and inflammation in rats that are dependent on their composition; nickel is highly toxic whereas TiO_2 is less so (Zhang et al., 1998). However, UF acid aerosol was found to be no more effective than fine acid particles in causing morphologic or ventilatory effects in rats. Nevertheless, UF acid did increase responses of rats to ozone, whereas fine acid PM did not (Kimmel et al., 1997). Ultrafine amorphous silica had more effect on rat respiratory epithelium than either carbon black or diesel exhaust UF particles (Murphy et al., 1998). Thus particle size per se does not appear to be a crucial single index of particle toxicity; rather, the chemical composition of the particle appears to play a key role in its effects once it has been deposited.

However, as discussed elsewhere, particle size is the primary determinant of the deposition pattern of inhaled PM. When an UF particle is deposited at a specific site within the respiratory

tract, the composition of the particle and the sensitivity of the tissues to those particle components may determine its toxicity. Physical particle characteristics (size, solubility) which influence the translocation properties of the particle (e.g., to the interstitium or vascular system), may also play a key role in its toxicity. Oberdörster et al. (1994) compared fine and UF TiO_2 using inhalation exposure and observed that the UF TiO_2 elicited greater inflammation, prolonged retention of UF particles with increased translocation to the epithelium, more epithelial effects, and impairment of macrophage function. Thus, in this case of identical particle composition, the physical properties associated with UF TiO_2 particles leading to their greater persistence within pulmonary tissues, especially in the alveoli and the interstitium, appear to be responsible for their greater toxicity.

8.5.3 Bioaerosols

Ambient bioaerosols include fungal spores, pollen, bacteria, viruses, endotoxin, and animal and plant debris. Bacteria, viruses and endotoxin are mainly found attached to aerosol particles, while entities in the other categories are found as separate particles. Data for characterizing ambient concentrations and size distributions of bioaerosols remain sparse. The proportion of particles that are bioaerosols is variable and they are present in both the fine mode and the coarse mode. The cytoplasmic content of spores and pollen may to be adhered to particles emitted by motor vehicles or particles of crustal origin.

Fungal spores form the largest and most consistently present component of biological aerosols in ambient air. Levels vary seasonally and spatially reaching higher levels during the summer and near some anthropogenic sources (agricultural activities, compost, etc.). Bioaerosols can contribute to increased mortality and morbidity. Association of fungal and pollen spores and fragments with exacerbations of asthma or allergic rhinits is well known.

In addition to fungal spores and pollen, other bioaerosol material can exacerbate asthma and can also induce responses in nonasthmatics. Occupational and experimental exposures of humans to endotoxin (lipopolysaccharide) is associated with increased airway responsiveness, changes in lung function, and airway inflammation. However, these levels vastly exceed those typically present in U.S. ambient air. A classic series of studies (Antó and Sunyer, 1990) proved that airborne dust from soybean husks was responsible for asthma epidemics and increased emergency room visits in Barcelona, Spain. These studies indicate that airborne fragments of

biological substances can produce severe health effects when present in high concentrations. A series of new studies suggest that diesel particulate matter can act as an adjuvant to increase the response to certain antigenic substances, including bioaerosols. Particles may act as carriers as well as promote the response to antigens, leading to the exacerbation of allergic rhinitis and possibly allergic asthma (Diaz-Sanchez et al., 1997).

Because of the extremely limited knowledge of ambient levels of bioaerosols and their composition and relative potency of various components, the small number of well conducted epidemiologic studies of bioaerosols, and the absence of controlled studies of ambient bioaerosols, the relative contribution of bioaerosols to the observed PM-associated morbidity and mortality effects cannot be determined with confidence at the present time. However, it seems unlikely that bioaerosols play more than a minor role in such effects.

