

## **V. CRITICAL ELEMENTS IN THE REVIEW OF THE PRIMARY STANDARDS**

### **A. Introduction**

This chapter summarizes key information relevant to assessing the known and potential health effects associated with airborne PM, alone and in combination with other pollutants that are routinely present in the ambient air. A more comprehensive discussion of this information can be found in Chapters 10 - 13 of the Criteria Document (EPA, 1996). The presentation here organizes the key health effects information into those critical elements essential for the evaluation of current and alternative standards for PM. Specifically, this chapter summarizes: 1) key dosimetry information and hypotheses regarding mechanisms by which particles that penetrate to and deposit in various regions of the respiratory tract may potentially exert effects; 2) the nature of effects that have been reported to be associated with PM in community air, largely drawn from the more recent epidemiologic information, 3) the identification of sensitive populations and subgroups that appear to be at greater risk to the effects of community air containing PM; 4) issues raised in assessing community epidemiologic evidence on PM, including alternative interpretations of the evidence; and 5) evidence and alternative interpretations of the effects associated with the two major components of ambient PM<sub>10</sub>, fine and coarse fraction particles.

The discussions of hypothesized mechanisms, effects, sensitive populations, and epidemiology include consideration of the full range of particle sizes and composition commonly found in urban and regional air. The PM epidemiological data base has greatly expanded since the last review, and suggests a variety of health effects are associated with ambient PM at concentrations extending from those found in the London episodes down to levels currently experienced in a number of U.S. cities (CD, p 13-1). Although a number of measures of PM have been used in such studies, based on an integrated assessment of the full range of laboratory and observational data, the revised CD and this staff assessment conclude that the ambient particles of greatest concern to health remain those smaller than 10 µm diameter. Accordingly, the discussion of effects, sensitive populations, and epidemiology highlights quantitative information on PM<sub>10</sub>, but also includes some quantitative and qualitative information derived from studies of physical and chemical components of PM<sub>10</sub>. Based on atmospheric considerations summarized here in Chapter IV and supporting health evidence, the CD recommends separate consideration of the

fine and coarse fractions of PM<sub>10</sub>. The final section of this Chapter evaluates the extent to which the available quantitative and qualitative evidence might be used to support separate standards for the fine and coarse fractions of PM<sub>10</sub>.

B. Mechanisms

This section briefly summarizes available information concerning the penetration and deposition of particles in the respiratory tract and outlines hypothesized physiological and pathological responses to PM. It is important to emphasize that, at present, available toxicological and clinical information yields no demonstrated biological mechanism(s) that can explain the associations between ambient PM exposure and mortality and morbidity reported in community epidemiologic studies. Thus, any discussion of possible mechanisms linking ambient PM exposures to mortality and morbidity effects is necessarily limited to hypotheses derived from animal or human studies conducted at exposure levels of PM constituents far higher than found in ambient air. The major purposes of the discussion presented here is to identify available information of greatest relevance that helps identify those fractions of PM that are most likely to be of concern to health, to examine possible links between ambient particles deposited in various regions of the respiratory tract and reported effects in humans, and to focus attention on the kinds of mechanistic research needed to provide a biological basis for elucidating mechanisms that may provide support for a causal link between ambient PM exposures and reported health effects. An expanded treatment of key particle dosimetry considerations, potential mechanisms by which PM exposure is hypothesized to produce effects in humans at ambient exposure levels, and the limitations of the current human clinical and toxicological database can be found in Appendix D and in Chapters 10, 11, and 13 of the CD.

An evaluation of the ways by which inhaled particles might ultimately affect human health must take account of patterns of deposition and clearance in the respiratory tract. The human respiratory tract can be divided into three main regions: (1) extra-thoracic, (2) tracheobronchial, and (3) alveolar regions (CD, Table 10-1, Figure 10-5). The regions differ markedly in structure, function, size, mechanisms of deposition, and sensitivity or reactivity to deposited particles (U.S. EPA, 1982b, CD, Figure 10-6). The junction of conducting and respiratory airways appears to be a key anatomic focus; many inhaled particles of critical size are deposited in the respiratory

bronchioles that lie just distal to this junction, and many of the changes characteristic of emphysema involve respiratory bronchioles and alveolar ducts (Hogg et al., 1968). Retention of deposited particles depends on clearance and translocation mechanisms that vary with each of the three regions (See Appendix D). Coughing, mucociliary transport, endocytosis by macrophages or epithelial cells, and dissolution and absorption into the blood or lymph are important mechanisms of clearance in the tracheobronchial region. Endocytosis by macrophage or epithelial cells and dissolution and absorption into the blood or lymph are the dominant mechanisms of clearance in the alveolar region (CD, pp. 10-55, 56).

Figure V-1 illustrates the regional deposition of particle distributions of varying aerodynamic diameter. In essence, regional deposition of ambient particles in the respiratory tract does not occur at divisions clearly corresponding to the atmospheric aerosol distributions shown in Chapter IV. The CD provides simulations of deposition of ambient particle distributions that indicate fine and coarse particles are deposited in both the tracheobronchial and alveolar regions (CD, Chapter 10). Table V-1 provides estimated deposition patterns in the human lung for typical particle size distributions found in Philadelphia and Phoenix; these simulations are for adult males with normal breathing. The CD shows that as mouth-breathing or workload increases so does deposition in the bronchial and alveolar regions. For those individuals considered to be mouth breathers, deposition increases for coarse particles in the tracheobronchial region (CD, pp. 166-168).

Evidence from epidemiological studies of occupational and historical community exposures and laboratory studies of animal and human responses to simulated ambient particle components suggests that at exposures well above current standards, particles may produce physiological and ultimately pathological effects by a variety of mechanisms. The previous criteria and standards review included an integrated extensive examination of available literature on the potential mechanisms, consequences, and observed responses to particle deposition organized according to major regions of the respiratory tract (EPA, 1982b). Based on this assessment and the composition of typical urban PM, staff concluded, with CASAC concurrence

**TABLE V-1. MODELED 24-HR REGIONAL DEPOSITION FOR MEASURED AMBIENT PARTICLE SIZE DISTRIBUTIONS (After CD Tables 10-21, 23)\***

City	Particle Fraction	Mode Size (MMAD)	Total Mass Deposition	Tracheobronchial Deposition	Alveolar Deposition
Philadelphia	Fine	0.436 $\mu\text{m}$	84 $\mu\text{g}$	9 $\mu\text{g}$	37 $\mu\text{g}$
	Coarse	28.8 $\mu\text{m}$	270 - 330 $\mu\text{g}^{**}$	3 - 7 $\mu\text{g}^{**}$	1-12 $\mu\text{g}^{**}$
Phoenix	Fine	0.188 $\mu\text{m}$	42 $\mu\text{g}$	8 $\mu\text{g}$	26 $\mu\text{g}$
	Coarse	16.4 $\mu\text{m}$	440 - 530 $\mu\text{g}^{**}$	10 - 15 $\mu\text{g}^{**}$	12 - 29 $\mu\text{g}^{**}$

\*Results for normal breathing for adult males. Particle size distribution from impactor data. Total mass assumed 50  $\mu\text{g}/\text{m}^3$ .

\*\*Separate estimated deposition of "intermodal" peak of 2.3 to 2.6  $\mu\text{m}$  in the original table is excluded for clarity, and because this peak may be an artifact of the sampling. Because it is possible that much of this mass (intermode) may be the "tail" of the coarse mode fraction, a range is given for coarse mode mass. The lower bound is the original estimate for the coarse mode. The upper bound is the sum of the estimates for the coarse model plus the intermode. This may tend to overstate coarse mode deposition relative to fine, which also contributes to the intermode.

(Friedlander, 1982), that particles that deposit in the thoracic region (tracheobronchial and alveolar regions), i.e. particles smaller than 10  $\mu\text{m}$  diameter, were of greatest concern for standard setting. The staff identified a number of potential mechanisms and supporting observations by which common components of ambient particles that deposit in the thoracic region, alone or in combination with pollutant gases, might produce health effects (Table 5-2, EPA, 1982b). While there has been little doubt in the scientific community that the historical London air pollution episodes had profound effects on daily mortality and morbidity, no combination of the mechanisms/observations advanced in the last review has been sufficiently tested or generally accepted as explaining the historical community results. Moreover, as noted above, the potential mechanisms cited in the last review were based on insights developed from laboratory and occupational/community epidemiological studies that involved concentrations that are substantially higher than those observed in current U.S. atmospheres, and in many cases using laboratory generated particles that may be of limited relevance to community exposures.

As discussed in the CD, the significant body of new epidemiologic evidence that has accumulated since the last review of PM criteria and standards provides "evidence that serious health effects (mortality, exacerbation of chronic disease, increased hospital admissions, etc.) are associated with exposures to ambient levels of PM found in contemporary U.S. urban airsheds even at concentrations below current U.S. PM standards" (CD, p. 13-1). This increasing evidence

has prompted renewed interest in generating testable hypotheses regarding potential mechanisms that might ultimately provide support for a causal link between health effects and particle exposure at these much lower levels. Table V-2 provides a very general summary of recent thinking concerning how particles may affect sensitive subpopulations as more fully discussed in the Criteria Document (CD, pp. 13-67 to 72, CD, pp. 11-179 to 185) and in Appendix D of this paper.

Because Table V-2 condenses and groups a number of hypotheses that have appeared in the literature and the CD in a summary fashion, several points should be noted. A complete definition of mechanisms of action for PM would involve description of the pathogenesis or origin and development of any related diseases or processes resulting in premature mortality; this is not currently possible. Some of the entries in the Table, on the other hand, may be more accurately described as intermediate responses potentially caused by PM exposure rather than complete mechanisms. The descriptions provide some rationale as to how such responses might conceivably contribute to the types of clinically relevant health endpoints reported in the literature, although evidence for action at low concentrations is presently lacking. It appears unlikely that the complex mixes of particles that are present in community air pollution would act alone through any single pathway of response. Accordingly, it is plausible that several responses might occur in concert to produce reported health endpoints. Some of the hypotheses in the Table may be more likely to be associated with effects from short-term rather than long-term exposure to PM, while others may relate to both. It is also important to note that a number of recent investigations have begun to examine promising new approaches involving new animal models, methods of concentrating ambient particles, and examination of the possibly more toxic constituents of PM such as ultra-fine particles and transition metals. This work, as well as future research, should provide important insights on mechanisms for the next standards review.

**Table V-2. Hypothesized Mechanisms of PM Toxicity\***

<b>Response</b>	<b>Description</b>
Increased Airflow Obstruction	PM exposure may aggravate existing respiratory symptoms which feature airway obstruction. PM-induced airway narrowing or airway obstruction from increased mucous secretion may increase abnormal ventilation/perfusion ratios in the lung and create hypoxia. Hypoxia may lead to cardiac arrhythmias and other cardiac electrophysiologic responses that in turn may lead to ventricular fibrillation and ultimately cardiac arrest. For those experiencing airflow obstruction, increased airflow into non-obstructed areas of the lung may lead to increased particle deposition and subsequent deleterious effects on remaining lung tissue, further exacerbating existing disease processes. More frequent and severe symptoms may be present or more rapid loss of function.
Impaired Clearance	PM exposure may impair clearance by promoting hypersecretion of mucus which in turn results in plugging of airways. Alterations in clearance may also extend the time that particles or potentially harmful biogenic aerosols reside in the tracheobronchial region of the lung. Consequently alterations in clearance from either disturbance of the mucociliary escalator or of macrophage function may increase susceptibility to infection, produce an inflammatory response, or amplify the response to increased burdens of PM. Acid aerosols impair mucociliary clearance.
Altered Host Defense	Responses to an immunological challenge (e.g., infection), may enhance the subsequent response to inhalation of nonspecific material (e.g., PM). PM exposure may also act directly on macrophage function which may not only affect clearance of particles but also increase susceptibility and severity of infection by altering their immunological function. Therefore, depression or over-activation of the immune system, caused by exposure to PM, may be involved in the pathogenesis of lung disease. Decreased respiratory defense may result in increased risk of mortality from pneumonia and increased morbidity (e.g., infection).

Cardiovascular Perturbation	Pulmonary responses to PM exposure may include hypoxia, bronchoconstriction, apnea, impaired diffusion, and production of inflammatory mediators that can contribute to cardiovascular perturbation. Inhaled particles could act at the level of the pulmonary vasculature by increasing pulmonary vascular resistance and further increase ventilation/perfusion abnormalities and hypoxia. Generalized hypoxia could result in pulmonary hypertension and interstitial edema that would impose further workload on the heart. In addition, mediators released during an inflammatory response could cause release of factors in the clotting cascade that may lead to increased risk of thrombus formation in the vascular system. Finally, direct stimulation by PM of respiratory receptors found throughout the respiratory tract may have direct cardiovascular effects (e.g., bradycardia, hypertension, arrhythmia, apnea and cardiac arrest).
Epithelial Lining Changes	PM or its pathophysiological reaction products may act at the alveolar capillary membrane by increasing the diffusion distances across the respiratory membrane (by increasing its thickness) and causing abnormal ventilation/perfusion ratios. Inflammation caused by PM may increase "leakiness" in pulmonary capillaries leading eventually to increased fluid transudation and possibly to interstitial edema in susceptible individuals. PM induced changes in the surfactant layer leading to increased surface tension would have the same effect.
Inflammatory Response	Diseases which increase susceptibility to PM toxicity involve inflammatory response (e.g., asthma, COPD, and infection). PM may induce or enhance inflammatory responses in the lung which may lead to increased permeability, diffusion abnormality, or increased risk of thrombus formation in vascular system. Inflammation from PM exposure may also decrease phagocytosis by alveolar macrophages and therefore reduce particle clearance. (See discussions above for other inflammatory effects from PM exposure.)

\*Summarization from the CD (p. 13-67 to 72; p. 11-179 to 185) and Appendix D of this document.

In conclusion, dosimetric information shows that both fine and coarse fraction particles smaller than 10  $\mu\text{m}$  can penetrate and deposit in the tracheobronchial and alveolar regions of the lung. Particles also may carry other harmful substances with them to these regions with the smaller particles having the greatest surface area available for such transport (see section IV). While a variety of responses to constituents of ambient PM have been hypothesized to contribute to the reported health effects, there is no currently accepted mechanism(s) as to how relatively low concentrations of ambient PM may cause the health effects that have been reported in the epidemiologic literature. Therefore, there is an urgent need to expand ongoing research on the mechanisms by which PM, alone and in combination with other air pollutants, may cause adverse health effects.

### C. Nature of Effects

The evidence for the kinds of health effects associated with exposures to PM comes from a large body of literature dating back more than 40 years. This section reviews and discusses the findings and conclusions concerning the principal health effects associated with PM exposure contained in the CD (CD, Chapters 11,12,13). Evidence for such conclusions and findings as well as for associations drawn from epidemiological studies, controlled human exposures, and animal toxicology is discussed and evaluated in the CD (CD, Chapters 11, 12, and 13), Appendix D of this document, and below. For reasons presented in the previous section, it is more likely that such effects are primarily related to particles smaller than 10  $\mu\text{m}$  in diameter. Evidence with respect to the fine and coarse fractions of  $\text{PM}_{10}$  is discussed in Section V.F.

The scientific information discussed and evaluated in the CD and in this staff paper suggests that the key health effects categories associated with PM include:

- Increased Mortality
- Indices of Morbidity associated with Respiratory and Cardiovascular Disease
  - Hospital Admissions and Emergency Department Visits
  - School Absences
  - Work Loss Days
  - Restricted Activity Days

- Effects on Lung Function and Symptoms
- Morphological Changes
- Altered Host Defense Mechanisms

Most of the effects categories listed above have been consistently associated with PM exposure from a number of community epidemiological studies, with supporting insights from animal toxicology and controlled human exposures of various constituents of PM conducted at higher-than-ambient levels. Primary evidence of PM-related morbidity comes from indicators of aggravation of existing disease. In addition, while mechanisms of lung injury by particles have not been elucidated, there is agreement that the cardio-respiratory system is the major target.

Before discussing the effects, it is important to note some key characteristics and limitations of the kinds of studies used to identify them. The strengths and weakness of epidemiological studies in general are discussed in some detail in the CD throughout Chapters 12 and 13. While epidemiological studies alone cannot be used to demonstrate mechanisms of action, they can provide evidence useful in making inferences with regard to causal relationships, as in the case of cardiovascular disease and cigarette smoking (CD, Chapter 12). The CD discusses criteria for the use of epidemiological studies as an aid to inferring cause-effect relationships rather than merely establishing associations (CD, Section 12.1.2). It then reviews the criteria used to assess the scientific quality of epidemiological studies of community air pollution containing PM<sup>1</sup>. Particularly important issues and uncertainties for evaluation of the PM epidemiology studies are related to model specification, control for potential confounders, exposure misclassification, and consistency and coherence. These issues are discussed in detail in the CD and summarized here in Section 5.E.

Based on a comprehensive evaluation of the extensive published community data, the CD concludes that "the weight of epidemiologic evidence indicates that ambient PM exposure has affected the public health of U.S. populations" (CD, p. 13-27). As the CD points out, however, "little non-epidemiologic evidence is presently available to either support or refute a causal

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<sup>1</sup> Community air pollution refers to the mix of outdoor ambient PM and other pollutants that occur in typical urban/suburban atmospheres.

relationship (i.e., to construct an exposure-dose-response continuum) between low ambient concentrations of PM and increased morbidity and mortality risks" (CD, p. 13-27 to 28).

Under ideal circumstances, animal toxicology and controlled human exposure studies can provide qualitative and quantitative support for environmental epidemiology. In the case of PM, however, the lack of published experimental human and laboratory animal studies involving relevant exposure levels and experimental subjects representative of sensitive subpopulations identified in the epidemiological studies presents problems in providing an integrated assessment (CD, p 13-2). Epidemiological studies describe relationships between regionally and temporally variable mixtures of particles and gases in community air pollution and mortality and morbidity in sensitive populations -- most notably the elderly and individuals with cardiopulmonary disease, which includes adults and children with asthma. In contrast, experimental studies of PM effects in humans tend to use healthy young adult humans (or those with only mild disease) and examine mainly reversible physiologic and biochemical effects from exposure to laboratory-generated acidic aerosols, sulfates or nitrates. Similarly, experimental studies on laboratory animals have tended to use genetically homogenous healthy animals to examine a broader range of effects from individual components of the PM mix. In both animal and human studies, the limited number of individuals exposed greatly limits the ability to detect effects at concentrations close to ambient levels. In addition, extrapolation of quantitative and qualitative results from animal studies to human is encumbered by methodologic difficulties from differences in dosimetry. The various species used in inhalation toxicological studies do not receive identical doses in comparable respiratory tract regions when exposed to identical aerosols (see Appendix D). Consequently few laboratory experiments have used appropriate models of susceptibility to PM which limits evaluation of possible mechanisms and potential quantitative effects comparisons.

However, at least qualitative support for some of the epidemiologic observations has been reported for specific components of the ambient particle mix in controlled clinical studies of humans as well as studies in animals. For such studies, the biological responses occurring in the respiratory tract following PM inhalation encompass a range of effects including: respiratory symptoms such as wheeze and coughing, changes in pulmonary function, altered mucociliary clearance, inflammation, changes in lung morphology and tumor formation (CD, p. 13-70, p. 11-

1). In the vast majority of studies, however, results were observed only at concentrations of specific substances or simple mixtures that are significantly higher than those found in contemporary atmospheres. Because the health effects produced by PM exposure are dependent on the chemical composition, size, and concentration of particles, as well as species tested, these aspects of experimental paradigms used to characterize PM toxicity are noted in the following discussion. However, in this discussion, the emphasis is placed on reported effects of PM in general, rather than a specific emphasis on particle size or composition.

Key evidence illustrating each of the major effects categories listed above is outlined below, with an emphasis on the more recent information.

## 1. Mortality

### a. Mortality From Short-Term Exposures to PM

#### i. Historical Findings From Community Epidemiology

The most notable reports of the health effects from community air pollution containing high PM have come from the dramatic pollution episodes of Belgium's industrial Meuse Valley (Firket, 1931); Donora, Pennsylvania (Schrenk et al., 1949); and London, England (Ministry of Health, 1954). In these cases, winter weather inversions led to very high particle concentrations in ambient air, which were associated with large simultaneous increases in mortality and morbidity (especially among individuals with preexisting cardio-pulmonary conditions). In a ten year follow-up study, survivors of the Donora, Pennsylvania pollution episode with either chronic disease prior to the episode, or those who became acutely ill during the episode, were found to have higher subsequent rates of mortality and illness (Ciocco and Thompson, 1961).

Analyses of a series of episodes in London indicated an excess of mortality (mostly from cardiopulmonary causes) occurred with abrupt increases in particles (including sulfuric acid) accompanied by simultaneously high levels of SO<sub>2</sub> (Martin, 1964; Martin and Bradley, 1960). Although the London studies measured PM as British Smoke (BS), gravimetric mass calibrations permitted development of quantitative mass-concentration relationships. There was general acceptance in the 1982 CD (EPA, 1982a) and in critical reviews of PM-associated health effects (Ware et al, 1981; Holland et al, 1979) that London air pollution at high levels (at or above 500 - 1000 µg/m<sup>3</sup> of both pollutants) was causally related to increased mortality.

During the previous review of the PM standards, the London mortality studies were augmented by several more extensive time-series analyses examining the PM pollution/mortality relationship across 14 London winters (e.g, Mazumdar et al, 1982; Schwartz and Marcus, 1986; Ostro, 1984). These studies used more sophisticated statistical techniques to examine relationships between routine variations in PM and sulfur dioxide levels and mortality. Such analyses showed a continuum of response across the full range of PM levels in London and suggested that effects from exposure to PM occurred at levels more similar to those observed in the U.S.. Some of these studies suggested, although not conclusively, that particles were more likely to be responsible for the associations of health effects with air pollution than SO<sub>2</sub> (e.g., Mazumdar et al 1982). These studies and analysis of associations of health effects with the lower levels of PM measured in the 14 London winters (150 µg/m<sup>3</sup> as BS) was influential in the selection of the level of the current 24-hour PM<sub>10</sub> standard (EPA, 1982b; 1986).

#### ii. Recent Findings

Beginning in 1987, two important developments took place. Investigators began to use more sophisticated statistical techniques, originally based on econometric techniques, to further evaluate the association between short-term variations in PM and mortality (CD, p 12-32). In addition the expansion of particle monitoring, related to the revision of the standard, increased the information concerning size-specific PM levels in cities throughout the U.S.. From 1987 to present, numerous epidemiological studies have reported statistically significant positive associations<sup>2</sup> between short-term exposures to PM and mortality. In these studies, investigators have observed statistically significant associations between increased daily or several-day average concentrations of PM (as measured by a variety of indices: TSP, PM<sub>10</sub>, PM<sub>2.5</sub>, COH, KM, and BS) and excess mortality in communities across the U.S. as well as in Europe and South America. Of 38 studies published between 1988 and 1996, most found statistically significant associations between increases in ambient PM concentration and excess mortality (CD, Table 12-2). These studies are consistent with the earlier analyses of the London winters, but extend the association

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<sup>2</sup> Unless otherwise noted, statistically significant results are reported at a 95% confidence level.

to lower concentrations for a large number of areas with differing climate, aerosol composition, and amounts of co-occurring gaseous pollutants such as SO<sub>2</sub> and O<sub>3</sub>.

Table V-3 presents a comparison of relative risk estimates reported for PM-related mortality expressed in terms of a PM<sub>10</sub> increment. A generally consistent association is found between changes in PM<sub>10</sub> levels and mortality in most of these studies, with a range of 2 percent to 8 percent increase in daily mortality for a 50 µg/m<sup>3</sup> increase in PM<sub>10</sub> for those with statistically significant results. In the studies with statistically significant results, mean PM<sub>10</sub> concentrations ranged from 18 to 58 µg/m<sup>3</sup> and maximum daily concentrations from 80 to 365 µg/m<sup>3</sup>. These studies were conducted in a number of different geographic locations in North America. Each of these locations differ significantly in pollution and weather patterns. Yet most of these studies finds a statistically significant association between increased mortality and PM<sub>10</sub> that is relatively consistent across the studies. It is of note that a rough estimate of the relative risk for a 50 µg/m<sup>3</sup> increase in PM (as PM<sub>10</sub>) for the 1952 episode in London (1.06) is in the range of those reported for the recent studies (Schwartz et. al., 1994).

### iii. Specific Causes of Mortality Associated with PM

Table V-4 summarizes the relative risks for total mortality, respiratory and cardiovascular causes of death, and mortality among the elderly for the community studies evaluating cause of death. Reported cases of "respiratory related" deaths were assigned to individuals who had been diagnosed with acute respiratory illness (e.g., symptoms involving the upper respiratory tract and pneumonia), as well as COPD and pneumoconioses when they died. In general, these studies reported stronger significant relationships between short-term PM concentrations and deaths in those with respiratory and cardiovascular disease than for other conditions, as well as a larger effect in the elderly (>65) than in the general population (CD, Chapter 12; Styer et al., 1995; Ostro, 1995a; Schwartz, 1994a; Pope et al., 1992). The CD notes that the relative risk for respiratory-related mortality was up to 4.3 times as large as that for total mortality (CD, p. 12-77). As noted in the CD, such results are supportive of the biological plausibility of a PM/air pollution effect on mortality.

### iv. Experimental Animal Studies

The vast majority of studies examining short-term exposures to animals of components of PM have found mortality only at concentrations well above ambient levels of PM, even in sensitive species (e.g., guinea pig). Such studies appear to be of little relevance to the effects observed in humans at ambient levels (CD, Table 11-18, p. 11-42,43).

b. Mortality From Long-Term Exposures to PM

Prior to 1990, cross sectional studies were generally used to evaluate the relationship between mortality and long-term exposure to PM. These, as well as more recent cross-sectional studies, are summarized in Tables 12-14 and 12-15 in the CD. These studies have reported, for at least one of the experimental designs used in each study, statistically significant positive associations linking higher long-term concentrations of various indices of PM with higher mortality rates across communities. However, absent other supporting evidence, the unaddressed confounders and methodological problems inherent in these studies have limited their usefulness. The previous staff paper concluded that such studies provided only suggestive evidence of long-term mortality associated with PM exposure (EPA, 1982b). In the recent literature, however, new prospective cohort studies have reported results that may lend additional support to the earlier results. These studies use subject-specific information and appear to provide more reliable findings (CD, section 13.4.1.1), although the uncertainties in controlling for a number of factors such as smoking, lifestyle, and exposure patterns are improved by the design of cohort studies, they remain greater than for short-term studies conducted in single communities. The results of three recent studies (Abbey et al., 1991; Dockery et al., 1993; Pope et al., 1995) are summarized in Table V-5 and described briefly below.

Dockery et al., (1993) analyzed survival of 8,111 adults followed for 14 years in six cities in the eastern U.S. (Six City Study). Extensive information was obtained regarding potential confounders for each individual, including, smoking, education level, and occupation. After adjustment for these co-variates, the authors found elevations in several measures of long-term PM concentration ( $PM_{15/10}$ ,  $PM_{2.5}$  and sulfates) were significantly associated with increases of total mortality. The adjusted increase in risk (26 percent, CI of 8-47 percent) from PM exposure was nearly equal for  $PM_{15/10}$ ,  $PM_{2.5}$  and sulfates between the cities with highest and lowest levels of air pollution.

A second prospective cohort study was conducted by Pope et al. (1995) which used 7-year survival data, between 1982 and 1989, for over half a million adults in 151 U.S. cities [American Cancer Society (ACS) study]. This study was designed to follow-up on the suggestion made from the Six City study that long-term exposure to fine particles is associated with increased mortality. To test this hypothesis, the association between multi-year concentrations of two fine particle indicators, sulfates and  $PM_{2.5}$ , and mortality was evaluated. As in the Six City study, information for each individual was used to adjust for important risk factors, such as age, sex, race, smoking, passive smoking, and occupation. After adjustment for the other risk factors,  $PM_{2.5}$  concentrations were found to be associated with a 17 percent (CI of 9-26 percent) increase in total mortality, with sulfate concentrations associated with a 15 percent (CI of 5-26 percent) increase in total mortality, between cities with the least and most polluted air.

The Six City study found somewhat higher RR estimates for mortality than the ACS study. The sensitivity of the RR estimates to important confounders can be assessed by evaluating the effects estimates for different subgroups of the populations (Table V-5). Two subgroups in this population with high potential for confounding are smokers and those with occupational exposures to PM. With regard to smokers, both the Six City and ACS studies evaluated the association between fine particle levels and total and cause-specific mortality by smoking status. The ACS study compared the risk of mortality associated with PM separately for those who never smoked and those who have at one time smoked. The Six City study compared risk of mortality associated with exposure to fine particles for the total population, former smokers, current smokers, and nonsmokers. All categories showed elevated risk; only the non-smoking category failed to achieve statistical significance. The ACS study, which had a much larger population and consequently greater statistical power, found a statistically significant association with total mortality and nonsmokers as well as for the total population and current and former smokers. It is possible that the RR estimates are sensitive to specification of smoking and occupational exposure, and as such adjusting for these variables in the Six City study may have been inadequate to fully capture the potential confounding from these variables.

The Six City study also evaluated the RR of mortality for the population non-occupationally exposed, defined as those who report no exposure to gases, fumes or dust. The

RR for non-occupationally exposed individuals similar to that for non-smokers, but also did not achieve statistical significance. The ACS study did not evaluate the occupational subgroup separately. However, the authors note that the RR was not sensitive to the inclusion of occupational exposure variables after adjusting for cigarette smoking.

Some reviewers have raised concerns regarding the adequacy of the adjustment for confounders in the prospective cohort studies, maintaining that other uncontrolled factors may well be responsible for the observed mortality rates (Lipfert, 1995; Moolgavkar and Luebeck, 1996; Moolgavkar, 1994). In particular, these authors have suggested that the Six City Study did not control adequately for smoking and other factors. However, both the Six City Study and the ACS study evaluated the association between PM and mortality among never smokers and found relative risks that were similar in magnitude, and for the much larger population in the ACS study, statistically significant. Lipfert (1995) evaluated the Six Cities using State average sedentary lifestyle data. Based on this evaluation, he suggested that much of the mortality associations in the Six Cities might be explained by this additional factor, if it had been included in the original study. Aside from the fact that such State average data suffers from the same problems that have plagued past cross-sectional analyses, both the Six City Study and the ACS study adjusted for body mass index as well as other factors using individual specific data that should provide adjustments that are related to sedentary lifestyle. The CD notes that it is unlikely that these studies overlooked plausible confounders, although the addition of unaccounted factors might well alter the magnitude of the association (CD, 12-180).

Both the Six City and the ACS studies evaluated specific causes of mortality associated with PM (Table V-5). As with the short-term studies, the increase in risk of mortality associated with PM was mostly attributed to increases in mortality from cardiopulmonary causes. The Six City study reported a 37 percent (CI of 11-68 percent) increase in mortality from cardiopulmonary causes associated with PM<sub>2.5</sub> levels, after adjusting for covariates, between the most polluted and least polluted city. Similarly, the ACS study reported a 31 percent (CI of 17-46 percent) increase in such mortality associated with PM<sub>2.5</sub> levels, after adjusting for covariates, between the most polluted and least polluted city. Taken together, the ACS study and the Six

City study did not find any other statistically significant associations between PM levels and specific causes of mortality other than from cardiopulmonary causes.

Neither study showed any statistically significant increase in risk for lung cancer associated with undifferentiated fine PM exposure, although the ACS study found a significant association with sulfates. While earlier studies provided some evidence suggestive of an association of increased cancer at high PM exposure levels, the 1982 CD could not draw any conclusions with regard to such an association. Thus, there continues to be little epidemiological evidence for an effect of ambient PM on cancer rates. Evidence of potential cancer risk from specific particulate matter components comes from laboratory studies. Polycyclic aromatic hydrocarbons (PAHs), commonly found as combustion products, are perhaps the best studied class of potential carcinogens in PM. Extracts of organic material from particle emissions have been shown to induce tumors in a variety of studies (CD, p. 11-123). Extrapolation to human risk from such studies are difficult because of different species and age, route of exposure (e.g., not inhalation assays in animals), physico-chemical properties of the material, and exposure concentration. In any event, no clear evidence of sulfates acting as a carcinogen have been reported in the toxicological literature in the CD.

A third prospective cohort study of about 6,000 white, nonhispanic, non-smoking long-term residents of California (Abbey et al., 1991, California Seventh Day Adventist Study), did not find a significant association between total mortality and TSP. However, this study has more limited statistical power than one of the other two studies because of the smaller number of deaths (4 percent of deaths reported in the ACS study). More importantly, the PM indicator (days of high TSP) is of questionable usefulness as an indicator of levels of exposure to  $PM_{10}$  or  $PM_{2.5}$ , particularly for cohorts residing in various locations in California. Cohorts classified with equivalent TSP exposure could experience varying exposures to fine and coarse fraction particles. For example, frequently high TSP exposures to cohorts near the South Coast could have less days of exposure to fine particle smog, while other cohorts could have similar high TSP exposures from dust storms.

The CD concludes that the Six City study and the ACS study, taken together with the earlier cross-sectional studies, suggest possible increases in mortality for specific disease

categories that are consistent with long-term exposure to airborne particles. Moreover, as discussed in Chapter 13 of the CD and below, at least some fraction of these deaths likely reflect cumulative PM impacts above and beyond those seen from acute exposures (CD, p. 13-34). To the extent that this is true, additional caution must be used in interpreting these studies because some of the effects may be due to historical exposures that are significantly higher than those used as an index of population exposures in these studies.

c. Extent of Life Shortening

An important consideration in evaluating mortality effects in a public health context is the potential shortening of lifespan ("mortality displacement" or "prematurity of death") associated with PM exposure in these studies. Epidemiological findings suggest ambient PM exposure affects mortality both in the short and long term, and promotes potentially life-shortening chronic illness in the long term (CD, p. 13-44). The relative risk estimates from the PM mortality cohort studies are considerably larger (Dockery et al, 1993) to somewhat larger (Pope et al, 1995) than those from the daily mortality studies, suggesting that a substantial portion of the deaths associated with long-term PM exposure may be independent of the daily deaths associated with short-term exposure (CD, p. 13-44).

Information concerning life shortening of only a few days comes from the daily time-series studies. These studies indicate greater incidence and severity of effects are associated with PM exposure in vulnerable individuals, primarily the elderly (i.e., 65 years of age or older) and individuals with preexisting respiratory disease. Thus, it is reasonable to expect that some of the mortality associated with short-term pollution is occurring in the weakest individuals who might have died within days even without PM exposure ("harvesting effect"). Such a pattern is often seen for some other environmental insults, such as high temperature (Kalkstein, 1991). However, direct evidence from short-term PM exposure studies concerning the degree of mortality displacement observed is limited (CD, p. 13-44).

The CD cites only two studies, Spix et al. (1993) and Cifuentes and Lave (1996), that have attempted to quantitatively test this hypothesis. Their analyses are based on the premise that if short-term "harvesting" is occurring, an observed increase in mortality on a day with high pollution should result in a corresponding decrease in mortality in subsequent days. The analysis

by Spix et al. suggests a small portion of the PM-associated mortality occurs in individuals who would have died anyway. The authors speculate, on the other hand, that exposure to PM may also lead to the extra stress that causes the death of a seriously ill person who may have otherwise recovered.

Cifuentes and Lave used two different methods to evaluate the potential for a "harvesting effect" from exposure to PM. In the first method, they examined a series of correlations to test the hypothesis that an increase in mortality in one day leads to a decrease in mortality in subsequent days (as evidenced by negative correlations). They report a negative correlation for a 2 day lag for all deaths, but it was not significant. While this result indicates some portion of deaths may be from those who would have died anyway, it is not an adequate test since it does not consider the effect of previous days of pollution. They extended the analyses by considering "episodes" of pollution, which are defined as multi-day periods of relatively high air pollution that are preceded and followed by periods of relatively low air pollution. Their result suggests that there is some mortality displacement of a few days occurring in a portion of the population. However, the Cifuentes and Lave estimates are for those deaths which occur in addition to deaths estimated from the regression model. The authors conclude "more research is needed to estimate which fraction, if any of the total deaths estimated ... is due to mortality displacement of a few days only".

An alternative explanation of the observed daily mortality results is that the sensitive subpopulations for PM effects could be continually changing as people contract disease and recover (Schwartz, 1994b; Samet et al., 1995; and Bates, 1992). Thus, it is possible that death might be substantially premature if a person becomes seriously ill and without the extra stress of PM would otherwise have recovered. This hypothesis can be explored by evaluating deaths that occur outside the hospital, based on the premise that patients with current life-threatening symptoms of disease would be more likely to be in a hospital. Schwartz (1994c) has reported an increase in sudden deaths for individuals who were not hospitalized on days with high PM levels in Philadelphia.

The CD suggests that a portion of deaths associated with long-term exposure to PM are independent of the short-term exposures and could be on the order of years (CD, p. 13-45).

Quantification of the degree of life shortening observed in the long-term cohort mortality studies (Dockery et al., 1993; Pope et al., 1995) is difficult and requires assumptions about life expectancies given other risk factors besides PM exposure, the ages at which PM-attributable deaths occur, and the general levels of medical care available in an area to sensitive subpopulations. Because of the uncertainties discussed above, the CD concludes that it is not possible to confidently estimate quantitatively the number of years lost (CD, p. 13-45).

## 2. Indices of Morbidity Associated with Respiratory and Cardiovascular Disease

Given the statistically significant positive associations between community PM concentrations and mortality outlined above, it is reasonable to anticipate that the same kinds of community-based observational studies should find increased morbidity with elevated levels of PM. This is indeed the case where morbidity effects are measured through increased hospital admissions indicating aggravation of existing disease in the elderly (Table V-6). There is coherence across these morbidity studies, the mortality studies discussed above, and discussions of sensitive subpopulations presented in section C below. The majority of such studies find effects associated with PM exposure to be linked to subpopulations with respiratory or cardiovascular disease (CD, section 13.4.3.5). Numerous studies have observed positive associations between exposure to PM and responses ranging from severe effects (e.g., increased hospitalization for respiratory and cardiovascular conditions) to moderate exacerbation of respiratory conditions. The key evidence for associations of PM exposure with such effects is summarized below.

### a. Hospital Admissions and Emergency Department Visits

A number of epidemiological studies report statistically significant positive associations between short-term exposures to PM and hospital admissions for respiratory-related and cardiac diseases. Hospital admissions and emergency room visits for these diseases reflect prevalence, severity, and patterns of health care utilization. Table V-6 summarizes the results for admissions for all respiratory disease and specific respiratory or cardiovascular diseases such as COPD (emphysema, chronic bronchitis, bronchiectasis, asthma, etc.), pneumonia, and heart disease (see also CD, Tables 12-8 to 12-11). Of the 13 studies included in the CD tables, 12 found statistically significant associations between increases in PM level and increased risk of admission to the

hospital, including evaluation of cause-specific admissions for respiratory diseases when only PM was in the model. As with the mortality studies, associations between PM exposure and hospital admissions (Table V-6) have been observed in communities throughout North America (Birmingham, Detroit, Spokane, Tacoma, New Haven, Utah Valley, New York State, Ontario, Canada). These studies reported 6 to 25 percent increases in hospital admissions for respiratory disease associated with a  $50 \mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{10}$ . Specifically, studies reported 6 to 9 percent increases in admissions for pneumonia, and 10 to 25 percent increases for COPD for the elderly, associated with a  $50 \mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{10}$ . A recent study of hospital admissions for cardiovascular illness (Schwartz and Morris, 1995) reported that  $\text{PM}_{10}$  was positively and significantly associated with daily admissions for ischemic heart disease, with  $\text{SO}_2$ , CO, and  $\text{O}_3$  making no independent contribution to the effect. In the same study  $\text{PM}_{10}$  and CO were both independently associated with congestive heart failure admissions.