8.5.4 Metals

Soluble transition metals play an important role in the effects induced by instillation (suspensions or supernatant) and inhalation of residual oil fly ash (Kodavanti et al., 1998). The predominant metals in ROFA particles are typically vanadium, nickel and iron. Other metals, including zinc and copper, are also present depending on the source of the ROFA. The characteristic responses to the individual metals vary as does their behavior in complex mixtures. Vanadium appears to be associated with airway inflammation and production of reactive oxygen species by alveolar macrophages. Occupational studies have identified vanadium as being associated with “boiler maker’s bronchitis.” Nickel is associated with pulmonary injury caused by ROFA, and thus increased levels of LDH and protein in bronchoalveolar lavage, and is also classified as a human carcinogen. Vanadium activates macrophages whereas nickel does not. There is some evidence that the effects of nickel are antagonized by the presence of vanadium. On the other hand, vanadium has a greater effect on alveolar macrophage ROS production when it is not in the presence of nickel and/or iron. Iron tends to produce less severe effects than either nickel or vanadium; it is associated with inflammatory responses in both humans and laboratory animals. It is apparent that different metal components of ROFA cause different effects and that the individual effects of these metals may not always be expressed to the same extent in mixtures; antagonism has been identified for some endpoints. These findings point to the

complexities of determining a mechanism of response to "PM" and further clouds the prospect of identifying a "magic bullet" that relates increased PM levels to increased human mortality.

8.5.5 Concentrated Ambient Particles (CAPs)

A number of new studies have examined the effects of concentrated ambient particles (CAPs) in animals and humans. Petrovic et al. (1999) have studied a small number of healthy volunteers exposed to CAPs (max concentration of 124 $\mu g/m^3$) from downtown Toronto, Canada. Cardiovascular and respiratory functions showed no adverse effects and there was no indication of pulmonary inflammation or respiratory symptom responses. However, there were trends for plasma fibrinogen and nasal neutrophils to increase.

In laboratory animals exposed to CAPs in Boston, MA (207, 733 and 607 $\mu g/m^3$) for 3 days, lavage fluid protein and neutrophils were elevated, suggestive of an inflammatory response (Clarke et al., 1999). In vitro studies using CAPs demonstrate an increased oxidative burst in exposed alveolar macrophages (Goldsmith et al., 1998). Gordon et al. (1998) found increased peripheral blood neutrophils and decreased lymphocytes after exposure to 110-350 $\mu g/m^3$ CAPs from New York City. Additionally they found a 10-20 beat/min increase in heart rate following the nose-only inhalation exposure. This study shows that ambient PM can cause systemic effects that influence the cardiovascular system.

Studies using diesel exhaust particles demonstrate that diesel particles can act as an adjuvant for inhaled antigens in the nose. In addition to nasal inflammation, diesel exhaust (particles and gases standardized to 300 $\mu g/m^3$ DPM) cause increased neutrophils, ICAM-1, and IL-8 in bronchoalveolar lavage fluid from exposed volunteers. It has also been shown that diesel exhaust causes transcription of IL-8 and other cytokines which are responsible for attracting and activating leukocytes. In support of the findings of Gordon et al. (1998), these studies also found increased neutrophils and platelets in peripheral blood following exposure (Salvi et al., 1999, 2000).

8.5.6 Summary

Particle impacts on the lung depend on particle size, chemical composition, deposition pattern, and particle retention. The effects range from pulmonary responses such as respiratory symptoms, airways inflammation, impacts on particle clearance, and epithelial cellular injury, to

systemic effects such as changes in blood clotting factors, increased peripheral blood neutrophils and changes in myocardial inflammatory mediators.

Smaller particles (PM < 2.5 μm) have greater deposition and long term retention in the respiratory (alveolar) region of the lung because there are fewer large particles in ambient air, their deposition efficiency in the respiratory region is low, and they are likely to be cleared rather than translocated to the parenchyma. However, specific particle components remain to be toxicologically identified with confidence as likely being responsible for the epidemiologically observed effects of ambient PM exposures. Rather, the influence of a given particle constituent varies with the biological function being examined as well as the presence (or absence) of other PM constituents. For example, metals can act additively or antagonistically with each other, and other PM chemical constituents may enhance the effect of biologic components. The number of combinations and interactions of various physical, chemical, and biological components of PM is just beginning to be investigated. Newer data expected to become available during the next several months will likely provide valuable additional information on toxicologically important PM constituents and mechanisms.

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