When viewed together, these studies demonstrate an association between hospital admissions for respiratory and cardiac causes and PM exposure (CD, Chapter 13). These results also suggest a greater effect on admissions for COPD than for other causes from exposure to PM, and are consistent with those of the mortality studies which also found a stronger association between respiratory-related mortality and PM exposure than for all causes of mortality.

b. School Absences, Work Loss Days and Restricted Activity Days

School absences, restricted activity days, and work loss days can also be used as indicators of acute respiratory conditions, though these are indirect measures compared to actual diagnosis and measurement of respiratory conditions. However, it is not clear whether the effects reported in this way result from aggravation of chronic disease (e.g., COPD), acute infection, or non-specific symptomatic effects. Nevertheless, the results of these studies show consistent statistically significant associations between such measures of morbidity and increased short-term levels of indicators of PM. Ransom and Pope (1992) have reported a statistically significant association between PM levels and school absences; this is consistent with an effect from PM exposure, since respiratory conditions are the most frequent cause of school absences (CD, Chapter 12). In addition, three other studies reported statistically significant associations between community air pollution, as indicated by PM, and work loss days and restricted activity days

(Ostro, 1983; Ostro and Rothschild, 1989; Ostro, 1987). More specifically, a study by Ostro and Rothschild (1989) reported significant associations between PM exposure and respiratory-related restricted activity days. All of these studies used two- to four- week lag times between elevations in PM levels and school absences, work loss days, and restricted activity days. This suggests that not only are there immediate effects after elevations of PM exposure (e.g., increased hospital admissions), but PM may elicit effects which are exhibited at a later time. These results are consistent with a hypothesis of increased susceptibility to respiratory infection resulting from exposure to PM.

### 3. Altered Lung Function and Symptoms

Community epidemiology studies of ambient PM levels, and studies of exposure of humans (clinical studies) and laboratory animals to PM components, show that PM exposure is also associated with altered lung function and increased respiratory symptoms. Effects on respiratory mechanics can range from mild transient changes with little direct health consequence to incapacitating impairment of breathing. Symptomatic effects also vary in severity, but at minimum suggest a biological response that is often more sensitive than lung function measurements.

#### a. Effects Related to Short-Term Exposures To PM

##### i. Community Air Pollution Studies

Table V-7 lists a number of community studies highlighted in the CD from U.S. communities that show associations between PM exposure and both respiratory symptoms and immediate pulmonary function changes [e.g., forced expiratory capacity for one second ( $FEV_1$ ) and peak expiratory flow rate (PEFR)]. Studies reporting symptoms have found associations between short-term exposures of PM and upper respiratory symptoms (e.g., hoarseness, sore throat), lower respiratory symptoms (chest pain, phlegm, and wheeze), fever, cough, and acute respiratory illness. Additional studies of European communities are reported in Table 12-12 of the CD. Four studies from Table 12-12 evaluated respiratory symptoms in all children (Schwartz et al., 1994; Hoek and Brunekreef, 1993; Hoek and Brunekreef, 1995; Schwartz et al., 1991), and all but one found positive statistically significant associations with exposure to PM with one or more symptoms. Two studies evaluated respiratory symptoms in asthmatic children (Pope et al.,

1991, Ostro, 1995) and found statically significant positive associations with exposure to PM, although in the Ostro (1995) study, the effect could not be separated from O<sub>3</sub>. A study of non-asthmatic symptomatic and asymptomatic children in Utah Valley found statistically significant positive associations between increased PM levels and all symptoms in the symptomatic children. For asymptomatic children, statistically significant positive and consistent associations were found between PM exposure and cough, although no statically significant associations were found for lower respiratory symptoms and inconsistent results for upper respiratory symptoms (Pope and Dockery, 1992). The four studies in adults were inconsistent. Taken together, these studies suggest that sensitive individuals, such as children (especially those with asthma or pre-existing respiratory symptoms) may have increased or aggravation of symptoms associated with PM exposure, with or without reduced lung function.

ii. Controlled Exposures to Laboratory Aerosols

The 1982 CD (EPA, 1982a) and staff paper summarized earlier literature on controlled human and occupational exposures to a variety of particulate substances. This summary (Table 5-2, EPA 1982) highlights studies which report that broncho-constriction and associated symptoms may be induced by chemical or mechanical irritation by high concentrations of inert dusts (e.g. Andersen et al., 1979; Constantine et al., 1959), re-suspended urban dust (Toyama, 1964), coarse organic dusts (e.g. Dosman, 1980), fine acid aerosols (e.g. Utell et al. 1981), and fine particles in combination with pollutant gases (Koenig et al, 1981; McJilton et al., 1976).

Measurements of pulmonary function and symptoms resulting from acid sulfate aerosols have been a primary focus of PM research in short-term (<24 hours) controlled human clinical and animal studies (CD, Table 11.2). Short exposures to fine H<sub>2</sub>SO<sub>4</sub> aerosols in environmental chambers, with short periods of exercise, have been reported to cause a slight concentration-related increase in lower respiratory symptoms (cough, sputum, dyspnea, wheeze, chest tightness, substernal irritation) (Avol et. al.,1988a,b).

Asthmatic subjects appear to be more sensitive than healthy subjects to the effects of acid aerosols on lung function (Utell et al., 1982), but the reported effective concentration differs widely among studies (CD, Table 11-2). Adolescent asthmatics may be more sensitive than adult asthmatics and may experience small decrements in lung function in response to H<sub>2</sub>SO<sub>4</sub> at

exposure levels less than  $100 \mu\text{g}/\text{m}^3$  (Koenig et al., 1989; CD, p. 11-24). A more recent study of  $\text{H}_2\text{SO}_4$  ( $<1 \mu\text{m}$  diameter) on subjects with asthma and COPD (emphysema or chronic bronchitis) found pulmonary function decrements at acid levels as low as  $90 \mu\text{g}/\text{m}^3$  (Morrow et al., 1994). Even in studies reporting an overall absence of effects on lung function, some individual asthmatic subjects appear to demonstrate clinically important effects (CD, p. 11-31).

Relevant to considerations of the characteristics of acid aerosols that may elicit effects in asthmatic subjects, lung function effects in asthmatic subjects have been correlated with hydrogen ion content of the sulfate aerosol (CD, p. 11-17) and affected by neutralization by oral ammonia (Utell et al., 1983; 1989) and buffering capacity of the aerosol (Fine et al., 1987b). Recent studies also suggest that submicrometer size aerosols may alter lung function to a greater degree than larger sized aerosols in asthmatic subjects (CD, p. 11-31; Avol et al., 1988a,b,) albeit at larger concentrations than found to affect adolescent asthmatics (Koenig et al., 1983, 1989).

Changes in clinical status of human subjects are often accompanied by changes in airway responsiveness as measured by the sensitivity to challenge by a broncho-constrictive agent. Airway responsiveness may be a predictor of responsiveness to acid aerosol exposure in asthmatic subjects (Utell et al, 1983b; Hanley et al., 1992). Accordingly, effects from exposures to pollutants which increase airway responsiveness may be clinically significant even in the absence of direct effects on lung function (Godfrey, 1993; Wiess et al., 1993). Despite the absence of effects on lung function in healthy subjects, Utell et al. (1983a) observed in healthy nonsmokers an increase in airway responsiveness to carbachol challenge 24 hours (but not immediately) following exposure to  $450 \mu\text{g}/\text{m}^3 \text{H}_2\text{SO}_4$  ( $0.8 \mu\text{m}$  diameter), which suggests the possibility of delayed effects. Other studies which have attempted to measure airway responsiveness immediately after acid aerosol exposure have reported little if any effect from low levels of acid aerosol exposure (CD, p. 11-33,34).

Studies in humans have suggested an increase in airway responsiveness to  $\text{O}_3$  following low concentrations of  $\text{H}_2\text{SO}_4$  aerosol exposure in both healthy and asthmatic subjects (Linn et al., 1994; Frampton et al., 1995; CD). Synergistic or interactive effects between sulfates and  $\text{SO}_2$  exposure have not been demonstrated (CD, p. 11-37). Indeed, given the low solubility of  $\text{SO}_2$  in acid aerosol, it is unlikely that fine acid particles could facilitate an interaction through transport

of SO<sub>2</sub> to the deeper regions of the lungs, to which SO<sub>2</sub> alone has difficulty penetrating (U.S. EPA, 1994c). Reflex broncho-constriction by high levels of SO<sub>2</sub> could, however, increase the deposition of particles in the tracheobronchial region by narrowing the conductive airways.

As described in the CD, controlled human studies of PM are limited as they tend to use pulmonary function and symptoms from exposure to acid aerosols as the endpoint of response, and few have examined airway inflammation or other more sensitive indicators related to pulmonary function changes. No studies have examined effects of particles or acid aerosol exposure on airway inflammation in asthmatic subjects (CD, p. 11-30).

Many laboratory animal studies have also been conducted using acid aerosol exposures with the most recent studies on effects on pulmonary function presented in Table 11-5 of the CD. In general, exposure to H<sub>2</sub>SO<sub>4</sub> at levels ranging above ambient but < 1000 µg/m<sup>3</sup> does not produce direct changes in pulmonary function in healthy animals except in guinea pigs (CD, Table 11-5). Airway hyper-responsiveness (alteration in the degree of reactivity to exogenous or endogenous bronchoactive agents resulting in increased airway resistance at levels of these agents that would not affect airways of normal individuals) from exposure to (<1µm diameter) H<sub>2</sub>SO<sub>4</sub> particles has been reported in several studies (Chen et al., 1992b; Gearhart and Schlesinger, 1986; and El-Fawal and Schlesinger, 1994). Hyper-responsiveness has also been observed to be increased in guinea pigs exposed to acid-coated particles in comparison to pure H<sub>2</sub>SO<sub>4</sub> aerosols of the same size (Amdur and Chen, 1989; Chen et al., 1992b). Whatever the underlying mechanism, the results of pulmonary function studies indicate that H<sub>2</sub>SO<sub>4</sub> is a broncho-active agent and can therefore alter lung function of exposed animals via contraction of smooth muscle (CD, p. 11-47).

b. Effects Related to Long-Term Exposures

Table V-8 summarizes effects estimates reported from studies highlighted in the CD which assess the association between long-term exposure to PM and pulmonary function changes and symptoms of respiratory disease. Two initial studies conducted in the Harvard six cities (Ware et al., 1986, Dockery et al., 1989) demonstrated that there is a statistically significant association of particulate pollution with respiratory symptoms in children, with no significant changes in lung function. As noted in the CD, the absence of significant findings in lung function effects in the Six City comparison may be due to the inherent variability of the measure. To follow-up on the

suggestions that respiratory symptoms and probably lung function were associated mostly with fine particle levels and acidity, a more comprehensive study of 24 cities across North America using the same questionnaire was conducted (Raizenne et al., 1996; Dockery et al., 1996). The cities were chosen to provide a gradient in aerosol acidity exposures. Air monitoring data was collected for one year. This study reported statistically significant positive associations between bronchitis and sulfate concentration and acidity as well as between changes in lung function (FVC) and  $PM_{10}$ ,  $PM_{2.5}$ , sulfate particle concentration, and particle acidity indicators.

Abbey et al. (1995a,b,c) in California reported elevated but marginally non-significant associations, which were in the range of the results of the other studies, between sulfate concentration and bronchitis well as acute obstructive disease, as defined in the studies. Two other long-term pulmonary function studies (presented in Table 12-22 of the CD) reported decreases in lung function in children (with no confidence level given) (Spector et al., 1991) and statistically significant decreases in lung function in adults (Ackermann-Liebrich et al., 1996) associated with long-term PM exposure.

The results from the long-term respiratory symptom studies are consistent and supportive of those reported for short-term studies. The CD concludes that the results are consistent with a PM gradient (CD, p. 12-372), and that while the evidence is suggestive for long-term exposure to PM being associated with pulmonary lung function decrements, it is more limited (CD, p. 12-202).

The CD points out that the increased risk for respiratory symptoms and related respiratory morbidity reported in the above studies is important not only because of the immediate and longer-term symptoms produced, but also because of the longer-term potential for increases in the development of chronic lung disease. Specifically, recurrent childhood respiratory illness has been suggested to be a risk factor for later susceptibility to lung damage (Glezen, 1989; Samet, 1983; Gold et al., 1989).

#### 4. Morphological Damage

Traditional epidemiology has not been used to evaluate the extent to which PM directly alters lung tissues and components, although some autopsy studies have found qualitative evidence of a community air pollution effect on the lung (e.g., Ishikawa et al. 1969). Evidence of

morphological damage from PM exposure has come from animal and occupational studies for acid aerosols and other PM components.

a. Acid Aerosols

Morphological alterations associated with exposure to acid aerosols have been most extensively studied and are outlined in Table 11-6 of the CD. Single or multiple exposures to H<sub>2</sub>SO<sub>4</sub> at fairly high levels (> 1 mg/m<sup>3</sup>) produce a number of characteristic morphological responses (e.g., alveolitis, bronchial and/or bronchiolar epithelial desquamation and edema) (CD, p. 11-52). Chronic exposure to H<sub>2</sub>SO<sub>4</sub> at concentrations ≤ 1 mg/m<sup>3</sup> produces a response characterized by hypertrophy and hyperplasia of epithelial secretory cells. Gearhart and Schlesinger (1988), however, show that chronic exposure of H<sub>2</sub>SO<sub>4</sub> (250 µg/m<sup>3</sup>, 0.3µm) also produces an increase in the relative number of smaller airways in rabbits which can be an early change relevant to clinical small airway disease (CD, p. 11-52). Long-term (68 months exposure) studies of combinations of SO<sub>2</sub> (1.1 mg/m<sup>3</sup>) and submicrometer sulfuric acid (90 µg/m<sup>3</sup>) exposure of dogs found no pronounced effects at the end of exposure, but a number of morphological changes, including an increase in interalveolar pores (incipient emphysema), was found to increase for up to 3 years following exposure (Hyde et al., 1978; Gillespe, 1980).

Morphologic and cellular damage to the respiratory tract following exposure to acid aerosols may be determined by methods other than direct microscopic observation (CD, p. 11-53). Animal studies of exposure to fine (0.3 µm) diameter and ultrafine (0.04 µm) diameter H<sub>2</sub>SO<sub>4</sub> aerosols (300 µg/m<sup>3</sup>) have reported lavage fluid to contain increases in lactate dehydrogenase and protein (markers of cytotoxicity and increased cellular permeability) following a single exposure to guinea pigs (Chen et al., 1992a).

In addition, modulation of biological mediators of inflammatory responses (e.g. eicosanoids) as well as smooth muscle tone (e.g. prostaglandins and leukotrienes) could be involved in damage to the respiratory tract after particle exposure. Changes in prostaglandins (Schlesinger et al; 1990b) have also been observed in lung perfusate after exposure to H<sub>2</sub>SO<sub>4</sub> and lavage. Since some of the prostaglandins are involved in regulation of muscle tone, changes in these mediators may be involved in the development of airway responsiveness found with exposure to acid sulfates (CD, p. 11-54).

b. Silica, Crustal Dusts, and other PM Components

Silica has long been considered to be a major occupational health hazard, with exposure to crystalline silica being associated with pulmonary inflammation and fibrosis (CD, p. 11-127). The differing forms of silica (amorphous versus crystalline) are thought to have differential potential for toxicity, but data on amorphous forms is limited (CD, p. 11-128). There are limited data on ambient concentrations of silica, which is generally found in the coarse fraction. Based on analyses of the silica content of resuspended crustal material collected from several U.S. cities as part of the last review, staff concluded that the risk of silicosis at levels permitted by the current long-term PM<sub>10</sub> NAAQS was low. This earlier conclusion is supported by the CD based on the integration of occupational and autopsy findings with ambient silica concentrations (CD, p. 13-79).

The 1982 staff paper (U.S. EPA, 1982b) reported that some risk of long-term exposure to crustal dusts is suggested by autopsy studies of farm workers and residents in the Southwest (Sherwin et al., 1979), desert dwellers (Bar-Ziv and Goldberg, 1974), and zoo animals and humans exposed to various crustal dusts near or slightly above current ambient levels in the Southwest (Brambilla et al, 1979). These studies found evidence of a silicate pneumoconiosis, which was related to local crustal materials. Responses ranged from the buildup of particles in macrophages with no clinical significance to possible pathological fibrotic lesions. No inferences regarding quantitative exposures of concern could be drawn from these studies (U.S. EPA 1982b).

Kleinman et al. (1995) have reported increases in alveolar wall thickness as well as alveolar chord length and cross sectional area from exposure of rats to road dust (900 µg/m<sup>3</sup>, 4 µm diameter), ammonium sulfate (70 µg/m<sup>3</sup>, 0.2 µm diameter), and ammonium nitrate (350 µg/m<sup>3</sup>, 0.6µm diameter). The authors suggest such morphometric changes could lead to a decrease in compliance or a "stiffening" of the lung.

Coating the surface of particles with certain transition metals, such as iron, may have the potential to enhance pulmonary injury to a variety of environmental particles (CD, p. 11-92; Costa et al., 1994a,b; Tepper et al., 1994). These metals can catalyze the oxidative deterioration of biological macromolecules and thus could potentially cause oxidative injury to the respiratory

tract (CD, p. 11-92). Silica particles have been reported to be rendered more toxic when complexed with iron. Rats fed with iron depleted diets (and thus having less iron available from body stores to complex intratracheally instilled silica particles and to decrease antioxidant molecules in lung tissue) exhibited less inflammation and fibrotic injury after such exposures (Ghio et al., 1994; 1992; Ghio and Hatch, 1993). However, there is difficulty in extrapolating the results of experimental paradigms used in these studies (intratracheally instillation) to ambient exposure situations.

#### 5. Effects on Host Defense Mechanisms

Responses to air pollutants often depend upon their interaction with respiratory tract defenses such as clearance and antigenic stimulation of the immune system. Furthermore, either depression or over-activation of these systems may be involved in the pathogenesis of lung diseases (CD, p. 11-55). Acid aerosols ( $\text{H}_2\text{SO}_4$ ) alter mucociliary clearance in healthy human subjects at levels as low as  $100 \mu\text{g}/\text{m}^3$  with effects being dependent on the concentration and duration of the acid aerosol exposure, the size and distribution of the acid particles, and the region of the airways being examined (CD, p. 11-56 to 60, Leikauf et al., 1984). In addition, the acidity of the aerosol has been reported to affect mucociliary clearance in animals (CD, p. 11-60). Acid aerosols have been shown to elicit a slowing in clearance that lasts several months following multiple exposures (Lippmann et al., 1981). Persistent impairment of clearance may lead to the inception or progression of acute or chronic respiratory disease, and may be a plausible link between acid aerosol exposure and respiratory disease (CD, p. 11-61).

Little is known about the effects of particles on humoral (antibody) or cell-mediated immunity. Since numerous bioaerosols (potential antigens) are present in inhaled air, the possibility exists that acid sulfates may enhance immunologic reaction and thus produce a more severe response with greater pulmonary pathogenic potential (CD, p. 11-67). There is evidence that  $\text{H}_2\text{SO}_4$  exposure may be a factor in promoting lung inflammation by acting as a vehicle to increase antigenicity (Pinto et al., 1979; CD, p. 11-69). Guinea pigs have been reported to show increased sensitivity to inhaled antigen (ovalbumin) with concurrent  $\text{H}_2\text{SO}_4$  exposure ( $1,910 \mu\text{g}/\text{m}^3 < 1 \mu\text{m}$  diameter) as demonstrated by hyper-responsive airways (Osebold et al., 1980). In addition, Fujimaki et al. (1992) have demonstrated that guinea pigs have altered mast cell function

after exposure to high concentrations of  $\text{H}_2\text{SO}_4$  (1000 and 3000  $\mu\text{g}/\text{m}^3$ ). These cells are involved in allergic responses including broncho-constriction (CD, p. 11-69).

Alveolar macrophages not only play a major role in defense against bacteria, but are involved in the induction and expression of immune reactions, and are capable of release of pro-inflammatory cytokines (CD, p. 11-56). In order to maintain the function of clearance, macrophages must be competent in a number of other functions including phagocytosis, mobility, and attachment to a surface (CD, p. 11-63).

Macrophages also produce a number of biologically active chemicals which are involved in host defense [tumor necrosis factor (TNF) release activity and production of superoxide radical] (CD, p. 11-66). Exposure to  $\text{H}_2\text{SO}_4$  (50 to 500  $\mu\text{g}/\text{m}^3$ , 0.3 $\mu\text{m}$  diameter) in rabbits produced reductions in TNF cytotoxic activity as well as reduction in superoxide radical in alveolar macrophages recovered by lavage (Zelikoff and Schlesinger, 1992). However, exposure to  $\text{H}_2\text{SO}_4$  (300  $\mu\text{g}/\text{m}^3$ , 0.3 and 0.04 $\mu\text{m}$  diameter) in guinea pigs enhanced TNF and hydrogen peroxide from alveolar macrophages (Chen et al., 1992a). Such differences in response may reflect either interspecies differences or differences in experimental conditions. Kleinman et al. (1995) have reported in their study of cellular and immunological injury by PM that respiratory burst activity by macrophages was depressed by exposure to fine ammonium sulfate (70  $\mu\text{g}/\text{m}^3$ , 0.2  $\mu\text{m}$  diameter), ammonium nitrate (350  $\mu\text{g}/\text{m}^3$ , 0.6 $\mu\text{m}$  diameter) particles, and road dust (900  $\mu\text{g}/\text{m}^3$ , 4  $\mu\text{m}$  diameter)

Animal infectivity models have been used to examine effects of  $\text{H}_2\text{SO}_4$  exposure on susceptibility to bacterial infection. Exposures of up to 1  $\text{mg}/\text{m}^3$  of submicrometer  $\text{H}_2\text{SO}_4$  aerosols for 30 days alone have not resulted in enhanced susceptibility to bacterially-mediated respiratory disease in mice (See Table 11-8 in the CD). However, Zelikoff et al. (1994) demonstrated an effect of high concentrations of acid alone in rabbits exposed for 2 h/day for 4 days to 500 to 1000  $\mu\text{g}/\text{m}^3$   $\text{H}_2\text{SO}_4$  and demonstrated reduction of intracellular killing and uptake of the bacterium *Staphylococcus aureus* by alveolar macrophages.

Multi-pollutant exposures have been shown to elicit changes in infectivity in mice after short-term exposure. For example, Gardiner et al. (1977) reported increased susceptibility to infection by exposing mice to  $\text{O}_3$  (0.1 ppm) followed by  $\text{H}_2\text{SO}_4$  (0.9  $\text{mg}/\text{m}^3$ ). Neither pollutant

produced any effect alone. Although conducted using high acid levels, the results of this study are of particular interest given the co-occurrence of O<sub>3</sub> and acid sulfates in summertime episodes over broad regions of North America.

D. Sensitive Subpopulations

The recent epidemiologic information summarized in the CD provides evidence that several subgroups are apparently more sensitive (susceptible) to the effects of community air pollution containing PM. As discussed above, observed effects in these groups range from the decreases in pulmonary function reported in children to increased mortality reported in the elderly and in individuals with cardiopulmonary disease. Furthermore, the same individual characteristics which can be described in those who succumbed to air pollution during the more extreme historical episodes are also present in those most susceptible to effects during routine fluctuations in PM level. Table V-9 is a qualitative assessment of the short-term and long-term PM epidemiologic evidence with regard to subgroups that appear to be at greatest risk with respect to particular health endpoints. It is a condensation of results presented in Tables 13-6 and 13-7 of the CD. The table summarizes the findings for the indicated health indices in the specified subpopulations.

**TABLE V-9. QUALITATIVE SUMMARY OF RECENT PM COMMUNITY  
EPIDEMIOLOGIC RESULTS FOR SHORT- AND LONG - TERM EXPOSURE\*\*\***

Age Class	Subpopulation	Mortality		Morbidity**		Lung Function Change	
		Acute (Exposure to PM)	Chronic (Exposure to PM)	Acute (Exposure to PM)	Chronic (Exposure to PM)	Acute (Exposure to PM)	Chronic (Exposure to PM)
<b>Adults</b>	Elderly	+	0	+	0	0	0
	Pre-existing Respiratory Disease*	+	+	+	0	0	0
	Pre-existing Cardiovascular Disease	+	+	+	0	0	0
<b>Children</b>	General	ID	+/-	+	+	+	+/-
	Pre-existing Respiratory Disease	0	0	+	0	+	0
<b>Adults and Children</b>	Asthmatics	0	0	+	+	+	0

\* Note, this includes those with pneumonia, acute bronchitis and COPD.

\*\* Note, morbidity includes hospitalization and emergency room visits and community morbidity and symptoms reported in table 13-6 of the CD.

\*\*\* Note; + indicates positive associations have been reported for this group with PM exposure; +/- means few pertinent studies identified, weight of evidence of PM related effect is somewhat positive but uncertain; 0 means that no pertinent studies have been identified; ID means insufficient data, at least 1 pertinent study identified but inference as to weight of evidence is not warranted.

The following section expands upon individual risk factors (including age, asthma, COPD, and cardiovascular disease), characteristics of those factors which may increase inherent susceptibility to PM effects, and incidence of such risk factors (as well as overall mortality associated with such factors) to provide some perspective on the scope of subpopulations at risk from PM exposure. Table 13-9 of the CD presents more detailed information concerning the incidence of selected cardiorespiratory disorders by age and by geographic region. In addition, Table 12-1 of the CD shows age-specific and age-adjusted U.S. death rates for selected causes in 1991 and selected components in 1979, 1990, and 1991. Information from these tables is

incorporated in the discussion below, and gives some indication of the relative sizes of sensitive subpopulations. Such subpopulations may experience effects at lower levels of PM than the general population, and thus, the subsequent magnitude of effects may be greater.

1. Individuals with Respiratory and Cardiovascular Disease

Both the early London episode studies and the most recent community studies in North America have found air pollution with elevated particle concentrations to be associated with increased mortality, hospital admissions, and symptoms in individuals with respiratory and cardiovascular disease (CD, Chapter 13). Because smoking is associated with the same types of cardiopulmonary diseases which characterize individuals also susceptible to PM exposures, smoking is an important variable to be controlled in epidemiologic studies attempting to investigate the effects of PM (see CD, p.13-86 for further discussion).

COPD is the most common pulmonary cause of death, the fourth leading cause of death overall (84,000 deaths in 1989, U.S. Bureau of the Census 1992), and a major cause of disability. COPD incidence increases with age of the population (e.g., excluding asthma, the incidence rate for those over 75 is approximately twice that as for those under 45 years of age) (CD, Table 13-9). Patients with COPD have a larger relative risk of mortality from PM exposure than the general population (CD, Chapter 12, see Section C of this document). COPD is a broad disease category used to cover patients with varying degrees of chronic bronchitis, emphysema and asthma, etc. COPD is characterized by airway obstruction in which there is increased resistance to airflow during forced expiration. According to the International Classification of Disease definitions and classification codes, COPD includes chronic bronchitis, emphysema, asthma, and pneumonitis. Many epidemiology studies use these codes and therefore reported effects such as hospital admissions for COPD include asthma admissions. The American Thoracic Society only includes emphysema and chronic bronchitis in their definition of COPD and, when referring to COPD, the CD uses this definition. Subcategories of COPD, emphysema, and chronic bronchitis may result in chronic inflammation of distal airways, destruction of the lung parenchyma, and loss of supportive elastic tissue leading to airway closure during expiration (CD, p. 13-84).

Recent community studies summarized in the previous section also found increased risk from death and morbidity (increased hospital admissions) due to cardiovascular causes associated

with exposure to increased PM concentration (Tables V-4, V-6). As with COPD, the preexisting condition of heart disease occurs at high frequency in the general population and contributes significantly to total mortality (represents 1/3 of all causes of mortality for all ages) (CD, Table 12-1). The pathophysiology of many lung diseases is related to cardiac function, and plausible, but undemonstrated mechanisms have been advanced that suggest possible links between effects of air pollution exposure and the presence of cardiovascular disease [Table V-2, Appendix D, Bates (1992)].

### 2. Individuals with Infections

Individuals with respiratory symptoms are at increased risk of morbidity and mortality from PM exposure and are often those with respiratory infection. Exposure to PM may exacerbate illness from infectious agents and increase risk of severe outcomes. In general, increased mortality associated with PM exposure from pneumonia and influenza has been reported for the elderly. Mortality rates from pneumonia and influenza combined are just somewhat lower than those for COPD and allied conditions (i.e., asthma) (CD, Table 12-1). As with COPD, there is also an increased rate of mortality from pneumonia and influenza with increasing age. An increase in respiratory symptoms in children has also been reported to be associated with PM exposure (see Section C of this Chapter).

### 3. The Elderly

Although recent epidemiology studies suggest higher relative risks for people over 65 years of age, currently little information suggests how aging in the absence of pathology might make the elderly more susceptible to the effects of ambient particles (Cooper et al., 1991). Length of exposure increases the cumulative lung burden (dose equals concentration times time) which may be related to susceptibility to particle effects. The elderly may be more sensitive to respiratory insult from PM because such exposure may have effects on pulmonary and cardiovascular function which augment decreases seen with increasing age. In addition, cardiorespiratory disease and infection (e.g., pneumonia and influenza) are more prevalent in the elderly which may predispose such individual to effects of PM exposure. In people over 75 years of age, 40% have some form of heart disease, 35% have hypertension, and approximately 10% have COPD (CD, p. 13-84).

#### 4. Children

Increased community morbidity, decreased lung function, and increased respiratory symptoms have been reported to be associated with PM exposure in children, both as a general group and in individuals with respiratory illness (CD, Table 13-6). Children have the potential to be inherently more susceptible to the effects of PM as they show a greater incidence of respiratory and other illness, suggesting decreased immunological protection, and higher deposition of particles than adults (CD, p.10-77). Children may spend more time outdoors and may have higher ventilation rates due to increased activity and thus have increased inhalation of outdoor pollutants (CD, Chapter 10). Infants in particular have been hypothesized to be a sensitive subpopulation for PM effects as exposure may increase the incidence or severity of acute respiratory infection including bronchitis, bronchiolitis, and pneumonia (Samet et al., 1995). However, recent studies in North America have not found clear evidence of increased mortality or morbidity associated with exposure to PM in infants or children (CD, Chapter 12). The rate of mortality from pneumonia and influenza is relatively high for children under 1 year of age (11 times that for children 1 to 4 years, twice that of adults 45-54 years of age) ( CD, Table 12-1).

#### 5. Asthmatic Individuals

Asthma is a lung disease characterized by (1) airways obstruction that is reversible, but only partially in some patients, either spontaneously or with treatment, (2) airways inflammation, and (3) increased airway responsiveness to a variety of stimuli. The airways of asthmatics may be hyper-responsive to a variety of stimuli including exercise, cigarette smoke, odors, irritating fumes, changes in temperature, humidity, allergens, pollen, dust, as well as viral infection (CD, p. 13-86). [A more complete discussion of the characteristics of asthma may be found in the SO<sub>2</sub> Staff Paper (U.S. EPA, 1994c)]. The heightened responsiveness of the airways of asthmatics to such substances and conditions raises the possibility of exacerbation of this pulmonary disease by PM.

Increases in PM have been associated with increased hospital admissions for asthma, worsening of symptoms, decrements in lung function and increased medication use (CD, Chapter 12, Tables V-6, V-7). There are approximately 13 million people in the U.S. with asthma and that number is increasing (National Center for Health Statistics, 1994). Incidence of asthma is higher

among children and young adults, with asthma being the leading cause of non-infectious respiratory mortality below age 55. Approximately 70% of all asthma-related deaths occur after age 55 (National Center for Health Statistics, 1993). The available studies of PM and mortality do not, however, single out asthma from the larger category of respiratory-related mortality. Thus, from the available evidence a direct association between PM exposure and asthma mortality has not been demonstrated.

E. Evaluation of the Epidemiological Evidence

The majority of the evidence concerning health effects of PM exposure comes from epidemiological studies. While severe effects at the high concentrations of air pollution in the historical episodes are widely accepted as being causally related, there is less consensus as to the most appropriate interpretation of studies finding associations of health effects with ambient levels of PM below the current NAAQS (e.g., Schwartz, 1994b; Dockery et al., 1995; Moolgolkar, 1995b; Moolgolkar and Luebeck, 1996; Li and Roth, 1995; Samet et al., 1996a; Wyzga and Lipfert, 1995). Thus, evaluation and interpretation of the epidemiological studies is key to assessing the weight of the evidence for causal relationships between health effects and PM exposures at ambient levels below the NAAQS. Evaluation of the epidemiological evidence for these purposes requires both assessing the individual studies as well as the body of evidence as a whole for drawing appropriate conclusions.

The CD summary of perspectives on the epidemiology studies is pertinent here:

"By far the strongest evidence for ambient PM exposure health risks is derived from epidemiologic studies. Many epidemiologic studies have shown statistically significant associations of ambient PM levels with a variety of human health endpoints, including mortality, hospital admissions and emergency room visits, respiratory illness and symptoms measured in community surveys, and physiologic changes in mechanical pulmonary function. Associations of both short-term and long-term PM exposure with most of these endpoints have been consistently observed. The general internal consistency of the epidemiologic data base and available findings have led to increasing public health concern, due to the severity of several studied endpoints and the frequent demonstration of associations of health and physiologic effects with ambient PM levels at or below the current U.S. NAAQS for PM<sub>10</sub>. The weight of epidemiologic evidence suggests that ambient PM exposure has affected the public health of U.S. populations. However, there remains much uncertainty in the published data base regarding the shapes of PM exposure-response relationships, the magnitudes and variabilities of risk estimates for PM, the ability to attribute observed health effects to specific PM constituents, the time intervals over

which PM health effects are manifested, the extent to which findings in one location can be generalized to other locations, and the nature and magnitude of the overall public health risk imposed by ambient PM exposure.

The etiology of most air pollution-related health outcomes is highly multifactorial, and the effect of ambient air pollution exposure on these outcomes is often small in comparison to that of other etiologic factors (e.g., smoking). Also, ambient PM exposure in the U.S. is usually accompanied by exposure to many other pollutants, and PM itself is composed of numerous physical and chemical components. Assessment of the health effects attributable to PM and its constituents within an already-subtle total air pollution effect is difficult even with well-designed studies. Indeed, statistical partitioning of separate pollutant effects may somewhat artificially describe the etiology of effects which actually depend on simultaneous exposure to multiple air pollutants. Furthermore, identification of anatomic sites at which particles trigger end-effects and elucidation of biological mechanisms through which these effects may be expressed are still at an early stage. Thus, it remains difficult to form incisive a priori hypotheses to guide epidemiologic and experimental research. Lack of clear mechanistic understanding also increases the difficulty with which available findings can be integrated in assessing the coherence of PM-related evidence.

In this regard, several viewpoints currently exist on how best to interpret the epidemiology data: one sees PM exposure indicators as surrogate measures of complex ambient air pollution mixtures and reported PM-related effects represent those of the overall mixture; another holds that reported PM-related effects are attributable to PM components (per se) of the air pollution mixture and reflect independent PM effects; or PM can be viewed both as a surrogate indicator as well as a specific cause of health effects. In any case, reduction of PM exposure would lead to reductions in the frequency and severity of the PM-associated health effects (CD, pp. 13-31)."

The CD also outlines major criteria useful in evaluating the adequacy and strength of the epidemiological studies and in interpreting them. These criteria include quality of the aerometric data, clear definition of study populations and health endpoints, appropriate statistical analysis, adequate control of confounders, and evaluation of the consistency and coherence of the findings with other known facts (CD, Chapter 12). The CD addresses each of these issues, including both the strengths and inherent limitations of such studies. The discussion below in Section V.E.1 focuses on several key factors identified in evaluating the

individual studies and outlines observations on sensitivity to model specification, exposure error, and potential confounding by weather and other pollutants. Individual studies can not be used by themselves to determine whether attributable health effects are occurring from current levels of PM because of inherent limitations in any single study. Thus, to evaluate the potential for PM to affect public health, the collective weight of evidence from studies must be evaluated together. Accordingly, the interpretation of individual studies is followed by a discussion of the consistency and coherence of the epidemiological evidence across studies.

## 1. Interpretation of Individual PM Study Results

### a. Model Selection and Specification

The recent epidemiological literature contains extensive discussion of model selection and specification for short-term mortality studies (CD, Section 12.6.2.1). The discussion has focused on a number of issues including distributional assumptions, assumptions about temporal structure or correlation, assumptions about random and systematic components of variability, assumptions about the shape of the relationship between response and covariate, and assumptions about additivity and interactions of covariates (CD, 13.4.2.3). Sensitivity of the effects estimates to model specification has been explored by many authors, and an in-depth discussion of model specification for short-term mortality studies is presented in Section 12.6.2 of the CD, where PM<sub>10</sub> studies of mortality are reviewed and analyzed (Pope et al. 1992a; Ostro et al., 1996; Dockery et al., 1992; Thurston and Kinney, 1995; Kinney et al., 1995; Ito et al., 1995; Styer et al., 1995). Also, importantly, alternative TSP mortality analyses for the same city, Philadelphia (Moolgavkar et al. 1995b; Li and Roth, 1995; Wyzga and Lipfert, 1995; Cifuentes and Lave, 1996; Samet et al., 1995; Schwartz and Dockery, 1992b) are reviewed and analyzed. Based on these assessments, the models appear to be most sensitive to the following specifications: adjustments for seasonality and for long-term time trends; adjustments for co-pollutants; and adjustments for weather (CD, p. 13-53).

While the CD finds that model specification is important and can influence the health effect estimates from PM exposure, it also notes that appropriate modelling strategies have been adopted by most investigators (CD, section 13.4.3.2), that have resulted in consistent PM effects estimates reported across the studies. These strategies include use of several standard models

(e.g. GLM, LOESS) and a number of particular specifications. For example, it is important to remove long-term trends in the data before evaluating the association between short-term changes in PM and health effects. As the CD points out, a several different methods used by the various authors are adequate for carrying out this adjustment, including nonparametric detrending, use of indicator variables for season and year, and filtering (CD, section 13.1.3.2). The CD concludes that, “the largely consistent specific results, indicative of significant positive associations of ambient PM exposures and human mortality/morbidity effects, are not model specific, nor are they artifactually derived due to misspecification of any specific model. The robustness of the results of different modelling strategies and approaches increases our confidence in their validity” (CD, p. 13-54).

b. Measurement Error

A difficulty in interpretation of the epidemiological studies, particularly for quantitative purposes, is the determination of uncertainties and possible biases introduced by measurement error in the outdoor monitors. In the ecological context of the daily mortality/morbidity studies, investigators estimate a population-level index of pollution exposure for those at risk of dying or experiencing illness. The variation in mortality/morbidity is modeled implicitly as a function of the variation in this index. Measurement error includes both the error in the measurements themselves and the error introduced by using a central monitor to estimate such population-level exposures. It is important to examine the possible effect measurement error may have on the reported associations in the studies, as it may bias the results in either direction. Unfortunately, most studies provide only qualitative assessments of this issue, as opposed to their more formal treatment of weather and some other confounders. The discussion that follows is drawn from the CD assessment of the relationship between the monitored pollutant levels (using TSP, PM-10, and fine particles as indicators) and exposure and on how the error in the measurements might bias the reported associations.

The CD points out that, although generally useful for qualitative epidemiologic demonstration of PM effects, TSP measurements can include large coarse-mode particles do not penetrate to the thoracic region. Thus, TSP can reasonably be expected to provide "noisy" estimates of exposure-effect relationships if such relationships are due to thoracic particle

fractions of the measured TSP mass. By definition,  $PM_{10}$  is a better index of thoracic particles than is TSP, and  $PM_{10}$  may be a better index of ambient fine particle exposure than TSP because the smaller particulate fraction contained in  $PM_{10}$  is more uniformly distributed in an urban area or region than are larger coarse particles also indexed by TSP. As discussed in Section 13.2.6,  $PM_{2.5}$  particles are generally likely to be more uniformly distributed than coarse particles within an urban airshed. For example, measurements of the coarse fraction of  $PM_{10}$  appear to be more variable from site to site, while  $PM_{2.5}$  levels have been shown to be particularly well correlated across at least one eastern metropolitan region, i.e., Philadelphia (Burton et al., 1996; Wilson and Suh, 1996), as well as in more limited data from Riverside, CA (Wallace, 1996). The use of a spatial average of multiple TSP or  $PM_{10}$  monitors in some studies (e.g., Philadelphia, Minneapolis) can reduce exposure uncertainties for these less uniform pollutant indicators.

Even if outdoor levels near population centers are well represented by monitors, the extent to which outdoor concentration fluctuations are found to affect indoor concentrations and personal exposures to outdoor-origin particles is still an issue of particular importance. Some of the sensitive populations in the short-term mortality and hospital admissions studies (i.e., the elderly and those with pre-existing disease) can be expected to spend more time indoors than the general population. Some commentators have expressed concerns regarding the lack of correlation shown in some cross sectional studies of outdoor and indoor or personal exposures, and suggest that confounding by indoor sources of PM might bias the effects/outdoor PM response function towards a linear relationship when a threshold model may be more appropriate.<sup>3</sup> The CD assessment of this issue, however, found longitudinal correlations of personal exposure to  $PM_{10}$  can be well correlated with outdoor measurements. The CD assessment concluded that "the exposure to indoor-generated particles will not be correlated with the concentration of ambient (outdoor-generated) particles, and time-series epidemiology based on ambient measurements will not identify health effects of indoor-generated particles" (CD, p. 1-10). Furthermore, the CD

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<sup>3</sup>Implicit in this suggestion is the hypothesis that indoor- and outdoor-generated particles are essentially the same with respect to those characteristics important to producing particular health effects of concern. While some indoor-generated particles may have composition similar to outdoor PM, there may be significant differences in the adsorbed components, acidity, and other physico-chemical properties of potential importance that are more unique to particles that originate in a complex urban atmosphere. The relative importance of such factors is critical to testing the above hypothesis.

assessment of the literature found that "the measurements of daily variations of ambient PM concentrations, as used in the time-series epidemiology studies of Chapter 12, have a plausible linkage to the daily variations of human exposures to PM from ambient sources, for the populations represented by the ambient monitoring stations. This linkage should be better for indicators of fine particles ( $PM_{2.5}$ ) than for indicators of fine plus coarse particles ( $PM_{10}$  or TSP), which, in turn, should be better than indicators of coarse particles ( $PM_{10-2.5}$ )" (CD, p 1-10). The strength of the correspondence between outdoor concentrations and personal exposure levels on a day-to-day basis serves to reduce, but not eliminate, the potential error introduced by using outside monitors as a surrogate for personal exposure.

The effect of instrument and "representativeness" components of measurement error of PM and other covariates on the association between PM and effects can vary with modeling approach. Measurement error in the exposure variable, PM, in a univariate regression can bias the association toward the null. However, in multivariate regressions, which are used in the PM literature, the association is also influenced by the relationship between PM and the other covariates which can bias the association in either direction. This issue has been discussed in two recent analyses, one of cardiovascular hospital admissions in Detroit, (Schwartz and Morris, 1995) and the other of mortality in the six cities of the Six City Study, (Schwartz et al, 1996). In the cardiovascular hospital admission study, Schwartz and Morris discuss the potential influence of measurement error from the other covariates, CO and weather on the PM/cardiovascular hospital admissions relationship. High correlation between the covariates and the exposure of interest represents potential influence of error in the covariates on the exposure of interest. They evaluated the correlation between the covariates and found the correlations between CO levels and the weather variables, and between CO and PM levels, were small. In addition, the correlation between PM levels and weather variables was also small. They conclude that such low correlations may imply it is likely significant portions of bias do not come from the covariates, but from the error in measuring PM, which would decrease the association between PM levels with hospital admissions. The authors point out, however, that this does not mean that the estimated magnitude of the associations was unbiased.

This issue is explored further in the short-term mortality study in the six cities of the Six City Study (Schwartz et al., 1996). The authors examine the potential influence of measurement error on the association between excess mortality and  $PM_{2.5}$  levels. They note that the correlations between  $PM_{2.5}$  level and the other covariates, (e.g., weather) are not large, and thus not likely to influence the measurement error in the level of  $PM_{2.5}$  itself. They examine this by leaving weather terms out of the regression model, which is similar to a large measurement error in these terms, and find a slight decrease in the effects estimate for exposure to  $PM_{2.5}$ . They further test the effects of measurement error in the city of Boston by creating 10 new  $PM_{2.5}$  exposure variables each based on the original  $PM_{2.5}$  measurement with additional random error. They then repeat the multivariate regression 10 times using each of the 10 new  $PM_{2.5}$  variables. They find the mean coefficient for PM effects with the added measurement error was reduced by 13% compared to the original effects coefficient. These two results suggest that the net effect of random measurement error in the multiple regression is to bias toward underestimating the particle effect.

Schwartz et al., 1996 did not, however, assess either the effect of differential measurement error among the various particulate components, or the effect of other co-pollutants. Because coarse fraction particles occurring at the lower concentrations found in most of the six-cities are likely measured with less precision than are fine particles (Rodes and Evans, 1985), any effects of coarse particles would tend to be underestimated relative to fine particles (CD, p. 13-52). This does not diminish the significance of the findings for fine particles or  $PM_{10}$ , particularly in view of the fact that the association remained highly significant even when limited to days with  $PM_{2.5}$  concentrations under  $25 \mu\text{g}/\text{m}^3$ . Measurement error would be expected to be greater for fine particles at these lower concentrations than for the full data set.

Although the issue of confounding by other pollutants (e.g.,  $\text{SO}_2$ ,  $\text{CO}$ ,  $\text{O}_3$ ,  $\text{NO}_x$ ,  $\text{NO}_2$ ) is addressed in a subsequent section, measurement error clearly has implications for separating the effects of individual pollutants from a complex urban mixture. When collinear pollutants having different degrees of exposure error are entered into a regression jointly, the variable with the least exposure error will tend to be assigned higher significance, all else being equal (Lipfert and Wyzga, 1995a).

While the magnitude of measurement error and its effect on the PM/health effect associations is unknown, it is possible to test potential influences of measurement error in the PM measure or the influence of other covariates. Some aspects of these issues have been discussed in two recent studies, suggesting -- although not conclusively -- that the influence of measurement error is to bias the estimate downward. Nevertheless, a comprehensive, formal treatment of exposure misclassification studies of PM and other community air pollutants is an important research need. As discussed below, however, the consistency of the PM/effects relationship in multiple locations with widely varying indoor/outdoor conditions and a variety of monitoring approaches makes it less likely that the observed findings are an artifact of exposure misclassification.

c. Potential Influence of other Covariates in Short-Term Studies

Other factors that vary temporally with PM may influence the estimated relationship between PM and health effects, either independently or through interaction with PM. Independent risk factors related to both PM concentrations and the health effect of interest which could potentially confound the apparent associations between PM exposure and health effects. Inadequate control for confounding can result in incorrect interpretations, e.g., regarding the reported effect as being the result of an observed risk factor, when a third variable (the confounder) is really responsible. The estimated relationship between PM and health effects can also be biased up or down by potential interactions between PM and other risk factors, particularly other pollutants.

Significant attention has been focused on addressing potential confounders in the short-term studies. The CD points out that it is preferable to control confounding by designing a study in such a way that potential confounders are avoided (CD, Section 12.6.3.4). However, in many studies this is not a feasible option because it is not possible to avoid some potential confounders, such as weather, and in some cases, the levels of PM and the confounders are highly correlated. This can also be a problem for areas in which co-pollutants are derived from a common mixture of sources, such as combustion.

The CD discusses the difficulty in conducting studies in enough cities to make the appropriate number of comparisons. As discussed more fully in section V.E.2 below, however, the observed

similarities in relative risk of health effects from PM exposure across study areas with large differences in the potential for confounding from copollutants adds credibility to the conclusion that the PM mortality effects are real (CD, p. 12-331).

Covariates associated with daily changes in health effects, such as weather, season and levels of other pollutants (e.g., SO<sub>2</sub>) potentially associated with PM levels need to be considered. Most of the epidemiology studies of PM have considered at least some of the potential confounders in their analysis. These studies have used a number of methods to address or reduce confounding, with varying degrees of success. Less attention has been given to effects modification from the interaction between co-occurring pollutants and PM. A summary of the major issues discussed in the CD regarding the potential influence of other potential risk factors on PM and the most relevant PM studies is presented below.

i. Weather

Weather is an important confounder in short-term PM studies because fluctuations in weather are associated with both changes in PM and other pollutant levels and health effects reported in the studies<sup>4</sup>. Individual studies have used a variety of approaches to separate the effects of PM exposure and weather with most treatments appearing to be adequate (CD, p. 13-54). Most studies include temperature and dewpoint as covariates in their studies (CD, p. 13-54). In addition, many investigators use statistical methods to adjust for weather and season on an annual basis when modeling the PM and health effect relationship. In several of these studies (Schwartz, 1993a, 1994a, 1994d, 1994e, 1994f) nonlinear functions have been used that can reflect the complex relationship between weather and health effects [e.g., the effect of temperature in Birmingham, Alabama (Schwartz, 1993a)]. In other studies, linear and categorical variables were used (e.g., for very high temperature days) to adjust for routine fluctuations in weather and extreme conditions (Kinney et al., 1995; Pope et al., 1992). In an examination of the sensitivity of the associations of exposure to PM<sub>10</sub> with health effects to control for weather, several studies reported distinct effects of weather on mortality that were largely separable from the effects of PM exposure in the areas studied. Moreover, elimination of all weather variables from the PM-mortality models did not substantially

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<sup>4</sup>The relationship between temperature and health effects over the course of a year tends to be "U" shaped, with increasing effects on days with very hot or cold temperatures (Moolgavkar and Luebeck, 1996).

affect the size of the observed associations between PM exposure and excess mortality (Schwartz et al., 1996; Schwartz and Dockery, 1992a, 1992b).

Because of the limitations in using temperature and humidity alone to examine the much more complex changes that accompany various weather patterns, two recent studies of pollution and mortality associations in Utah Valley (Pope and Kalkstein, 1996) and Philadelphia (Samet et al., 1996b) further examined confounding by weather through the use of synoptic weather categories. In these studies the synoptic weather categories were defined independently of the health effects information, in an approach first recommended by Kalkstein (1994). Both studies show that the reported association between PM exposure and excess mortality was relatively insensitive to the changes in weather. All of the studies of daily PM levels and mortality use some method to adjust for weather, and report consistent associations between PM exposure and health effects.

The CD concludes that the PM coefficient is relatively insensitive to different methods of weather adjustment, as recently demonstrated in the recent studies and the reanalysis by HEI (CD, p. 13-54). Recent studies have adequately addressed the role of weather-related variables. (CD, p. 13-54). Clearly, weather affects human health; however, it is highly unlikely that weather can explain a substantially greater portion of the PM attributable health effects than has already been accounted for in the models (CD, p. 13-54).

ii. Confounding By Other Pollutants

One of the concerns raised by a number of authors conducting reanalyses of the mortality studies is whether the observed PM effects are confounded or modified by other pollutants commonly occurring in community air such as SO<sub>2</sub>, O<sub>3</sub>, NO<sub>2</sub>, and CO (Samet et al., 1995, 1996a; Moolgavkar et al., 1995b; Moolgavkar and Luebeck, 1996; Li and Roth, 1995). Based on successive reanalyses, Moolgavkar has advanced the contention that PM is serving as a surrogate for the general ambient air pollution mixture and that the reported health effects are more appropriately attributed to the mixture rather than to PM alone (Moolgavkar 1995b; Moolgavkar and Luebeck, 1996). Much of the support for this interpretation comes from the recent reanalyses of the Philadelphia data where it has proven

to be difficult to separate individual effects of multiple pollutants (Samet et al., 1995, 1996a; Moolgavkar et al., 1995b; Moolgavkar and Luebeck, 1996; Li and Roth, 1995). The HEI investigators concluded that "...a single pollutant of the group TSP, SO<sub>2</sub>, NO<sub>2</sub>, and CO cannot be readily identified as the best predictor of mortality" based only on analyses of the Philadelphia data (Samet et al., 1996a).

The CD examined the evidence for confounding in these and other studies in some detail in Section 12.6. It concludes that other pollutants can play a role in modifying the relationship between PM and health effects. The CD also notes that some studies have found little change in the PM relative risk (RR) after inclusion of other copollutants in the model and in analyses where the PM RR estimate diminished, the RR typically remained statistically significant (CD 13-57). Based on an evaluation of the existing studies and its assessment of confounding within and across a number of areas with differing combinations of pollutants, the CD concludes that the PM health effects associations are valid and, in a number of studies, not seriously confounded by copollutants (CD, p. 13-57). The role of co-pollutants in modifying the apparent RR associated with PM is less clear. The following discussion summarizes evidence regarding PM confounding and effects modification for each of several criteria pollutants.

Sulfur Dioxide (SO<sub>2</sub>). SO<sub>2</sub>, which was present at high concentrations with PM during the historical episodes, has long been seen as a potential confounder of the PM effect. Reanalyses of the extensive London data (Schwartz and Marcus, 1986) provided some support for the suggestion of Mazumdar et al., (1981) that at lower SO<sub>2</sub> values in London, mortality effects may be associated with PM alone. The more recent studies, in particular short-term exposure mortality studies, have applied several approaches to address SO<sub>2</sub> confounding, including restriction (studies in areas with low SO<sub>2</sub> levels) and more direct means. The discussion below highlights key findings from the recent epidemiological studies together with other pertinent information from SO<sub>2</sub> and PM air quality relationships and from studies of the penetration of SO<sub>2</sub>, alone and in combination with particles, to the respiratory tract described below.

In areas where the potential for confounding from SO<sub>2</sub> is relatively high, investigators have adjusted for SO<sub>2</sub> in the model (Ostro et al., 1995a; Toulomi et al., 1994; Schwartz and Dockery, 1992a). These studies have also conducted sensitivity analysis of the association between PM and health effects, by evaluating the association before and after adding SO<sub>2</sub> to the

model. These analyses produced inconsistent results. Studies conducted in Santiago Chile, Philadelphia, PA and Sao Paulo, Brazil, found that the association between PM and mortality remained positive and significant after the addition of SO<sub>2</sub>; whereas, the association between SO<sub>2</sub> and mortality became insignificant (Ostro et al. 1996; Schwartz 1992a; Saldiva et al., 1995). A similar analysis in Athens, Greece found that after modeling both SO<sub>2</sub> and PM, the association with SO<sub>2</sub> remained significant and positive (Touloumi et al., 1994). The estimates of associations with health effects for both pollutants were reduced, however.

The PM/SO<sub>2</sub> confounding issue has been thoroughly explored in Philadelphia through extensive analysis by several investigators, where SO<sub>2</sub> and PM are highly correlated (Schwartz, 1992a; Moolgavkar, 1995b; Li and Roth, 1995; Samet et al., 1995, 1996a). In these studies, investigators have been concerned about the potential for confounding from SO<sub>2</sub> in the observed TSP/mortality association. The original analysis by Schwartz and Dockery (1992a) evaluated the association between TSP and mortality in Philadelphia between 1973-1980. They found the association between TSP and mortality remained significant after adding SO<sub>2</sub> to their model; whereas, the relationship between SO<sub>2</sub> and mortality became insignificant. Moolgavkar et al. (1995b) evaluated the association between TSP and mortality in Philadelphia between 1973-1988. In this study, they attempted to account better for modification of the effect of air pollution on mortality by factors that vary with season (e.g., weather, pollutant mix, activity patterns). The Philadelphia daily air pollution/mortality data set is one of those large enough to conduct such seasonal analyses without undue loss of statistical power. Modeled individually, both pollutants were found to be significantly associated with mortality in each season. In models where TSP and SO<sub>2</sub> were included simultaneously, they concluded that TSP was positively associated with mortality in the summer and fall, and SO<sub>2</sub> was positively associated in all four seasons<sup>5</sup>.

HEI evaluated both of the Philadelphia data sets discussed above (Samet et al., 1995; Samet et al., 1996d) and conducted their own analysis on data collected directly from the National Center for Health Statistics and EPA's AIRS database. Although the overall results of the

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<sup>5</sup>In a seasonal analysis of the later years of the Philadelphia data (1983-88), Cifuentes and Lave (1996) found somewhat different results. In their analysis, SO<sub>2</sub> was only significant in the winter, and only without TSP in the model, while TSP was significant in spring and summer and the coefficient was stable across all seasons (CD, p. 12-53).

reanalyses were similar to those of the original authors, the new HEI analyses used techniques that revealed a more complex, non-linear set of relationships among pollutants, season, and mortality. The authors concluded that the Philadelphia data showed a relationship between air pollution and mortality, but that it would be difficult to use the results of this single study to attribute such effects solely to particles. The combined pollutant mortality relationships are of some interest. The first HEI analysis explored the relationship between SO<sub>2</sub> and TSP in depth. The relationship between TSP and mortality indicates a monotonically increasing response occurs only at particle levels above 100 µg/m<sup>3</sup> TSP. This result is consistent with either a no-observed-effects level for TSP at 100 µg/m<sup>3</sup> or a reduced association caused by a correlation with SO<sub>2</sub> at lower concentrations. Conversely, SO<sub>2</sub> displays a monotonically increasing concentration response function from the lowest levels to about 40-60 ppb, where the curve flattens out. It is difficult to find a plausible mechanism for such a concentration-response relationship for a single pollutant, suggesting confounding is likely.

Dockery et al. (1995) commented on the HEI analysis, suggesting that TSP and SO<sub>2</sub> are indicators of a more appropriate risk factor, such as fine particles. The facts that fine particle sulfates and SO<sub>2</sub> share a common source in Philadelphia and that the coarse fraction of TSP is poorly correlated with the fine fraction (CD, Table 6-15) indicate that either or both pollutants could reasonably serve as a surrogate for fine particles. In this event, SO<sub>2</sub> itself might play no direct role in causing effects, with only a fraction of TSP participating. Resolution of the merit of the original investigator's suggested hypothesis, however, must await the results of subsequent studies that use fine particle indicators in lieu of TSP.

In evaluating the findings in Philadelphia, an important consideration is the evidence on the penetration and deposition of particles in the respiratory system as compared to SO<sub>2</sub>. Although quantitative support is lacking, the discussion of controlled human and animal studies of particles indicates that smaller particles can more effectively penetrate to the portions of the lung where irritation or other interactions with lung tissues might produce effects. (See section V.A above). Beyond reflex broncho-constriction observed only at very high peak levels, however, deep lung effects of SO<sub>2</sub> are minimal because gas-phase SO<sub>2</sub> is generally efficiently removed in the extrathoracic region in humans (U.S. EPA, 1994c). This lack of penetration in the lung greatly

reduces the likelihood that SO<sub>2</sub> alone could produce significant cardio-pulmonary effects, particularly for sensitive individuals spending more of their time indoors where SO<sub>2</sub> concentrations are low due to rapid removal by indoor surfaces. However, one mechanism by which SO<sub>2</sub> can be transported deeper into the lung is absorption or dissolution onto the surfaces of atmospheric particles (See Section V.F). In this case, the complex results reported by HEI in regard to effects associated with SO<sub>2</sub> exposure might be partially reflecting varying atmospheric interactions of the two pollutants, rather than a direct SO<sub>2</sub> effect.

Given the difficulty in ascribing effects to a single pollutant in Philadelphia or similar cities where elevated particles are associated with SO<sub>2</sub>, confounding by SO<sub>2</sub> can be addressed by assessing the PM/mortality relationship in areas with low levels of SO<sub>2</sub>. Dockery et al., (1993) found no association between SO<sub>2</sub> and mortality in Kingston and St. Louis, areas with considerably lower SO<sub>2</sub> levels. While consistent associations between PM and health effects are observed across the different studies, the reported association between health effects and SO<sub>2</sub> can vary widely. In Steubenville, the association between SO<sub>2</sub> and mortality was ten-fold greater than in Philadelphia (i.e., coefficients of 0.0104 versus 0.00132 per ppb) (Schwartz and Dockery, 1992a,b) although the two areas have comparable SO<sub>2</sub> levels.

In a single city such as Philadelphia, where SO<sub>2</sub> and PM levels are highly correlated, it is more difficult to ascribe the observed mortality effects to a single pollutant. In such cases, consideration of the observed relationships and relevant information on air quality, indoor exposures, dosimetry, and mechanisms suggest that it is unlikely that an independent effect of SO<sub>2</sub> is occurring that does not involve PM. Moreover, given the number of studies using different methods to correct for potential confounding in areas of high and low SO<sub>2</sub> that find an association between PM and mortality, it is unlikely that SO<sub>2</sub> is responsible for all of the observed associations between PM and mortality. Similarly, when the more severe morbidity endpoints such as respiratory-related hospital admissions are considered, the presence or absence of SO<sub>2</sub> is also seen to have little effect on observed PM associations (see Table V-11, Schwartz, 1995a) in most cases.

Ozone. The co-occurrence of episodes involving high temperatures with elevated levels of O<sub>3</sub> and PM raised the potential for confounding, particularly during the O<sub>3</sub> season in large regions

of eastern North America, Los Angeles, and some other cities). In such cases, covariate adjustment has often been used to try to distinguish the effects of multiple pollutants. A number of studies using such methods have found PM to be a stronger predictor of mortality than O<sub>3</sub> (Dockery et al. 1992b; Saldiva et al., 1995; Kinney et al., 1995; Ostro et al., 1996). Adjusting for the presence of O<sub>3</sub> did not significantly affect the associations with PM and mortality. For example, in Los Angeles, which has the highest concentrations of O<sub>3</sub> studied, investigators found a significant association between both PM and O<sub>3</sub> mortality when each pollutant was entered into the model separately, but found no significant association between O<sub>3</sub> and mortality in models that included PM (Kinney, 1995). On the other hand, the coefficient for PM remained stable when O<sub>3</sub> was in the model along with PM, but the uncertainty in the PM association increased, making it marginally significant; this finding suggests that the PM-mortality association was not completely independent of O<sub>3</sub> (CD, p. 13-55). In Santiago, where a negative correlation exists between O<sub>3</sub> and PM levels, no association was observed between O<sub>3</sub> and mortality across a full year even without PM in the model; this was despite summertime values of O<sub>3</sub> that were twice the U.S. standard (Ostro et al., 1996). In the Utah Valley, O<sub>3</sub> and PM were also negatively correlated, and the inclusion of O<sub>3</sub> as a covariate strengthened the estimated PM effect (Pope et al. 1995a, Table V-3). Furthermore, the relative risk estimates for PM were relatively unchanged and there was little increase in the width of the confidence interval after inclusion of O<sub>3</sub> in the model, and indicating little evidence of confounding of the PM effect (CD, p. 13-52).

Samet et al., (1996a) extended their analysis of the Philadelphia mortality data by examining combinations of multiple pollutants (TSP, O<sub>3</sub>, NO<sub>2</sub>, SO<sub>2</sub>, and CO). This analysis found a low correlation between PM and O<sub>3</sub>, indicating independence between the two pollutants. Ozone had a stable and significant association with mortality that appeared to be independent of the other pollutants. The effect estimate for TSP was lowered, but remained significant when O<sub>3</sub> was added to the model. The CD reanalysis of the HEI results suggests that O<sub>3</sub> may be a potential confounder of TSP in the summer, but not in other seasons (CD, p. 12-297).

In some locations, the potential for O<sub>3</sub> to confound the effects caused by PM is minimized by the low concentrations of O<sub>3</sub> observed during seasons which show a robust PM effect. Examples include Utah Valley and Santa Clara, where O<sub>3</sub> levels are minimal in the winter when

the PM levels are high (Pope et al., 1992a; Fairley, 1990). The discussion above of confounding by weather notes a number of cities with cooler climates, where particles are associated with mortality, which would have low O<sub>3</sub> levels.

There is a higher potential for O<sub>3</sub> confounding for the risk of respiratory-related morbidity, because multiple studies have demonstrated apparent separable associations between respiratory effects and PM and O<sub>3</sub> concentrations. Moreover, the recent review of the O<sub>3</sub> criteria found that the biological basis for O<sub>3</sub> aggravation of respiratory symptoms was supported by controlled human and animal studies (EPA, 1986c). The respiratory-related hospital admission studies often find O<sub>3</sub> and PM are each singularly associated with respiratory-related admissions (Schwartz, 1994d; Schwartz, 1996; Burnett et al., 1994). When both pollutants are modeled together, the association between PM and respiratory-related admissions in general remains relatively unchanged, indicating a separable effect independent of O<sub>3</sub>. The potential for O<sub>3</sub> confounding for cardiac-related hospital admissions appears to be much lower. Two studies have reported that PM is associated with cardiac hospital admissions but O<sub>3</sub> is not (Burnett et al., 1995; Schwartz and Morris, 1995).

Carbon Monoxide (CO). The lethality of high concentrations of CO is well documented; as such, it must be considered as a potential confounder in community studies (U.S. EPA, 1991). Three of the short-term PM exposure studies examined the effect of CO on the PM/mortality relationship. A study in Athens found a significant association between mortality and CO and PM when each pollutant was considered separately (Touloumi et al., 1994). When considered together, only PM remained significantly associated with mortality. However, there was a high correlation between CO and PM making such separation difficult. Similarly in Los Angeles, where CO and PM were also correlated, positive associations between each pollutant and mortality were reported when both were evaluated simultaneously (Kinney et al., 1995). However, in Chicago, insignificant associations were reported between CO and mortality (Ito et al., 1995). The recent analysis by HEI of Philadelphia also evaluated the role of CO in mortality (Samet et al., 1996a). Similar to the other studies they found a moderate correlation between TSP and CO concentrations, and they considered CO, along with SO<sub>2</sub> and NO<sub>2</sub> to be interrelated with TSP because of their common sources. Their results show that the average CO

concentration on current and previous day was never significantly associated with mortality, whereas CO lagged by three and four days, was significantly associated with mortality. The authors note that this finding was not expected given the mechanism of CO toxicity and the half-life of carboxyhemoglobin. With TSP and lagged CO in the model, they find both TSP and lagged CO level are each significantly associated with mortality. Based on an extended analysis of these results, the CD finds that TSP effects can be reasonably distinguished from CO in all seasons (CD, p. 12-297).

The results from these studies are inconsistent with respect to CO. Because of the nature of urban sources of CO as well as indoor sources, exposure misclassification may introduce significant problems, which reduces the ability of community studies to detect a CO effect. In addition, while cardiovascular effects are plausibly linked to CO, controlled studies do not suggest CO is a respiratory irritant (U.S. EPA, 1991). It is therefore unlikely to confound studies reporting respiratory related mortality, hospital admissions, or aggravation of conditions such as asthma, all of which are linked to PM.

The potential relationship of CO and PM to cardiovascular effects was examined in the Schwartz and Morris (1995) study of hospital admissions for cardiovascular diseases in Detroit. They found an association between CO and PM and ischemic heart disease and congestive heart failure admissions when evaluating each pollutant separately. When evaluated together, CO was no longer associated with ischemic heart disease admissions, but the association with admissions for congestive heart failure for both pollutants remained relatively unchanged, suggesting each pollutant had a separable, independent association with congestive heart failure. While significant exposure to CO in microenvironments characterized by high CO levels may render a hypoxic effect on patients with cardiopulmonary disease, which may aggravate heart disease (see section B above and Appendix D), it is unlikely that most patients would be exposed to such a level of CO. In addition, once taken to the hospital or to other places with low CO the carboxy hemoglobin levels of such patients would rapidly decline.

Nitrogen Dioxide (NO<sub>2</sub>). By comparison, fewer of the mortality studies have directly assessed NO<sub>2</sub> as a potential confounder of PM<sub>10</sub> effects. Several such studies have reported high correlations between NO<sub>2</sub> and PM in Los Angeles, CA; Toronto, Canada; and Santiago, Chile

(Kinney, 1991, Ostro et al., 1996, Özkaynak et al., 1994). Mixed results were reported concerning the association between NO<sub>2</sub> and mortality. Kinney and Özkaynak (1991) found a statistically significant relationship with NO<sub>2</sub> and mortality in Los Angeles, but reported that these results were interchangeable with CO and PM, since the correlations were so high between these pollutants. In Los Angeles and some other Western U.S. cities, nitrogen oxide emissions are themselves a major source of fine particles and nitric acid. The Santiago study found, however, that NO<sub>2</sub> was not associated with mortality when included in the model of PM and mortality (Ostro et al., 1996). Furthermore, the association between PM and mortality remained relatively unchanged after addition of NO<sub>2</sub> to the model. Similar results were found in the Sao Paulo study, where NO<sub>2</sub> was not associated with mortality in adults after including PM<sub>10</sub> in the model (Saldiva et al., 1995). All these studies were conducted in areas of relatively high NO<sub>2</sub> levels; Santiago had the lowest mean level of 0.0556 ppm. A study in St. Louis, with a lower mean level of 0.02 ppm, found no significant association between mortality and NO<sub>2</sub> (Dockery et al., 1992b). While the association between NO<sub>2</sub> and health effects in these studies is inconsistent, the association between PM and health effects remains positive and consistent, both across study areas with varying levels of NO<sub>2</sub> and after controlling for NO<sub>2</sub> in the model (Ostro et al., 1996; Saldiva et al., 1995; Schwartz et al., 1994).

NO<sub>2</sub> was also included in the multi-pollutant analyses of mortality in Philadelphia. Moolgavkar and Luebeck (1996) found that, when all co-pollutants were entered simultaneously into their model, NO<sub>2</sub> appeared to emerge as the most important pollutant. By contrast, the recent HEI multi-pollutant analysis (Samet et al., 1996a) of mortality in Philadelphia found that with both TSP and NO<sub>2</sub> in the model, the coefficient and the t-value for TSP increased. NO<sub>2</sub>, on the other hand, was not significantly associated with mortality when modeled alone, and when TSP or all pollutants combined were included in the model, the coefficient for NO<sub>2</sub> became significantly negative. In essence, the more limited results for NO<sub>2</sub> and mortality to date do not show a consistent association.

## 2. Consistency and Coherence of the Epidemiological Studies

While individual studies indicate health effects are associated with PM, a more comprehensive synthesis of the available evidence is needed to evaluate fully the likelihood of PM

causing effects at levels below the current NAAQS. Because individual studies in themselves are inherently limited as a basis for addressing causality, the consistency and coherence of the effects across the studies must be considered. As noted above, it is too difficult to resolve the question of confounding using these results from any single city because of the correlation among all the pollutants (Samet et al, 1996a). The HEI investigators conclude that "insights into the effects of individual criteria pollutants can be best gained by assessing effects across locations having differing pollutant mixtures and not from the results of regression models based on data from single locations" (Samet et al., 1996a). The consistency of the association is evidenced by its repeated observation by different investigators, in different places, circumstances and time; and by the consistency of the associations with other known facts (CD, Chapter 13; Bates, 1992). A complement to consistent associations found for individual endpoints is coherence, which is the logical or systematic interrelationship among different health indices, which should be demonstrated across the studies of different endpoints. As the CD notes, the discussion of the consistency and coherence of the epidemiological studies must be largely qualitative because it relies on a series of judgments concerning the reliability of the individual studies (CD, p. 13-58). The consistency and the coherence of the PM epidemiological evidence is discussed and evaluated below.

a. Consistency

The CD summarizes over 80 community epidemiological studies evaluating associations between short-term PM levels and mortality and morbidity endpoints in tables 12-2 and 12-8 to 12-13. Over 60 of these have found consistent, positive, significant associations between short-term PM levels and mortality and morbidity endpoints. These studies have been conducted in a number of geographic locations throughout the world, including the US, Canada, Europe and Latin America, using a variety of statistical techniques, and with varying temporal relationships. Despite the variations in the approaches, the effects estimate for each health endpoint is relatively consistent among the studies. Figure V-2 displays the estimated relative risk per 50  $\mu\text{g}/\text{m}^3$   $\text{PM}_{10}$  increase derived from the U.S. and Canadian short-term studies of mortality and morbidity effects presented in Tables V-4, V-6, and V-7.

Clearly, the relative risk estimates exhibit some variation for particular endpoints. For example, the relative risk estimates for mortality associated with a 50  $\mu\text{g}/\text{m}^3$  increase in PM<sub>10</sub> range from 1.02 to 1.08. The CD observes that this kind of variation in the RR estimates would be expected for the following reasons: 1) the relative toxicity of PM varies from region to region; 2) the demographic and socioeconomic characteristics of the population vary regionally; 3) the health status, and thus the distribution of the sensitive population vary regionally; and 4) ambient PM levels vary regionally. Thus, the CD concludes that some variation in the RR estimates is not inconsistent with a real effect of PM exposure on daily mortality (CD, Section 13-4.1.1). Similarly, some variation in the RR estimates for morbidity endpoints would be expected, as is observed in Figure V-2.

The large number of studies in a number of different geographic areas, provides an opportunity to evaluate the consistency and sensitivity of the PM estimates to different levels of potential influence by weather and copollutants. Such an evaluation allows consideration of both the potential for confounding from these factors and interpretation of whether the observed health effects are attributable to PM or to the complex air pollution mixture. As for confounding, the CD notes generally similar RR estimates for acute mortality in different studies with different levels of potential confounding copollutants lend credibility to the conclusion that the PM mortality effects are real (CD, p. 12-33).

If PM is acting independently, then a consistent association should be observed in a variety of locations of differing relative proportions of particles and potential gaseous pollution confounders. If, instead, the observed PM effect results from influence from another pollutant, either through confounding or synergistic interaction, the associations with PM would be expected to be consistently high in areas with high concentrations of the pollutant, and consistently low in areas with lower concentrations of the pollutant. In addition, consistent PM effects across a range of pollutants indicates would indicate that it is more likely that there is an independent effect from PM, that is not confounded by other components of the air pollution mix. Figure V-3 shows the reported relative risk of PM<sub>10</sub> effects and associated levels of SO<sub>2</sub>, NO<sub>2</sub>, O<sub>3</sub>, and CO from studies conducted in the U.S. as reported in Table V-3. The relative risks are those reported in each of the studies, unadjusted for the other pollutants. The figure indicates that

the association with  $PM_{10}$  remains reasonably consistent through a wide range of concentrations of these potentially influential pollutants. While it is possible that different pollutants may serve to confound or otherwise influence particles in different areas<sup>6</sup>, it seems unlikely that this would lead to such similar associations and relative risk numbers for particles. Within the observed range of relative risk, however, it is certainly possible that other pollutants might modify the apparent effects of particles by atmospheric interactions (e.g., through dissolution/adsorption or aerosol formation reactions) or by independent effects on sensitive populations (e.g. respiratory function changes from  $O_3$  or  $SO_2$ ) as described in the previous section. Moreover, the possibility of exposure misclassification for primary gaseous pollutants (e.g., CO,  $SO_2$ ) could diminish their apparent significance. Nevertheless, epidemiological studies have been conducted in a broad range of areas across the U.S. and Canada, where meteorological and pollution patterns vary distinctly. These studies find a consistent, positive association between PM and mortality and morbidity effects. The CD has concluded that the effects are unlikely to be explained by weather (CD, p. 13-54), that the PM effects are not sensitive to other pollutants and the "findings regarding the PM effects are valid" (CD, p. 13-57).

b. Coherence

In addition to the consistently observed associations for each effect, this collection of studies shows coherence in the kinds of health effects associated with PM exposure. The CD provides a qualitative review of the coherence of the health effects associated with both short-term and long-term exposure to PM (CD, Tables 13-6 and 13-7). Short-term exposure to PM is related to a number of effects ranging from mortality to morbidity and changes in lung function and respiratory symptoms. The association of PM with mortality is mainly linked to respiratory and cardiovascular causes, which is consistent with the range of observed morbidity effects, from respiratory and cardiovascular-related hospital admissions to changes in lung function. In

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<sup>6</sup>In this interpretation of the results advanced by Moolgavkar and Luebeck (1996), CO, for example, would lead to a false association with particles in Utah Valley where  $SO_2$  was low, and  $SO_2$  would lead to a false particle signal in Philadelphia, where CO levels were more modest. Such a serendipitous combination of variable confounding would make the more ubiquitous pollutant, particles, appear to be consistently associated with the effect. In this event, at least two other pollutants, or an unidentified substance(s) correlated with them, would be associated with mortality and other effects.

addition, the CD tables show a number of similar health effects are associated with both long-term and short-term exposure to PM.

This qualitative coherence is further supported by quantitative coherence across several endpoints as demonstrated in Figure V-2 and Table V-10 which also provides some perspective on the baseline incidence for effects of concern. Observations of increases in cardiovascular and respiratory mortality associated with PM should be accompanied by more frequently occurring increases in hospital admissions for the same causes. Table V-10 shows this to be the case. Using the RR estimates developed in Chapter 12, the CD finds about 0.3 respiratory deaths expected per day per million for all age groups attributable to a  $50 \mu\text{g}/\text{m}^3$  increase in PM. The CD notes a higher expected increase in respiratory-related hospital admissions of 2.0 per day per million in the total population. Similar results are found for cardiovascular deaths, with 0.9 cardiovascular deaths and 2.3 cardiovascular hospital admissions per million per day associated with a  $50 \mu\text{g}/\text{m}^3$  increase in PM. There are some numerical inconsistencies in Table V-10, but, given the diversity of the studies and analytical methods used to derive the estimates, the coherence between the mortality and morbidity endpoints is consistent with expectations (CD, p. 13-64).

The coherence is further strengthened by multiple studies demonstrating associations with a range of effects in the same population. Studies in Detroit, Birmingham, Philadelphia and Utah Valley show increased frequency of a variety respiratory and cardiovascular related health effects associated with PM exposure in the same population (CD, Section 13.4.3.5). For example, studies in Utah Valley have shown a number of closely related outcomes associated with PM exposures, including decrements in lung function, increased respiratory symptoms, increased medication use in asthmatics, and increased elementary school absences (frequently due to upper respiratory illness). Finally, there is coherence in the sense that the observed health effects, which are related to respiratory and cardiovascular causes, are those that would most likely to be associated with the inhalation route.

The CD concludes there is evidence for increased health effects risks associated with PM exposure ranging in severity from asymptomatic pulmonary function decrements, to respiratory and cardiopulmonary illness requiring hospitalization, and finally to excess mortality from respiratory and cardiovascular causes (especially in those older than 65 years of age) (CD, p. 13-

67). Such a coherence of effect greatly adds to the strength and plausibility of the association (Bates, 1992).

F. Health Effects Associated with Fine and Coarse Fraction Particles

The health effects information summarized in previous sections of this chapter and in the criteria document provides substantial evidence that ambient PM, alone or in combination with commonly occurring pollutant gases, is associated with small but significant increases in mortality and morbidity in some sensitive populations at concentrations below the levels of the current ambient standards for PM. An examination of potential confounders and other methodologic issues associated with these studies suggests that these associations are valid (Section V.E). Taken together, the extensive body of recent epidemiologic studies show both qualitative and quantitative consistency suggestive of causality, although supporting evidence for plausible mechanisms of action that have been hypothesized is lacking in the published literature. The purpose of this section is to examine the health effects evidence most useful in determining which PM measure(s) are the most appropriate surrogate(s) or indicators for those components of PM that are most likely to be associated with the array of health effects discussed in the previous sections of this chapter.

A substantial body of quantitative effects information exists for  $PM_{10}$ , which is the indicator most frequently used in recent community studies (CD, Tables 13-3, 13-5). Particle dosimetry and mechanistic considerations continue to suggest that typically occurring ambient particles capable of penetrating to the thoracic regions of the respiratory tract (i.e.  $<10\mu m$  diameter) are of greatest concern to health (Section V-B). As discussed in Chapter IV,  $PM_{10}$  occurring in ambient atmospheres is composed of two distinct mass fractions (fine mode and coarse mode fractions). Based on atmospheric chemistry, exposure, and mechanistic considerations, the CD concludes it would be most appropriate to “consider fine and coarse mode particles as separate subclasses of pollutants” (CD, p. 13-94) and to measure them separately in order to plan effective control strategies.

Accordingly, this section summarizes evidence on the health effects associated with fine and coarse fraction particles<sup>7</sup>, with an emphasis on epidemiologic results the criteria document judges as most useful in making quantitative conclusions. While the epidemiological data providing a direct comparison of the health effects of fine and coarse particles are quite limited in comparison to that of PM<sub>10</sub> (which contains both coarse and fine mode fractions), multiple indicators of fine mass and/or its constituents (PM<sub>2.5</sub>, SO<sub>4</sub>, COH, KM, BS) have been associated with short term effects in over 15 different cities on three continents. In addition, in community studies where PM<sub>10</sub> is known to be dominated by fine (e.g. Philadelphia) or coarse (e.g. Anchorage) particles, some qualitative inferences can be made about the dominant fraction. The following sections review the epidemiologic evidence presented in the CD for health effects associated with fine and coarse mode particles and discusses their implications. The discussion addresses 1) community studies using fine particle indicators, 2) community studies directly comparing fine and coarse fractions, 3) studies of PM<sub>10</sub> effects in communities with high coarse particle levels, and 4) insights from air quality, toxicology, and controlled human studies on particle characteristics as they relate to the potential toxicity of the two fractions.

The focus of this examination is on evidence that permits a quantitative evaluation of the extent to which fine and coarse fractions of PM<sub>10</sub> are most likely to be associated with the key health effects categories of mortality, morbidity, symptoms, and functional changes in sensitive populations. This is a more meaningful and tractable comparison than that between PM<sub>10</sub> and the fine fraction of PM<sub>10</sub>, which is inherently confounded. Given the profound physicochemical differences between the two subclasses of PM<sub>10</sub>, it is reasonable to expect some differences may exist in both the nature of potential effects and in the relative concentrations required to produce similar responses. In this regard, components within both pollutant classes could be implicated in causing effects, but the level and nature of risk posed may vary between the two. In that event, the most appropriate protection from the effects of particles smaller than 10 µm would be

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<sup>7</sup>Tables 13-6 and 13-7 of the CD provide a qualitative summary of the strength of the epidemiologic evidence for several alternative indicators of PM, including thoracic, fine, coarse, and individual components of fine particles (sulfate and acids).

provided by consideration of more than one indicator in developing control strategies. (CD, p. 13-94).

#### 1. Epidemiological Studies using Fine Particle Indicators

This section briefly summarizes the epidemiological evidence on the health effects associated with fine particles as measured by a variety of indicators. As noted in the CD (Tables 13-6, 13-7), community studies have shown fine particles to be associated with a range of health outcomes, including mortality in sensitive population groups, increased hospitalization, respiratory symptoms, and decreased lung function. While a number of the studies used an indicator of fine particle mass, such as sulfates, many of them employed  $PM_{2.5}$  or  $PM_{2.1}$  instruments. These studies are listed in Tables V-11, V-12 and V-13, with key aspects summarized below.

##### a. Short-Term Studies

Tables V-11 and V-12 lists 18 studies identified in the CD as evaluating short-term associations between mortality and morbidity and a number of different measures of fine particles. Table V-11 lists studies that used filter based optical techniques (BS, KM, COH, see Appendix B), which provide mainly qualitative support for an association of mortality and fine particles, while Table V-12 lists quantitative results from studies reporting gravimetrically measured components that serve as indicators of particles in the fine fraction (i.e. sulfates and acids), and direct measures of  $PM_{2.5}$  or  $PM_{2.1}$ . These tables indicate that statistically significant associations have been found between fine particles and mortality in a number of cities. Six of these studies found statistically significant associations with mortality and fine particles as measured with filter-based optical techniques (BS, KM and COH), while two others could not separate effects of particles from potential confounding by other pollutants (Kinney and Özkaynak, 1991) or the effects of a heat wave (Katsoyanni et al., 1993). More quantitative results on fine particles ( $PM_{2.1}$ ) and mortality are provided by Schwartz et al (1996a), which includes 6 cities (Table V-12). This study is reviewed in detail in the subsection V.F.2 below, along with other studies that provide direct comparison of effects associated with fine and coarse particles.

Nine studies in the U.S. and Canada have found positive associations between short-term exposure to gravimetrically measured fine particles or components (including sulfates and acids)

and indicators of morbidity, including increased hospital admissions, increased respiratory symptoms and decreased lung function (Table V-12). All the studies found a positive association between  $PM_{2.5}$  and measured health effects; in eight of the studies the associations were significant. A particularly informative study was conducted by Thurston et al. (1994b) in Toronto, which evaluated the associations of respiratory-related hospital admissions with a range of particle indicators. This study is discussed below in subsection V.F.2.

b. Long-Term Studies

Table V-13 lists the studies the CD finds most useful for presenting quantitative estimates of effects associated with long-term exposure to PM (CD, Table 13-5). Two recent prospective studies, the Six City Study and the ACS study, reflect significant methodological advances over earlier cross-sectional studies and provide the best evidence of the association between long-term PM exposure and mortality. The relative strength of the results for fine and coarse indicators is discussed below in subsection V.F.2.

The designs and approaches of the Six City and ACS studies are complementary in nature (See Section V-13). The Six City study provided a more complete consideration of co-occurring pollutants that might confound the results ( $O_3$ ,  $SO_2$ ,  $NO_2$ ), but lacked some power due to the limited number of cities and the size of the total population included. The ACS study was designed to test the major hypothesis derived from the Six City study, namely that long-term exposure to fine particles (as  $PM_{2.5}$  or sulfates) was associated with increased mortality. The ACS design improved upon the Six City study by evaluating a larger population in many more cities across the U.S. (151) but, based on the earlier findings, did not include multiple pollutants. The ACS study found a significant association between mortality and both  $PM_{2.5}$  and sulfates (Table V-13). For reasons discussed in Section V.C., the staff concludes the somewhat smaller effects estimates from the ACS study are likely more useful for risk assessment of long-term mortality than those from the Six City study. In addition, consideration must be given to the role of earlier exposures to higher concentrations with respect to the applicability of these estimates based on a few years of monitoring (CD, P 12-366). If the effects are the result of long-term exposures, as opposed to the sum of episodic or daily effects, then the reported relative risk estimate are apt to be high.

Cross-sectional studies conducted by Özkaynak and Thurston (1987, 1989) and Lipfert (1988) provide some additional insights into the relationship between long-term exposure to fine particle indicators and mortality. Özkaynak and Thurston's cross-sectional analysis of various particle measures and 1980 total mortality across US cities found the most consistent and significant associations with fine particles and sulfates. In their analysis, TSP and  $PM_{15}$  were often found to be nonsignificant predictors of mortality. Lipfert also analyzed 1980 total mortality across US cities in relation to different particle measures (CD, p. 12-15). In general, when evaluating single site TSP or  $PM_{15}$  and sulfates or  $PM_{2.5}$  in models with the same covariates, the effects estimates for sulfates and fine particles were generally larger than those for TSP or  $PM_{15}$ . Some model specifications also show significant associations between mortality and multi-station TSP. A supplemental analyses of the Lipfert 1980 data in the CD found that the introduction of numerous potentially confounding variables (e.g. water hardness, sedentary lifestyle) reduced but did not eliminate the  $PM_{2.5}$  effect on mortality (CD, Fig 12-7)<sup>8</sup>. Clearly there are inherent methodological issues with these ecological approaches, but they show evidence of associations between long term measures of fine particles, including sulfates, and mortality that are quantitatively more consistent with the lower risk estimates found in the ACS study (CD, p 12-177).

Several studies have evaluated the association between long-term fine particle exposure and increased respiratory symptoms and decreased lung function most which have been conducted in children (Table V-13). The 24 city studies are of particular interest. These studies evaluated the association between different measures of long term PM ( $PM_{10}$ ,  $PM_{2.5}$ ,  $SO_4$  and  $H^+$ ) and respiratory symptoms and pulmonary function in children (Raizenne 1996; Dockery et al. 1996). The one year surveys found a significant increase in bronchitis in children (one episode or more) associated with particle strong acidity and fine particulate sulfates. Elevated, but nonsignificant associations were observed between reporting a bronchitis and  $PM_{2.5}$  and  $PM_{10}$ . No other

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<sup>8</sup>In this example, the  $PM_{2.5}$  effect was reduced from 0.045 to 0.02 deaths per  $\mu g/m^3$ . While it is likely, that addition of some of these variables to the Six Cities and ACS cohort studies would reduce the effects estimates for these two studies as well, the relevance and independence of including all of their variables (e.g., sedentary lifestyle and overweight) can be questioned.

respiratory symptoms, including asthma symptoms, were significantly associated with any of the pollutants.

In contrast to the earlier 6 city results, annual mean particle strong acidity, total sulfates,  $PM_{2.5}$  and  $PM_{10}$  were all significantly associated with FVC and FEV1 deficits (Table V-13). A slightly larger FVC decrement was found for children who were lifelong residents of their communities, though it was not significantly different. For the 24 cities, there was a strong correlation between particle strong acidity and sulfates ( $r=0.90$ ) and  $PM_{2.1}$  ( $r=0.82$ ), but not with  $PM_{10}$  ( $r=0.47$ ). Thus, it is difficult to ascribe the association to any one of the 3 fine particle indicators.

## 2. Community Studies Comparing Effects of Fine and Coarse Fraction PM

Several studies provide quantitative information directly comparing the association between health effects and fine and coarse particles. They include an examination of short-term PM exposure mortality in the Harvard six cities (Schwartz et al., 1996), a short-term exposure hospital admission study (Thurston et al., 1994b), and the long-term exposure mortality Six City Study (Dockery et al., 1993). Supporting information on long term effects can also be found in the data from the ACS study (Pope et al., 1995b) and the 24 city study reports (Spengler et al., 1996; Dockery et al., 1996; Razienne et al., 1996).

### a. Short-Term Comparisons

A recent analysis of mortality in six cities by Schwartz et al (1996) evaluated the association between mortality and 5 different particle measures: coarse fraction particles ( $PM_{15/10}$  minus  $PM_{2.5}$ ); thoracic particles ( $PM_{15/10}$ ),  $PM_{2.5}$ , Sulfates, and  $H^+$ . Table V-14 highlights the results for coarse fraction, thoracic, and  $PM_{2.5}$  particles. The estimated increase in mortality associated with  $PM_{10/15}$  was positive in all the cities except for Topeka, where there was no association (Table V-3). In all of the other cities, the observed increases ranged from 3.0 to 6% for a  $50 \mu\text{g}/\text{m}^3$  increase in  $PM_{10}$  (Table V-3), consistent with the range reported for previous  $PM_{10}$  studies (2 to 9%). A graphical display of the results for the components of  $PM_{10}$  suggests, however, that most, if not all, of the  $PM_{10}$  effect in these cities appears to be due to fine particles (Figure V-4). The estimated increase in daily mortality associated with  $PM_{2.5}$  was consistently positive in all 6 cities (0.8 to 2.2% for a  $10 \mu\text{g}/\text{m}^3$   $PM_{2.5}$  increase) and statistically significant in 3

cities. In contrast, the relative risks for mortality associated with coarse particles was inconsistent across the 6 cities (-1.3% to 2.4% for a  $10 \mu\text{g}/\text{m}^3$  increase in coarse particles) (Table V-14). The association with coarse particles was significant only in Steubenville, but it is difficult to interpret these results given the high correlation between fine and coarse particles ( $r=0.69$ ) in this city. All of the other cities have  $r$  of 0.45 or less. The negative but non-significant association between  $\text{PM}_{10}$  and mortality in Topeka noted above appears to be driven by the coarse fraction. Although Topeka has the highest percentage of crustal particles and the second highest average coarse mass, coarse particles have a nearly significant negative association with mortality, while fine particles have a positive but non-significant association. While greater measurement error for the coarse fraction (see Section V.E above) could depress a potential coarse particle effect, this would not explain the results in Topeka relative to other cities. Even considering relative measurement error, these results provide no clear evidence implicating coarse particles in the reported effects.

In a combined analysis across the 6 cities,  $\text{PM}_{2.5}$  was significantly associated with an increase in mortality of 2.1% (CI 1.5% to 2.6% for a 25<sup>th</sup> to 75 percentile increase in  $\text{PM}_{2.5}$ ). In contrast, the coarse particles were associated with a small but insignificant increase in mortality, 0.4% (CI -0.1% to 1.0%, for a 25<sup>th</sup> to 75<sup>th</sup> percentile increase in coarse particles). To determine whether coarse particles were independently associated with mortality, both fine and coarse particles were considered simultaneously in the regression across all six cities. The estimated effect for  $\text{PM}_{2.5}$  across the interquartile range remained unchanged with a significant association with mortality (2.1%, CI 1.5% to 2.6%). Conversely, the coarse particle estimate was substantially lowered (-0.2%, CI -0.8% to 0.4% for the interquartile range). This study provides clear evidence that fine particles are more likely to be responsible for the numerous observed associations between  $\text{PM}_{10}$  and mortality. The study also evaluated the association with fine particles by age and cause of death. Similar to studies of  $\text{PM}_{10}$  and mortality, a higher RR estimates for deaths from ischemic heart disease and deaths from chronic obstructive pulmonary disease was found in their analysis (Table V-14). The authors note that this is a similar pattern to that seen in London during the 1952 dramatic pollution episode.

Thurston et al. (1994b) evaluated the association between summertime respiratory and asthma related hospital admissions and 5 different particle measures: acids, sulfates, fine particles, coarse particles and  $PM_{10}$ . Without adjusting for the risk associated with concurrent  $O_3$  levels, the investigators found a significant association between respiratory-related hospital admissions and all measures of particles except the coarse fraction. Only fine acids and sulfates were significantly associated with asthma admissions in the univariate models. When  $O_3$  was included in the model, only acids and sulfates remained significantly associated. The authors note the high correlations between the other particle measures and  $O_3$  concentration make it difficult to select a best indicator, but these results provide no evidence of a coarse particle association with respiratory admissions in an area meeting the  $PM_{10}$  standards. The authors conclude that, based on the relative strengths of hospital admissions associations, the particle indicator, could be ranked as  $H+ > \text{sulfates} > PM_{2.5} > PM_{10}$ .

b. Long-Term Comparisons

The Six City study evaluated the relationship between mortality and long-term exposure to particles using several indicators; total particles, inhalable particles, fine particles, coarse particles, sulfate fine particles and non-sulfate fine particles (Dockery et al., 1993). Figure V-5 plots the relationship between mortality risk and each of the particle indicators. Although such comparisons involving only 6 cities should be viewed with caution, there is a trend toward increasing associated of relative risk of mortality with the particle indicator as the size of the particle indicator decreases (CD, Chapter 13). Although some association is apparent for TSP alone, the “super-coarse” fraction of particles larger than 10-15  $\mu\text{m}$  does not appear to be clearly linked with mortality, particularly in areas other than Steubenville. This further supports the notion that extrathoracic particles present a lower risk than thoracic PM. The distinction between  $PM_{2.1}$  and coarse fraction ( $PM_{10-2.1}$ ) particles is less clear, although -- as was the case in the short term mortality results above -- the relative risk for the city with the highest proportion of crustal materials (Topeka) appears to be more consistent with a fine particle effect. For the other cities, there is less difference between fine and coarse rankings.

Some additional insight into the Six City results is found in an ecological analysis of data from the ACS study (Pope et al., 1995b). Figure V-6 shows scatterplots of adjusted mortality

and PM as indicated by sulfate and TSP taken from the ACS study. These figures show a pattern consistent with a sulfate mortality effect across a large number of cities, but no clear relationship for TSP. The relative position of the six cities in these figures shows that, consistent with the original study design (Ferris et al, 1986), which selected cities to show gradients in both TSP and sulfur oxides, the mortality risk in the six cities shows an apparent relationship with both sulfates and TSP. The similarity in gradients for mortality for both fine particles (sulfates) and TSP in the six cities is not typical of the full set of 151 cities in the ACS study. Given the strong significant association between fine particles and mortality in the full ACS and Six City cohort studies and the lack of significant association with TSP in the ACS data (Pope et al., 1995b), the evidence for chronic mortality effects appears to be stronger for fine particles than for coarse.

Both the ACS study and the Six City study found the increase in risk of mortality associated with fine particle matter was mostly attributed to increases in cardiopulmonary mortality. As noted in Section 5.C, the Harvard Six City study reported a 37 percent increase in cardiopulmonary mortality associated with  $PM_{2.5}$ , and the ACS study reported a 31 percent increase in cardiopulmonary mortality associated with  $PM_{2.5}$ .

The negative results of the third prospective cohort study (Abbey et al, 1991) do not diminish the above conclusions. As noted in section V-C, despite the theoretically improved approach to exposure classification in this study (CD, p. 12-162), the choice of PM indicator (days  $>200 \mu\text{g}/\text{m}^3$  as TSP) for a large number of California sites limits the inferences that can be made about smaller particles sizes. Peak TSP in various times and places in California may be associated with coarse agricultural or road dust or high photochemically derived fine particles. Unlike other national cross sectional comparisons that use mean TSP from multiple monitors in metropolitan areas spanning the East and Midwest U.S. (e.g. Lipfert, 1993 ), peak TSP in California is less likely to be a useful surrogate for fine or thoracic particles. Thus, while neither this study nor the ACS study finds a significant mortality effect of long term exposures to TSP, only the ACS study tested this hypothesis with respect to fine particles using appropriate measurements.

Staff also further examined the data in the 24 city studies of the effects of PM on lung function in children (Raizenne et al., 1996). As noted above, the authors report significant

associations between lung function and strong acids, sulfates,  $PM_{2.1}$ , and  $PM_{10}$ , but did not report on any analyses for coarse fraction particles. Figure V-7 plots the lung function results for the 22 cities where such data were taken against both  $PM_{2.1}$  and coarse fraction ( $PM_{10-2.1}$ ). The lack of any significant association of coarse particles is apparent. The careful selection of the cities and study participants was intended to provide a clear gradient across regions with elevated fine acid aerosols and areas with lower levels, and to provide for a separation of potential  $O_3$  and PM effects. Multiple pollutants and indoor conditions were considered. The use of children of similar socioeconomic status and race reduces much of the confounding. This study provides clear evidence of an effect of fine particles that is independent of coarse fraction particles.

A longitudinal study by Johnson et al. (1990) in five Montana cities evaluated the association between lung function and TSP, fine and coarse particles in school children over one school year. They found significant decrements in FEV1 for TSP and significant decrements in FVC for fine particles, but at best, results were insignificant and inconsistent in effects for coarse particles.

### 3. Epidemiological Studies of Areas Dominated by Coarse Particles

The studies discussed in Section V.F.2 above are the only ones cited in the CD to have evaluated the association between directly measured coarse particles and health effects. In general, such studies have found equivocal results, suggesting an inconsistent or insignificant association between coarse particles and mortality and morbidity. However, with the possible exceptions of Steubenville and Topeka, the concentrations of coarse particles were relatively low and below those of fine particles, and measurement error could have influenced the results. The CD identifies only two additional studies as suggesting morbidity effects associated with short-term episodes of coarse particles (p. 13-47). In these cases, coarse particles were not measured, but ancillary evidence indicates that measured  $PM_{10}$  is likely to be dominated by coarse particles, at least during significant episodes or seasons..

A study in Anchorage, Alaska evaluated the association between  $PM_{10}$  and daily outpatient visits taken from insurance claims for employees for the State of Alaska and the Municipality of Anchorage (Gordian et al, 1996). They collected data on asthma, bronchitis, COPD, congestive heart failure, diarrhea and upper respiratory illness ( defined as upper

respiratory problems such as sore throat, sinusitis, earaches, rhinitis, and other nonspecific upper airway problems). They were not able to evaluate COPD and congestive heart failure because of insufficient number of cases. The investigators report that there are no industrial sources of the fine portion of  $PM_{10}$  in Anchorage, and the scanning electron microscopy of 10 random samples found over 80% of the  $PM_{10}$  mass was between 2.5 to 10  $\mu m$  in diameter. Daily  $PM_{10}$  values ranged from 5 to 565  $\mu g/m^3$  (corresponding to a volcanic eruption), with an average over the 22-month study period of 45.5  $\mu g/m^3$ . Gordian et al., report a 3-6% increase in visits for asthma and a 1-3% increase in visits for upper respiratory illness associated with 10  $\mu g/m^3$  increase in  $PM_{10}$ . They found no association with visits for bronchitis. They also found a nonsignificant association with  $PM_{10}$  in the period immediately after a volcanic eruption, and significant associations in the period excluding the volcanic eruption. The authors suggest that personal intervention minimized exposure after the eruption.

Hefflin et al., (1994) evaluated the potential influence of dust storms on emergency room visits for respiratory disorders in three Southeast Washington State communities. The investigators report that particle exposure is mostly from windblown soil and related natural crustal materials (the majority volcanic in origin). Thus, PM is likely dominated by coarse particles. This area also had high levels of  $PM_{10}$ , with peak 24-hour values ranging from 1 to 1,689  $\mu g/m^3$  with an average of 40  $\mu g/m^3$ . Aside from the periodic dust storms, the authors provide no additional evidence regarding the size composition of  $PM_{10}$  (e.g. extent of wood stoves, other sources). In contrast to Gordian, Hefflin et al. found a significant 0.35% increase in emergency room visits for bronchitis associated with a 10  $\mu g/m^3$  increase in  $PM_{10}$ . They also found a significant 0.45% increase in emergency room visits for sinusitis for a 10  $\mu g/m^3$  increase in  $PM_{10}$  levels over 150  $\mu g/m^3$ . There was no association with asthma. They found a slight association between emergency room visits and two high dust storms days where particle concentrations were over 1,035 and 1,689  $\mu g/m^3$ , but suggested that the reduced unit risk could have been related to mitigating behavior in these severe conditions.

These studies are suggestive of potential associations between high concentrations of coarse particles and health effects, but with some inconsistencies. The effects estimates for the Hefflin et al. study are much smaller than the Gordian et al. study. In addition, the Gordian et al.

study found an association between PM-10 and asthma but not with bronchitis, and the Hefflin study found the opposite. This contrast should be interpreted cautiously due to possible difference in disease classifications in the two study areas. Hefflin et al. (1994) have found overall asthma incidences in the region to be lower than expected, reducing the power of the study to detect effects. Both studies report multiple exceedences of the PM<sub>10</sub> standard. The apparent diminished response of the very highest days suggests that mitigative measures such as staying indoors on days of perceived dust episodes offered some protection against the effects of coarse particles on asthma and upper respiratory illness. Based on the Gordian results and the potential for significant deposition of coarse particles in the tracheobronchial regions of the lung where they may irritate sensitive receptors in asthmatics, the CD concludes that particles in the coarse fraction appear to be associated with the exacerbation of asthma via ambient exposure (CD, p. 13-51).

#### 4. Relevant Physicochemical Differences between Fine and Coarse Fraction Particles

Current understanding of the toxicology of ambient PM suggests that fine and coarse particles may have different biological effects (CD, p. 13-91). The discussion below summarizes information the CD presents regarding differences in potential toxicity between the two fractions based on composition and size related properties.

##### a. Comparisons of fine and coarse component toxicity in laboratory studies

A comparison of the major components of typical ambient particles (Table IV-2) and the size and composition of particles studied in the recent toxicologic literature (CD, Chapter 11) suggests that, while substantial work has been conducted on simulated constituents of fine particles such as acid aerosols, trace elements, and components of diesel particles, very little attention has been focused on health effects from exposure to ambient coarse particles or their significant components. The only study in humans of a coarse aerosol (10 µm diameter NaCl, see Table IV-2) cited in Chapter 11 (CD, Table 11-1) was considered to be a control for an acid fog exposure. Furthermore, because of size limitations of particles that can appreciably deposit in the tracheobronchial and alveolar region in small laboratory animals, most experimental animals studies involve fine particle exposures (CD, p. 13-44). The most clear and relevant comparison between the different constituents typically found in the fine and coarse fractions of PM was that

of Kleinman et al (1995), who found that the relative cellular and immunological toxicity of fine particle components, sulfate ( $70 \mu\text{g}/\text{m}^3$ ,  $0.2\mu\text{m}$  diameter  $(\text{NH}_4)_2 \text{SO}_4$ ) and nitrate ( $350 \mu\text{g}/\text{m}^3$ ,  $0.6\mu\text{m}$  diameter  $\text{NH}_4\text{NO}_3$ ) were greater than that of a typical resuspended coarse fraction component - road dust ( $900 \mu\text{g}/\text{m}^3$ ,  $4\mu\text{m}$  diameter), in the rat. While it is clear from the results of the study that the road dust elicited effects and was present in some concentration in thoracic region of the rat, the extent of deposition was not given in the study and it is possible that some of the differential toxicity shown between fine and coarse particle constituents in this study are due to differential penetration efficiencies of the particles.

Chapter 11 of the CD highlights the results of a volcanic ash study (Raub et al, 1985) as a comparison of fine and coarse mode particles. This study used intratracheal instillation of large amounts of  $12.2 \mu\text{m}$  and  $2.2 \mu\text{m}$  diameter volcanic ash into rats. The authors report finding a number effects at the higher concentration used, but essentially no difference in several measures of toxicity. While these result are of interest, the  $2.2 \mu\text{m}$  particles should not be characterized as fine mode, but rather as the "tail" of the coarse mode. Thus, this study suggests little or no difference in the toxicity of coarse mode particles of different sizes, but even this conclusion is limited by the artificial nature by which the particles were deposited in the animals.

Raub et al. (1985) also found no differences in toxic responses between normal and emphysemic animals inhaling  $9600 \mu\text{g}/\text{m}^3$  submicrometer sized volcanic ash for short durations. Mauderly (1990) found that emphysematous rats had less effects than normal animals because of the sparing effects of emphysema to high levels of diesel particles. However, Raabe et al. (1994) exposed rats with induced emphysema to two fine particle mixtures intended to simulate a London aerosol (ammonium sulfates, coal fly ash, lamp black carbon) and a California aerosol (ammonium sulfates and nitrate, graphitic carbon, clay, and trace metal sulfates). Even at the lowest levels tested ( $550$  - $800 \mu\text{g}/\text{m}^3$ ), 3 to 30 day exposures resulted in significant responses that were greater than those seen in normal animals (CD, p 11-176).

b. Toxicity of Fine and Coarse Mode Chemical Components

Table IV-2 lists the key differences in chemical composition of fine and coarse particles. The CD review highlights a number of specific components of PM that could be of concern to health, including typically fine components (e.g., acids, certain metals, diesel particles, and

ultrafines), and typically coarse components (e.g., silica and bioaerosols). It is clear that components of both modes can produce responses, although in general, the fine mode appears to contain more of the irritant substances potentially linked to the kinds of effects observed in the epidemiological studies. The following is a brief summary of the potential toxicity associated with fine and coarse substances.

Most of the aerosol acidity is contained in the fine fraction. Section V-C details a variety of effects associated with acids in community epidemiology and at high levels in laboratory studies. Acids may produce effects as liquid droplets or surface coatings in mixtures. For example, Chen et al. (1990) exposed guinea pigs to fly ash derived from either low or high sulfur coal. The acidity of the resulting particles was proportional to sulfur content with the greatest pulmonary functional response noted for the high sulfur fly ash.

Acid aerosol exposure has been associated with changes in airway morphology as well as airway responsiveness (Gearhart and Schlesinger, 1988; Kleinman et al., 1995; Chen et al., 1992b; Gearhart and Schlesinger 1986; and El-Fawal and Schlesinger, 1994) in experimental animals. Markers of cytotoxicity and increased cellular permeability, following a single exposure to fine or ultrafine H<sub>2</sub>SO<sub>4</sub> aerosols, have also been reported (Chen et al., 1992a). Levels of biological mediators of inflammatory responses, as well as smooth muscle tone, have been shown to be altered after exposure to fine acid aerosols (0.3 μm diameter) and lavage. Fine acid aerosol exposure has been shown to alter macrophage function, production of tumor necrosis factor cytotoxic activity, and superoxide radical production, all of which are related to host defense mechanisms. Fine aerosols of ammonium sulfate and nitrate at relatively low levels have also been shown to alter antigen binding and respiratory burst activity by macrophages (Kleinman et al., 1995).

As noted in the 1982 Staff Paper, extractable organic matter from particles with potential carcinogenic activity is also preferentially derived from the fine fraction. The CD (p. 5-10) notes that the majority of diesel exhaust particles is in the fine mode and both short and long term inhalations of diesel particles are associated with respiratory effects at higher than ambient levels in experimental animals. Occupational studies report (at levels higher than ambient

concentrations) bronchitis, impaired respiratory function, cough, and wheezing (CD, Table 11-11), all of which have been reported in community air pollution studies of PM.

Ultrafine aerosols ( $<0.1 \mu\text{m}$ ) are a class of fine particles that have the potential to cause toxic injury to the respiratory tract as seen in studies conducted both *in vivo* and *in vitro* (CD, p. 13-76). An important aspect of their potential toxicity is their relatively low solubility (CD, p. 13-77). Studies on a number of relatively insoluble ultrafine particles (diesel, carbon black), present in the ambient air as aggregated ultrafines, indicate that inhalation exposure to these as well as  $\text{TiO}_2$  to rats are associated with epithelial cell proliferation, chronic pulmonary inflammation, pulmonary fibrosis, and induction of lung tumors at high concentrations (CD, p. 13-77). Ultrafine particles have also been shown to evade macrophage phagocytosis and penetrate the interstitium more easily than larger sized particles (Takenaka et al., 1986; Ferin et al., 1990, CD, p. 13-77). There is also evidence that some aggregated insoluble ultrafine particles dissociate into singlet ultrafine particles in the lung which would facilitate transport across the epithelium (Takenaka et al., 1986; Ferin et al., 1990; Oberdörster et al., 1994; CD, p. 13-77). Because of their short lifetime, it is unclear that unaggregated ultrafine particles make up any significant fraction of the mass of fine particles or of  $\text{PM}_{10}$ , other than in the vicinity of significant sources of ultrafine particles. The relationship between ultrafine numbers (or mass) and the mass of fine or thoracic particles found in typical community air pollution has not been established. Although the CD provides little direct information, it might be expected that penetration and persistence of unaggregated ultrafine particles to indoor environments would be limited. For these reasons, it is questionable whether ultrafine aerosols could be playing a major role in the reported epidemiologic associations between the measured mass of fine or  $\text{PM}_{10}$  particles and health effects in sensitive populations. Because of the potential toxicity suggested by the available literature, however, this is an area where significant additional research is needed.

The only major coarse particle components highlighted in the CD summary are silica and bioaerosols. The majority of silica particle mass is found in the coarse fraction (CD, p. 11-127). Occupational, but not community exposures to crystalline silica has been associated with pulmonary inflammation and silicosis (pulmonary fibrosis from silica) (Spencer 1977; Morgan et al 1980; Bowden, 1987). Although some evidence of long term accumulation of silicate material

at near ambient levels has been noted (Section V-C), the CD provides no evidence of any significant short term effects of ambient silica. Thus, there is no evidence suggesting that this class contributes to the observed daily mortality and morbidity effects.

Bioaerosols (which includes fungal spores, pollen, bacteria, viruses, endotoxins, and animal and plant debris) can be distributed in both fine and coarse fractions and are capable of producing serious health effects. Strong sources (e.g., grain elevators) of these materials may have obvious effects on allergic individuals. However, as the CD points out, the annual variability, relative mass, and distribution of such materials suggests that they too “appear to be unlikely to account for observed ambient (outdoor) PM effects on human mortality and morbidity demonstrated by epidemiology studies reviewed in Chapter 12” (CD, p. 11-136).

c. Physical Aspects of Fine and Coarse Particles

Figure IV-2 and Table IV-2 show key differences between fine and coarse particles. The fine fraction contains by far the largest number of particles and a much larger aggregate surface area than the coarse fraction. As noted above, the size range of particles containing the largest number of particles ( $<0.02 \mu\text{m}$ ) is not that with most of the mass of the aerosol (fine or coarse). However, most of the aggregate surface area of the entire size distribution of typical urban particles is contained in the fine size range of  $0.1$  to  $1.0 \mu\text{m}$  diameter (CD, Figure 13-4; Figure IV-2). Unlike the case with particle number, therefore, it is clear that the aggregate surface area of  $\text{PM}_{10}$  is likely to be strongly related to the mass of fine particles (see Figure IV-). This relationship should be a common property of PM in a variety of different urban settings.

The greater surface area of the fine fraction means this fraction has a substantially greater potential for absorption of other potentially toxic components of PM (e.g. metals, acids, organic materials), as well as for dissolution or absorption of pollutant gases. It is the surface of a particle that is primarily in contact with respiratory cells and surfaces (CD, p. 13-68). The total surface area of a particle may be important in the presentation of active groups on the surface of the particle to cell surfaces (CD, p. 13-26). Biological effects on epithelial cells or macrophages may depend on the number of cell surface receptors stimulated or occupied by particles. Consequently, numbers of particles may be relevant to their toxic effect (CD, 13-27). Therefore, in comparison to coarse mode particles, fine mode particles will have the greatest probability of

interactions with potential respiratory targets of toxicity through increased numbers of particles as well as surface area (see Appendix D).

The CD notes that the presence of surface coatings can increase the toxicity of particles. Such considerations may be important when trying to ascertain the appropriate dose metric for evaluation of lower respiratory tract health outcomes (CD, p. 13-24). For example, 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, CD, p. 13-24). Various biological responses (e.g., reduction in lung volumes and diffusion capacity, alteration in biochemical markers, and changes in lung tissue morphology) in guinea pigs have been reported after exposure to ultrafine zinc coated with a surface layer of  $H_2SO_4$  (CD, Chapter 11, Chen et al., 1992b,1995). These responses were much greater than those following exposure to larger size  $H_2SO_4$  in pure droplet form yet having similar mass concentration of acid. A possible mechanism for the differential toxicity of the two aerosols is the difference in particle numbers deposited at target sites. At an equal total sulfate mass concentration,  $H_2SO_4$  existed on many more particles when layered on the ZnO carrier particles than when dissolved into aqueous droplets. In addition, a recent study by Chen et al., (1995) confirmed that the number of particles in the exposure atmosphere, not just total mass concentration of acid, is an important factor in biological responses following acidic sulfate particle inhalation when aerosols having the same size distribution were compared (CD, Chapter 11).

Coating the surface of insoluble particles with certain transition metals (e.g. iron) has been shown to enhance pulmonary toxicity (Costa et al., 1994a,b; Tepper et al., 1994). Accordingly, fine particles may serve as an efficient carrier of more toxic material to respiratory tract targets. Coating of micrometer-sized particles with formaldehyde has been shown to increase the delivery of formaldehyde and consequently increase irritant responses in human subjects (CD,13-76). Jakab and Hemenway (1993) suggest that reaction products on particle surfaces may be more toxic than the primary material. Exposure to  $O_3$  was shown to increase the toxicity of carbon black particles in mice. The authors hypothesized that this result was due to a "reaction of  $O_3$  on the surface of the carbon black particles in the presence of adsorbed water, producing surface bound, highly toxicologically reactive oxygen species" (CD, p. 11-161).

Increased surface coating of water or the presence of hygroscopic sulfates, nitrates, and organic compounds found as droplets in the fine fraction may also increase the potential for delivery of irritant species such as SO<sub>2</sub>, hydrogen peroxide, and aldehydes to more sensitive regions of lung, which, when in the gas phase, would normally be removed in the extrathoracic region (CD, p 13-9). The potential for increasing delivery of pollutant gases provides some basis for expecting some interaction among PM as a pollutant and gases observed in community studies.

d. Deposition in Sensitive Individuals

As shown in Table V-1, both fine and coarse particles penetrate to and deposit in the tracheobronchial and alveolar region. Based on the epidemiological results and deposition considerations, it is reasonable to expect that high levels of coarse particles alone could aggravate asthmatics through tracheobronchial deposition. However acids and fine particles have also been associated with hospital admissions for asthma in areas with relatively low coarse mass (Thurston et al., 1992). Receptors that have been linked to an asthmatic response have been demonstrated to be in areas of the lung where both coarse and fine particles deposit (see Appendix D). Moreover, certain insoluble coarse particles can deposit and remain for extended periods in the alveolar region, although the relation to the chronic effects observed in epidemiologic studies is unclear..

The epidemiological studies suggest greater mortality and morbidity effects in individuals with cardiopulmonary disease. In this regard, it is of note that fine particles have been shown to have a greater deposition in the lungs of individual with chronic respiratory disease than in normal subjects (CD, Chapter 13). Such individuals also have reduced clearance for these particles (see Appendix D). Thus, the potential for greater target tissue dose in susceptible patients is present (CD, Chapter 11). Simulations discussed in Chapter 10 of the CD, suggest that adolescent children (14-18 yrs of age) are predicted to have greater respiratory tract daily mass deposition of submicron particles than adults.

5. Summary and Conclusions

The staff assessment of the evidence finds substantial quantitative and qualitative information on the effects of fine particles and its constituents. Because of the remarkable volume

of pertinent literature produced in the last 9 years, far more quantitative epidemiologic data exist today for relating fine particles to mortality, morbidity, and lung function changes in sensitive populations on a short- and long-term basis than was the case for  $PM_{10}$  at the conclusion of the last review.<sup>9</sup> Like the  $PM_{10}$  studies, the fine particle studies consistently find positive, significant associations between fine particle levels and mortality and morbidity endpoints, with over 20 studies conducted in a number of geographic locations throughout the world, including the US, Canada, and Europe. This collection of studies shows qualitative coherence in the types of health effects associated with fine particle exposure including mortality, morbidity, symptoms, and changes in lung function (Tables V-11 to V-13). The association with mortality is mainly attributable to respiratory and cardiovascular causes, which is consistent with the range of observed respiratory and cardiovascular-related morbidity effects, from respiratory and cardiovascular-related hospital admissions, respiratory symptoms to changes in lung function.

By contrast, the CD and this staff assessment find much less direct evidence in the recent epidemiologic and toxicologic literature regarding the potential effects of coarse particles. The previous staff assessment of occupational and toxicologic literature (EPA 1982a,b) as well as the present review have found ample qualitative reasons to be concerned about elevated levels of coarse particles smaller than 10  $\mu m$ . These effects (e.g., asthma) are consistent with enhanced deposition of coarse particles in the tracheobronchial region (CD, p. 13-51). However, unlike the case for fine particles, the clearest community evidence regarding coarse particles finds such effects only in areas with numerous marked exceedences of the current  $PM_{10}$  standard (CD, p. 13-51). In this regard, it appears that the weight of the available evidence allowing direct comparisons suggests that ambient coarse particles are either less potent or a poorer surrogate for community effects of air pollution than are fine particles.

It is clear, however, that still more quantitative evidence exists today for  $PM_{10}$ , which includes both fine and coarse particles. The above assessment does not conclusively demonstrate that coarse particles play no role in the effects associated with  $PM_{10}$  at levels below the standard.

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<sup>9</sup>The 1986 staff assessment of the quantitative basis for the standard cited studies conducted in essentially 3 locations for the 24-hour standard and 4 studies involving a total of 10 cities for the annual standard; none measured  $PM_{10}$  (EPA, 1986).

The potential role of coarse particles in producing such effects could be masked in community studies by potential differences in measurement error and exposure patterns between fine and coarse particles. As noted in the CD, fine particles tend to be more uniformly distributed than coarse mode particles within (and among) urban areas. Moreover, the apparent greater infiltration ratio (penetration and settling) of fine particles indoors means that variations in both short- and long-term personal exposures to outdoor PM will be more influenced by fine than coarse particles.

It is also important to note that some of the more important components of ambient fine particles (e.g. acid sulfates) have no notable indoor sources, while a substantial fraction of indoor coarse particles comes from indoor resuspension of local crustal (e.g. deposited or tracked in on footwear) and other coarse materials (Wallace, 1996). This means that any effects that are potentially produced by coarse particles (from outdoor air and indoor resuspension) are more likely to be decoupled from outdoor concentrations. The less even urban distribution of coarse particles and stronger indoor sources would tend to diminish the power of community studies of outdoor air to detect the effects of such crustally derived materials as compared to fine particles (CD, p. 1-9). Viewed from another perspective, this also suggests that efforts to reduce any such effects by controlling outdoor coarse particles would be less successful than a program to reduce outdoor fine particle effects. Thus, while the epidemiologic data are not conclusive with regard to the potential effects of coarse particles, they more strongly support the notion that fine particles are a better surrogate for that fraction of ambient PM that is most clearly associated with the health effects observed in community air pollution studies at levels below the current standards. This view is also supported by qualitative considerations derived from a consideration of the toxicologic implications of the profound physical and chemical differences associated with components of these fractions.